EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2012
EMA/428835/2012
Patient Health Protection

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

GVP Module IX – Signal management

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

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

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

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We appreciate the concise and comprehensive guideline, but would like to suggest more detailed explanations/recommendations concerning “active surveillance”.

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 49-50		Comment: Where will new information related to potential beneficial effects be captured? These effects should be an integral part of benefit-risk analyses. Proposed change (if any):
Line 52		Comment: Often spontaneous reports can not easily be validated due to limited access to the data. Proposed change (if any):
Line 125		Comment: Does this imply “active surveillance” by the competent authorities or the holder of the marketing authorization? How would this be managed from an operational point of view? Proposed change (if any):
Line 129		Comment: This recommendation is very difficult to be applied to signals detected from public websites, social networks and blogs (see lines 122-123). Proposed change (if any):
Lines 303-304		Comment: Please explain “signals identified […] with potential high media […] interest”? Does this imply a different level of signal awareness, if media might get involved? 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 375-376		Comment: Why is the modal verb “should” used here? What would be examples for not communicating results of signal assessments to marketing authorisation holders? Proposed change (if any): Please change “should” to “shall”.

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall AEFI finds GVP Module 9 on Signal Management a well structured and comprehensive description of both signalling routines and how the interaction and communication between stakeholders should work in Europe. However, from our point of view it is more focussed in activities for big pharma companies than in providing guideline to perform signal detection tasks in small companies. It's relevant to highlight the following point**:** AEFI considers that the requirements to implement detailed quality system procedures for all signal management processes will need **an 24 months transitional period** for these requirements. In the case of generic products, when the signal detection is performed by the Agency, will the MAHs have to perform some monitoring of these 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')*
83-86		Comment: Pharmacoepidemiology data is an important source of signals, which is not mentioned. Proposed change: Add in line 84 “and pharmacoepidemiology data”
Lines 113-118		Comment: *Please specify whether the signal detection should be done exclusively for medicinal investigational products for which the laboratory is MAH/sponsor or whether the signal detection should be done considering all existing trademarks/generics including the same substance.* Proposed change (if any): Comment: (115) Results of registries or studies initiated by the MAH is covered by Module VIII. Proposed change: The reference in parenthesis “(see Module VI)” should be replaced with “(see Module VIII)”.
119-121		Comment: PASS results must be communicated to NCA within 12 months from the end of data collection according to Module VIII, regardless of manuscript acceptance. Introducing different requirements in different GVP Chapters does not simplify and as stated here it risks create inconsistency between countries/NCAs. Proposed change: Replace this whole paragraph with: “MAHs shall submit the study report of all PASS to competent authorities within 12 months from the end of data collection or where required completion of data validation (see Module VIII).
121-125		Comment: It will be very difficult to obtain follow-up information from Internet and digital media. It is also important to consider if the quality of the information published in these types of media justifies the effort to follow-up all the suspected experiences.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 monitorization of adverse experiences should only be mandatory for the industry for the internet pages and digital media sponsored by the MAHs. Proposed change: “Other sources of information include the internet, digital media or other systems through which patients and customers may communicate adverse experiences with medicinal products. The MAH should review these type of media periodically and follow up any adverse experience they became aware of from such sources”.
Lines 157-158		Comment: *Could you give some examples of the additional data which would be needed for signal detection in a study when only aggravated results are obtained?* Proposed change (if any):
Lines 177-178		Comment: *Please provide an example of classification for major and minor possible health impacts.* Proposed change (if any):
186-187		Comment: Please clarify the type of cases that should be excluded from the analysis.
223-224		Comment: Please include the type of cases that should be excluded from the analysis.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 292-293		Comment: *When patterns of medicinal product utilization is mentioned (off-label or misuse) there should be specified whether it needs to be analysed only when a safety issue is presented together with these situations (i.e. off-label use with an associated adverse drug reaction).* Proposed change (if any):
Lines 322-324		Comment: *Please specify what the agreed or operational definition of the medicinal issue means.* Proposed change (if any):
Lines 350-353		Comment: *If the signal has appeared only for the substance but not specifically for the trademark/generic of the MAH, who should be the responsible for sponsoring these kind of PASS?* Proposed change (if any):
Lines 354-359		Comment: *If the signal has appeared only for the substance but not specifically for the trademark/generic of the MAH, who should be the responsible for sponsoring these kind of prospective studies?* Proposed change (if any):
Lines 370-374		Comment: *Please specify form, content and ways to communicate to competent authorities such validated signals.* Proposed change (if any):
373, 492, 564		Comment: (555) Proposed change (if any): *Shall monitor all available data and information for signals that MAH becomes*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		aware. Comment: The terms “immediately” and “forthwith” for MAHs to communicate validated signals to authorities and for the Agency to communicate PRAC conclusions to the MAH are prone to differing interpretations. Proposed change: Specify the intended timeframes for these communications in clear wording, e.g. within 15 days.
401		Comment: The term “Potential signals” risk being subject to varying interpretation. Proposed change: The term “Potential Signal” should be defined and added to the Definitions module.
406		Comment: From our point of view, the training on signal management activities should be limited to pharmacovigilance staff. In case a signal support program is placed, the risk management plan should consider a specific training for the departments involved in these programs.
458-460		Comment: (458) The frequency of monitoring should be at least once monthly (for MAHs). Proposed change (if any): It is possible for MAHs to have the possibility to extend the periods by giving a justification of the case (eg: no ICSRs or safety information received for the period) ? Comment: We consider that MAHs should be informed about the initial frequency of monitoring of their products applied by the Agency and the National Regulatory Authorities. Proposed change: to include the initially intended frequency of monitoring (if other than monthly) in the listing published by the Agency

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
467-475		Comment: It is unclear if the Agency shall support the monitoring of the data in the EV database by providing the specified accesses also for MAHs. Proposed change: Specify if the Agency will support the specified accesses also for MAHs or only for the authorities.
482-487, 506-510, 532-536		Comment: MAHs need to be informed about the result of the activity that the Agency or National Regulatory Authorities undertake to confirm any validated signals communicated by the MAH (whether the validity is confirmed or not) within 15 days.
557-559		Comment: We consider that the monthly signal detection should be limited to medicines under intensive monitorization. Older products should need less frequent monitorization (e.g. at least once a year).

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
AESGP

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We agree with the flexibility and risk-based approach provided in this module to determine the most appropriate monitoring frequency of EudraVigilance. However, we consider that 'at least once monthly' is an excessive monitoring frequency for many products, including non-prescription products, with a well known safety profile and few reported reactions. A number of MAHs currently adopt a risk-based approach to signal detection and monitor their own safety data less often than monthly for certain products where this is considered to be appropriate.

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')*
43-48		Comment: The agency provides in this section a definition of signal as proposed by the CIOMS and states, that for the purpose of this module only new information related to adverse reaction will be considered. A signal definition is still unclear. Proposed change: Please include in the annex on definition, a complete definition of signal and cross-refer to it in this module.
60-62 428-430 556-557		In our opinion the requirements to monitor signals from the EudraVigilance database are inconsistent. - On line 60-62 it is stated that the signal management process (it is assumed that this refers to signal management process of the MAH) is limited to signals arising from outside the EudraVigilance database or not directly supported by the EudraVigilance database. - On lines 428-430 it is stated that for medicinal products authorised in accordance with Regulation No 726/2004 or Directive 2001/83/EC, the monitoring of data in EudraVigilance shall be performed by the EMA or the national competent authorities. - On line 556 it is stated that the MAH shall also monitor the data in EudraVigilance at least once monthly. The responsibilities of data monitoring in the EudraVigilance database should be clearly stated and wherever possible avoid duplication between the work of the competent authority and that of the MAH.
82-127		Comment: The content of this section is to some extent redundant (lines no. 83-86 and 108-112) and not structured. Included information outside the scope of the section (line no. 113 – 118) Proposed change: Please provide a more structured section on the data source for signals. For example: 1. spontaneous reporting 2. studies 3. literature 4. internet, etc.
99-103		Comment: The inclusion of “PSURs” in this paragraph contradicts with the content from Module VII (Periodic safety update report) which states that: *The PSUR should not be used to provide the initial notification of*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted (lines 203-205 from Module VII) Proposed change: Therefore, we propose to remove "periodic safety update reports (PSURs)" from this paragraph.
122-124		Comment: The sentence on line 124- is redundant with the requirement outlined in greater details in module VI. We refer to our comments under that module. The sentence on line 126-127 should be rephrased to allow for a risk-based approach Proposed changes: ~~Marketing authorisation holders and competent authorities should try to gain further information related to reactions they become aware of from such sources.~~ If the available information is limited but despite this potentially indicative of an impact on the risk-benefit balance of the product or implications on public health, suspected serious adverse reactions should be confirmed if possible in other data sources such as EudraVigilance.
139		Comment: Severity of the event should also be considered Proposed change: Different factors may be taken into account for the prioritisation of signals, namely the fact whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness or severity of the reaction involved and factors related to the documentation of the reports in the EudraVigilance database.
165-168		Reference is made to detailed guidance on methods of signal detection published by CIOMS working group, but no methods are proposed in this module. Proposed change: We propose to add that in principle two methods may be used in signal detection: Review of individual cases (in case of isolated and good documented cases) and statistical analysis in case of large data basis.
472-474		Comment: Stratification of data by 'at risk patient groups' would indeed allow for clear differentiation of non-therapeutic usage of company products (overdose, abuse, misuse, off-label use) opposed to therapeutic use.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		It would be useful to have a tool to discriminate in such way.
498-517		Comment and proposed change: The mention that the lead/co-lead Member State will inform the MAH in case of a detected signal should be added.
518 – 540		Comment and proposed change: The mention that the NCA will inform the MAH in case of a detected signal should be added.
558 - 560		Comment: We agree with the flexibility and risk-based approach provided here to determine the most appropriate monitoring frequency of EudraVigilance. However, we consider that 'at least once monthly' is excessive for many products, including non-prescription products, with a well known safety profile and few reported reactions. A number of MAHs currently adopt a risk-based approach to signal detection and monitor their own safety data less often than monthly for certain products where this is considered to be appropriate. Proposed change: The sentence "The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information" should be replaced with "The frequency of monitoring shall be proportionate to the identified risks, the potential risks and the need for additional information".
561-563		Comment: The role of MAH in this context is not clear. Proposed change (if any): Shall monitor all emerging data and perform signal detection activities in countries where its products are marketed.
612 – 613		Comment: Any signal, which has been detected and validated, should also be communicated to the marketing authorisation holder, even when immediate action is not needed. Proposed change: Any signal that has been detected and validated by the Agency or a national competent authority should be communicated to the MAH and sent to the PRAC for consideration.
Minor / editorial changes		
95		Comment: Change "of" to "on" before "periodic monitoring"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: based on periodic monitoring of large databases such as the EudraVigilance database.
120		Comment: Remove the semi-colon Proposed change: as possible after the acceptance of the manuscript of the results of post-authorisation
132		Comment: Change “that” to “than” Proposed change: require other methodological strategies than other medicinal products.
224		Comment: Correct used to uses Proposed change : Where signal detection uses an automated screening of a database
250		Comment: Refer to the two bullets Proposed change: In principle only signals not falling under the above two categories should be validated
261		Comment: Add an A at the start of the sentence Proposed change: A signal becomes a validated signal if the verification process of all relevant documentation
495		Comment: Change “to” to “with” Proposed change: should collaborate with the signal validation performed by a national competent authority

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
532 – 536		Comment: The start of the “15 day clock” seems to be unclear with regards to the way of notification and quality of signal submission (in case of poor quality data , the validation of this signal is maybe difficult, if not even impossible and requires more time than 15 days thus resulting in a switch of responsibility from MAH to the Agency and NCAs Proposed change (if any): The 15 day clock starts, when the provided information from MAH is in sufficient quality for the Agency and NCAs. Development of adequate and harmonised quality standards might be useful.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 APRIL 2012

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

Comments from:

Name of organisation or individual
ALEXION Europe SAS

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 122-123		Comment: Consumers should be rather encouraged to report adverse events using a classical way (HCP, regulatory agencies). In addition as data on blogs may be unverifiable we would not push to screen these for the purpose of signal detection unless the MAH becomes aware of such a signal from such a medium. Proposed change (if any): To delete this statement on blogs, websites, networks.
Lines 331-333		Comment: Please clarify the meaning and detail the “staged approach for signal assessment”. Please clarify the meaning of “temporary measures” in the first stage of assessment. Proposed change (if any):
Line 580		Comment: What about orphan drugs, what should be the frequency for the reviewing of statistical output? Is it the same as for all other drugs? Proposed change (if any): Add a statement for orphan drugs

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

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

Comments from:

Name of organisation or individual
AstraZeneca

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
	AstraZeneca welcomes the opportunity to provide feedback to GVP Module IX – Signal management' (EMA/827661/2011) AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to those. Additionally, AstraZeneca would like to provide one further specific 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')*
564-565		**Comment:** This states: *The marketing authorisation holder:* • *shall validate any detected signal and shall forthwith inform the responsible competent authority in line with the list as published by the Agency (referred to in lines 463-464) [IM Art 25(4)];* **Proposed change (if any):** Further clarification is required. The qualification of the second half of this bullet (underlined above) indicates that this would only apply to centralized products, as lines 463-464 refer to products authorised in accordance with Regulation (EC) No 726/2004. However, I understand that the applicable Implementing Measure will not necessarily apply only to centralized products, instead being applicable to all products marketed within the EU. If so, this apparent inconsistency between the IM and the GVP module will require resolution so that MAHs are clear as to which signals on which products should be communicated 'forthwith' to competent authorities.

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)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Certainly builds on the Signal Detection and Evaluation section of Vol IXa.
	Whilst in Vol IXa, Signal detection and review was one of the topics to be covered by a procedure, far more definition was provided in Module IX relating to Signal Detection and Evaluation and a specific and documented process.
	Definition of a Signal and its sources appears consistent with CIOMS VII.
	EudraVigilance database will gradually become agency's principle denominator data set. MAHs should monitor EV according to their access at least once/month- at least following the audit of functionality.
	Sources of safety information and therefore signals is far wider- implying that all possible sources relevant to that medicinal product should be reviewed.
	As with CIOMS VII, Module IX allows for different signal methodologies appropriate to the medicinal product, and that the methodology should be part of a system (QMS) to ensure the quality of the activity including methodology and periodicity of the review.
	Resource allocated to Signal Detection and Evaluation should always include clinicians based on the clinical review of the data. Statistical analysis should be supportive to that activity. This shouldn't be an issue based on availability of resource already in place for the clinical review of ICSRs.
	Signal validation allows for signals to be refuted, rejected, confirmed, strengthened, or put on that back burner due to insufficient information. All signals should (i.e. must) be tracked and monitored. All outcomes of signals should be tracked. Might be an issue depending on software used, and also if no software is used. Traceability of every signal might be problematic.
	The need for action should be considered throughout the signal management process. Exchange of information between competent authorities, marketing authorisation holders and other concerned parties may be needed to share information on signals, collect additional data, further evaluate the safety issue and take decisions to protect patients' health.
	All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps need to be recorded and tracked systematically, and audit trails kept. That system should be subject to audit.
	Training should be provided to all staff involved in signal management activities, but also but also staff who may become aware of potential signals or support signal management. This will add to the training burden (and how effectiveness of that training is measured will be interesting).

Stakeholder number *(To be completed by the Agency)*	General comment
	European medicines web-portal will include information for the public including PRAC assessments and recommendations following the review of signals. This will be an interesting issue for litigation and access to information (and situations where action was not taken).

2. Specific comments on text

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

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Bayer HealthCare

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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')*
612-632 (subsection IX.C.3.)		Comment: There should be a process in place ensuring information of concerned MAHs on signals validated by the agency and sent to the PRAC. This ensures rapid action by all concerned stakeholders. Proposed change: “Any signal that has been detected and validated by the Agency or a national competent authority should be sent to the PRAC **and the MAH** for consideration.”

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)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It may be helpful to perform separate statistical analysis of ICSRs following overdose, misuse or medication error (separate to ICSRs reporting ADRs associated with the use in accordance with the SPC).

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.B.3.3. Signal validation **Line 229 – 276**		Comment: A more detailed presentation which data according to which priorisation should be included would be helpful. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

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

Comments from:

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

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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')*
96		Comment: Suggest that text should read as ‘based on periodic monitoring’ rather than ‘based *of* periodic monitoring’.
115-117		Comment: “Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific and medical literature for those journals/active substances not included in the list screened by the Agency.” Can clarification be provided with respect to when this list will be available? Additionally, what is the expectation of CAs with respect to screening by MAHs of journals not included in the screening performed by the Agency for a specified active substance?
122-127		Comment: The guidance is not explicitly clear with respect to the expectation for MAH and competent authorities regarding monitoring of other sources of information (e.g. data from the internet or digital media as defined in lines 122-123 of the text). Clarification that active monitoring is not explicitly required would be helpful. Proposed change (if any): The wording could be strengthened to indicate that there is not a requirement for MAH and competent authorities to actively search all such sources of information, but that if they become aware of reactions from such sources then the actions defined should be performed.
155-156		Comment: Signal analysis and prioritisation appears to be essentially a duplication of effort of the validation step with the outcome only differing in that MAH should assign a timeframe for the assessment of a signal and justify the allocated timeframe for each signal detected. For companies with small data sets, signal detection is likely to be based on a review of ICSRs as the use of complex statistical tools (which may justify additional steps for signal validation, analysis and prioritisation) would not be appropriate. As implied by the text in lines 155-156, can clarification and confirmation be provided with strengthened

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		wording to indicate that signal validation, analysis and preliminary prioritisation of a detected signal may be performed as one step in the signal management process for MAH with small data sets? Additionally, it would be helpful if the guidance could provide some quantification regarding what could be considered as a small data set based either on total number of reports or average number of reports received per month or year for an active substance used in a pharmaceutical product. Proposed change (if any): Perhaps text similar to the following could be added, possibly after line 310: “For MAH with small data sets whose signal detection activities are primarily based on a review of ICSRs, the steps of signal validation, analysis and prioritisation of any detected signal may be performed as one combined step in their signal management process.” Quantification in the guidance with respect to what could be considered to represent a small data set.
173 and 561		The guidance states that “data from all appropriate sources should be considered” and that MAH shall monitor all emerging data; this is a very broad definition. Can clarification/examples be provided in the guidance?
274-277 (also 309-310, 379-384 and 399-403)		Comment: In the guidance, the use of tracking systems for the outputs from each step of the signal management process is required. Clarification should be provided regarding any specific requirements for the tool use to track such outputs e.g. validation status. Proposed change (if any):
408-414		Comment: With respect to training, guidance is provided regarding staff that should be specifically trained in signal management activities, including appropriate staff not working within safety departments. The guidance includes a sentence that indicates training should include MedDRA etc. but it is not clear if this level of training would be expected only for staff working within safety departments or would also be required for those staff working outside of safety departments for whom some training is considered appropriate. Clarification is

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		required. Proposed change (if any): Expansion of the text in this section of the guidance to indicate the level of training considered appropriate for staff working within safety departments in comparison to those staff in other departments (e.g. regulatory).
556-560		Comment: The guidance states that MAH shall monitor the data in EudraVigilance and that the frequency of the monitoring should be at least once monthly. In this module, which relates to the signal management process, it is not explicitly clear whether this requirement for MAH to monitor EudraVigilance (to the extent of their accessibility) is in order for them to search for additional data to support signals already detected by the MAH, or as a source of information that MAH should monitor in order to try to detect signals (which would essentially be a duplication of the work carried out by the EMA and other competent authorities). Clarification is required.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The most important prerequisite of signal management is the well-founded individual management of single cases by PhV-experts with medical and scientific expertise. A clearer distinction between companies with large amounts of safety data and such with small amounts of safety data would be desirable. In this context it should be noted that complex quantitative methods based on "drug-event" combinations are very important, but they are only useful for extremely large safety data amounts. MAH´s with relatively small safety data amounts need to acquire a pragmatic approach for signal detection.

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 61 - 62		**Comment**: Since marketing authorization holders should collect also safety information´s arising from use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure (DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT), this information is not necessarily associated with an adverse reaction.
Line 183 - 192		**Comment**: It should be added that especially an accumulation of listed and non-serious adverse events (e.g. allergic reactions) should be intensively monitored since such an accumulation could be associated with possible issues regarding the product quality.
Line 193		**Comment**: According to EMAs Guidance on signal detection, the following aspects should be also considered: a) Grouping of substances (e.g. API with a similar action profile); b) Class effect detection; c) For the MAH it should be apparent, how big EMAs database is and what the variables are and what the analysis is referring to, e.g.: “MAH’s signals versus all cases in the database”; c) Exclusion of cases without causality; d) Exclusion of cases from off label use;

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		e) A relation to incidences/estimations of signal of disproportionate reporting from originator. Furthermore, EMA should generate an option to detect possible class effects (directly in the EMA database).
Line 207 - 210		**Comment**: According to statistical assumptions or methods, the approximate number of cases needed at least to yield a possible signal (e.g. Gaussian distribution etc.) should be provided (minimum number of cases for detecting a signal of disproportionate reporting is provided in the EMA 2008 guideline with N=3. The minimal number of reference cases for a mathematically acceptable approach should be also provided).
Line 211 - 212		**Comment**: Different EU competent authorities require various intervals in which a signal detection assessment report (SDAR) should be done (weekly, monthly, quarterly, annually). Clarification is needed, who should do signal detection in what intervals (e.g. when a product is under intensified monitoring versus regular surveillance).
Line 226 - 227		**Comment**: A clear support on which statistical methods may be applicable in what situations would be advantageous. Examples would be helpful.
Line 229 - 276		**Comment**: When a signal has been detected, the workflow for signal validation should include: (1) How to deal with double reports? (2) How to deal with off label use? (3) What kind of sources should be used (studies/ post marketing safety/ epidemiological analysis/single literature review)? (4) Are prospective versus retrospective data analysis to be weighted differently? Note: In this section only signals from postmarketing ADR data are concerned at first stage.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 254		**Comment**: Availability of other relevant sources of information providing a richer set of data on class effects should be detectable; therefore a (sub-) group-analysis of classes of active pharmaceutical ingredients (APIs) would be necessary. Potential class effects would very much precede late-detected effects in certain APIs, e.g. such with low patient exposures.
Line 289 - 294		**Comment**: Attention should also be given to biological plausibility as defined by medical history, age related effects, genetic disposition (acetylation) etc..
Line 311 - 329		**Comment**: A signal evidenced in one country, can be no signal in another, as the SPCs of different MAHs are usually not identical, e.g. with respect to expectedness, contraindications, and warnings etc. This should be assessable. Alternatively, an MAH should be able to indicate, whether he is originator of a product or not. As during signal detection also the number of own cases is a variable in the equation, the whole equation can depend on the number of cases that one has in the database. The number of these, however, might be negligible compared to those of the originator. Therefore, signals from an originator might have a higher impact than signals coming from generics with low number of cases overall.
Line 324 - 329		**Comment**: The popular abbreviation SMQ for standardized MedDRA queries should be used/mentioned – this makes a search for a keyword within the document easier.
Line 368		**Comment**: It would be preferable that the agency publishes a form or spreadsheet, which refers to the necessary points

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		to be considered electronically, for that signals can be easily reported (e.g. as xml-File). Reporting of signals e.g. into a certain gateway in Eudravigilance would be advantageous => generating a third gate: 1. clinical trials gateway 2. other studies gateway 3. detected signals gateway May it is also possible to refer to existing tools of risk communication, such as defined by the Rapid alert or non emergency information system?
Line 378 - 383		**Comment**: The quality of signal detection strictly depends on the quality of reports in the database. One important issue has not been described, which is 'data-cleaning', redundancy and double reports within the EMA-database. This should be addressed. Who can be responsible for detection, assessment and, if applicable, removal of double reports on the level of the EU-database- Only someone who has unlimited access to the complete database!
Line 518 - 539		**Comment**: When assessing a signal, it should be taken into consideration, how many marketing authorizations in a certain country versus EU exist, and whether the situation/signal detected at company level refers to how many countries. A procedure is needed, that a detected signal at EU level could be validated by national competent authority.

<Date of submission>

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

Comments from:

Name of organisation or individual
Celgene Europe Ltd.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	While the new PV legislation and the guideline on signal management provide a clear description of structures, processes and requirements to detect new risks or changes in known risks of human medicinal products, there is heavy focus on the risk side of the equation and little guidance on the Agency's expectations regarding how benefits are taken into account within the context of a benefit-risk scale. The sections on signal validation, analysis, prioritisation and assessment may have considerable overlapping in practice. Consideration should be given on combining these sections under one general heading of Signal Validation and Assessment. It is not clear which signal detection methods the EMA would employ for MAH products. Since no single system or process yields a perfect result, an appropriate level of diversity in signal detection methods must be communicated in the guidelines. Additionally, it would be helpful to the global community if the Agency publishes an analysis of the impacts (potential economic, public health and safety, distributive impact, equity, etc.) of the new rule/guidance to ensure that the selected regulatory approach maximizes the net benefits. An area of concern would be if the new rule would have significant or disproportionate impact on small entities.

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 - 127		Comment: Inclusion of internet and digital media as a data sources for signal management needs to include a statement regarding validation of reliability of these sources. Proposed change (if any): Insert after line 125: Reliability of these sources (e.g., the availability of an identifiable patient or reporter) should be validated and taken into account when using them as information sources for signal detection.
224 - 225		Comment: The guidance stipulates that “where signal detection uses an automated screening of database, corresponding ICSRs should be individually reviewed.” Caveats need to be stated here as an automated screening can result in many false positives which do not need individual review of ICSRs. Proposed change (if any): Insert after line 224: It is recognised that automated screening of spontaneous databases suffer from important biases and limitations. These limitations must be kept in mind when interpreting signal detection algorithms which may result in false positives.
325 - 330		Comment: The guidance states that “Signals sometimes need to be assessed at the therapeutic or system organ class level or at the level of standardised MedDRA query.” It should also be noted that an important stratification of signals is at the patient or patient group level where quantitative methods may have a role in monitoring the safety of medicines in special populations.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Insert after line 329: Signals may also need to be assessed based on patient groups or levels such as conducting focused signal detection in narrow age groups or identification of new safety signals arising from numerator/denominator-based methods of collecting safety data such as in clinical trials. Quantitative methods may have a role in monitoring the safety of medicines in special populations.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
In section IX.B.1 Data sources for signal management,		Does an assessment of signal detection by a public database (EudraVigilance) not need adverse events as well as adverse reactions as signal detection is normally performed with adverse event data. Line 86 mentions "Spontaneous reports of adverse reactions may be notified to pharmacovigilance systems..."?

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)

Comments from:

Name of organisation or individual
Council for International Organizations of Medical Sciences (CIOMS). c/o WHO, 20 Avenue Appia, CH-1211, Switzerland

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, non-profit organization (NGO) established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO). Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. Two major themes for CIOMS within the field of biomedicine have been bioethics and the development and use of drugs. In 1986, CIOMS set up its first pharmacovigilance working group to discuss international reporting of Adverse Drug Reactions (ADRs). Following that several different CIOMS Working Groups (WGs) have published consensus reports covering specific areas of drug development and drug safety such as terms and definitions for vaccine pharmacovigilance, SMQs, the Development Safety Update Report (DSUR), practical aspects of safety signal detection and management. The most recent report (vaccine pharmacovigilance) was published in collaboration with WHO January 2012. Working Groups are presently ongoing covering the area of a harmonized tool kit for risk management and meta-analysis of regulated biopharmaceutical safety data. Each WG has consisted of scientists invited to the group based on their recognized specific expertise and, if required, in consultation with their background institution. Regulatory agencies, health authorities, research-based biopharmaceutical companies and academia have been globally represented. As the CIOMS WGs have no legal jurisdiction or mandate to make binding decisions the goal have been to achieve harmonization and standardization across regulatory jurisdictions. Consequently the CIOMS' reports have served as internationally harmonized recommendations that could be implemented in regional/national legislation. It has also been used as educational material at various training institutes and seminars and in particular for new staff within the pharmaceutical industry and regulatory authorities. The document on the GVP Module IX – Signal management is concise, well-written and generally and overall endorsed. It is also with great appreciation that some of the concepts and recommendations put forward in the CIOMS' publication on "Practical Aspects of Signal Detection in Pharmacovigilance" are referred to in the section addressing the signal management process. It is also acknowledged that for the purpose of this Module, the signal definition has been limited to consider only new information related to an adverse reaction, and not to potential

Stakeholder number *(To be completed by the Agency)*	General comment
	beneficial effects. It is noted that some important definitions used in the context of pharmacovigilance and signal management are mentioned in this document but missing in the GVP document 'Annex I – Definitions' -see comment in the section “Specific comments”.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 104-105		Comment: As “Active surveillance “, “Prescription event monitoring” and “sentinel networks” are used terms in this section. Proposed change (if any): It is suggested that these definitions are added to the GVP document 'Annex I – Definitions'.
Lines 62-63		Comment: For the purpose of the EudraVigilance database, only signals related to an adverse reaction shall be considered [IM Art 23(2)]. Proposed change (if any): Please clarify. Should this nor apply to all signals also originating from other sources?
131-132		Comment: Lingusitic comment: ....may for example 131 require other methodological strategies *that* other medicinal products... Proposed change (if any): Change to may for example 131 require other methodological strategies *than* other medicinal products...

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 187		Comment: What are inadequately documented cases? Proposed change (if any): In review if any cases are excluded, then there should be a clear and profound argumentation about the reason for the exclusion. It should not be sufficiently just to write: X cases are inadequately documented and are there for excluded.
Line 249- 253		Comment: It should be made clear that the list is not complete and that e.g. new interactions or new patient groups could also make it necessary to validate a signal. Proposed change (if any): add e.g. instead of just the full stop
Line 374-375		Comment: Addition suggested ensuring exchange of information in all directions. Proposed change (if any): Competent authorities should communicate results of **relevant** signal assessments to marketing authorisation holders, **and to the Agency and other national competent authorities.**
Line 402		Comment: for the audit trail it would be nice to see the outcome of the validated signals, has the MAH or NCA communicated/ handled the signal correctly. Proposed change (if any): Audit trail should also allow traceability of how validated signals have been investigated and handled/ communicated to other parties.

Please add more rows if needed.

<18 April 2012>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall the EFPIA finds GVP Module 9 on Signal Management a comprehensive description of both signalling routines and how the interaction and communication between stakeholders should work in a European environment. The main concerns from EFPIA are the following: The requirement for MAHs to routinely monitor **all available data seems too broad** and unrealistic, so it should be limited to data in MAH's possession. The specification of **a fixed frequency of monthly searches** by MAHs in EudraVigilance is **neither risk proportionate nor** necessarily **adds significant value** for certain products, so the EFPIA proposes a more flexible frequency, using a risk-based approach. The process to **communicate validated signals/safety issues by MAH to competent authorities is unclear**. Since signals must be reported as soon as they are validated, it seems difficult for this communication to include any MAH proposal for actions, which normally would require a full assessment. **The Agency and national authorities should consider earlier communication of validated /confirmed signals** to the concerned MAH, not only following the conclusion of signal assessment by the PRAC, so that the MAH can contribute all available data to the assessment. **It is important that signal management is described consistently across all GVP Modules** (Module IX, VII, Annex I...) and other related documents (IM, CIOMS VIII report, ICH E2C R2...). The EFPIA understands that IM is virtually final so its terminology cannot be modified at this stage. Therefore, when using specific EU terms (as per IM) which are different from the international terms for equivalent concepts or processes, the GVP module should provide a clarification to avoid confusion. All the points above are also further developed in the Specific Comments below.

Stakeholder number *(To be completed by the Agency)*	General comment
	Regarding **transitional measures** the EFPIA considers that the requirements to devise, document and implement detailed quality system procedures, including a potential IT tool for a tracking system with an audit trail, for all signal management processes will necessitate at least **an 18- months transitional period** following publication of the finalised Module IX.

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')*
83-86		**Comment:** Pharmacoepidemiology data is an important source of signals, which is not mentioned. **Proposed change:** Add in line 84 “and pharmacoepidemiology data”.
104-107		**Comment**: The statement “*Active surveillance aims to stimulate the reporting of adverse reactions by healthcare professionals through specially designed systems such as prescription event monitoring or sentinel networks based on general practitioners or hospitals. They may be used to facilitate reporting of particular adverse reactions or adverse events for specific drugs*” seems to contradict the definition of Active Surveillance in draft Module VIII (PASS). The primary focus of Active Surveillance is **not** to stimulate reporting of adverse reactions by healthcare professionals. While stimulated reporting sometimes occurs, the major component of active surveillance involves claims or epidemiological data bases. These latter approaches do not involve activities to stimulate healthcare professional reporting. **Proposed change**: Use the broader definition of “*active surveillance*” that appears on Line 739 of Module VIII on Post-Authorisation Safety Studies which is “*active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process*”. These terms should also be accurately reflected in GVP Annex I (Definitions).
113		**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')*
		Results of registries or studies initiated by the MAH are covered by Module VIII. **Proposed change:** The reference in parenthesis "(see Module VI)" should be replaced with "(see Module VIII)".
119-121		**Comment:** PASS results must be communicated to NCA within 12 months from the end of data collection according to Module VIII, regardless of manuscript acceptance. Introducing different requirements in different GVP Chapters does not simplify and it risks creating inconsistency between countries/NCAs. **Proposed change:** Replace this whole paragraph with: "MAHs shall submit the study report of all PASS to competent authorities within 12 months from the end of data collection or where required completion of data validation (see Module VIII)."
122-127		**Comment:** Experience with focused monitoring of social media in general is limited and is also the subject of intense research. The last sentence of this paragraph should be removed from the requirements until consensus guidelines and standards are established. **Proposed change:** Revise to read: "*Other sources of information include the internet, digital media (such as public websites, social networks, blogs) or other systems through which patients and consumers may communicate adverse experiences with medicinal products (see Module VI). Marketing authorisation holders and competent authorities should try to gain further information related to reactions they become aware of from such sources.* ~~***If the available information is limited, suspected serious adverse reactions should be confirmed if***~~

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		~~possible in other data sources such as EudraVigilance~~.”
141 (Section IX.B.3.)		**Comment**: The terminology, sequence, and logic for each step of the signal management process are not fully clear and could be misinterpreted. **Proposed change**: Clarify the terminology, sequence, and logic for each step of the signal management process. Preferably, and as far as possible, in alignment with the CIOMS VIII report. Update GVP Annex I with appropriate definitions and include a statement in Module IX that refers readers to the definitions in Annex I.
186		**Comment**: Anaphylactic shock is not the best example of a signal generated by a single case since not only seriousness but also rarity and drug attributability are important factors. There are many common causes of anaphylaxis besides drugs, and caution should be exercised against implying or stating that a report of anaphylaxis is automatically a signal, as defined and used in this document (and in GVP Annex I). Consistency with examples in consensus documents is desirable. **Proposed change**: Replace “*anaphylactic shock*” with “*Stevens-Johnson Syndrome*” or “*aplastic anaemia*,” which are the examples of Designated Medical Events (DMEs) used in the Guideline on the Use of Statistical Signal Detection in the Eudravigilance Data Analysis System (EMEA/106464/2006).
187-192		**Comment**: It would be desirable to specifically mention “de-challenge and re-challenge” since these terms are provided in line 238 as an alternative to the expression “*the clinical outcome in relation to drug continuation or*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		discontinuation". **Proposed change**: Revise to read: "*The information to be reviewed should include the number of cases (after exclusion of duplicates and inadequately documented cases), the patient's demographics (e.g. age and sex), the suspected medicinal product (e.g. dose administered) and adverse reaction (e.g. signs and symptoms), the temporal association**,** the clinical outcome in relation to drug continuation or discontinuation (**i.e., de-challenge / re-challenge information)**, the presence of potential alternative causes for the adverse event, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.*"
209		**Comment:** The term "seriousness of the adverse events" may be understood as event seriousness in ICSRs, while based on EV access policy, data elements described in Annex 1, seriousness will be available at the case level and not at the event level. **Proposed change:** Replace "the seriousness of the adverse events" by "the type of events (e.g. designated medical events considered rare and serious)".
229-233		**Comment:** The term "signal validation" used in this GVP Module IX and in IM is not mentioned at all in the CIOMS VIII report and it might seem to represent an additional process required for signal management in the EU compared to the rest of the world. However, when reading the full description provided in section IX.B.3.3, it is apparent that "signal validation" actually corresponds to the full "signal evaluation" process mentioned by CIOMS Group VIII report and E2C R2. In fact, the first paragraph of section IX.B.3.3 mentions an evaluation of data "to verify that the available documentation is strong enough to suggest a new potentially causal association....", but the corresponding paragraph in IM mentions "sufficient evidence demonstrating 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')*
		existence of a new potentially causal association...". Therefore, to avoid overloading Health Authorities with insufficiently evaluated signals which subsequently are not confirmed, further clarification should be provided on the specific EEA terms "signal validation" and "validated signal". **Proposed change:** Add a new paragraph after line 233, explaining that "signal validation" is not a preliminary step in signal management but corresponds to a full "signal evaluation" in order to either refute the signal or confirm that it corresponds to a potential / identified new or changed risk.
235		**Comment:** "into" is missing **Proposed change:** Replace "taken account" by "taken into account"
236-243		**Comment:** Several points listed under "Clinical relevance" seem to relate to signal **prioritisation** rather than to signal validation; in fact, 3 of the 5 points listed here are repeated in section IX.B.3.4 on signal prioritisation. As this is somewhat confusing EFPIA recommends that the "clinical context" and "drug -drug interactions occurring in special populations" bullet points are moved to section IX.B.3.4 and that "clinical relevance" is replaced with "strength of evidence". **Proposed change:** The information in lines 236-243 should be replaced with the following : • Strength of evidence for a causal effect o number of reports, taking into account exposure o temporal association o plausible mechanism o de/rechallenge data o alternative explanation or confounding factors.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
250		**Comment:** It is not fully clear that the sentence "In principle only signals not falling under the above categories should be validated" just refers to the bullet point “Previous awareness” and not to the categories listed in the prior bullet point. **Proposed Change:** Replace the above sentence with “In principle only **signals for which there is no previous awareness as described above** should be validated”.
261 - 263		**Comment:** As mentioned above, the wording “Signal becomes a validated signal if the verification process of all relevant documentation ***is suggestive of a new potentially causal association, or a new aspect of a known association, and therefore justifies further assessment”*** is softer than IM Art. 22 which mentions “demonstrating” instead of “suggesting”. This may lead to signal over reporting due to confusion of a “validated signal” with a “signal”, whose definition is not very different, i.e. *“information…* ***which suggests a new potentially causal association, or a new aspect of a known association…to justify verificatory action”.*** **Proposed change:** An explanation should be added to make it clear that those signals not corresponding at least to a potential risk should be refuted during the validation process, so that a “validated signal” in practice is equivalent to a “potential or identified 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')*
278		**Comment:** The content of this section reflects an “impact analysis and prioritisation” per CIOMS VIII and use of the term “signal analysis” without qualification could be confused with signal assessment. **Proposed change:** IX.B.3.4 Title to be reworded to “Signal Analysis for prioritisation”
283-289		**Comment:** The impact on patients is more relevant than the strength and consistency of the evidence. We suggest the order of the first two signal prioritisation factors to be changed. **Proposed change:** ~~- The strength and consistency of the evidence (...)~~ ~~- The impact on patients (...)~~ - The impact on patients (...) - The strength and consistency of the evidence (...)
308, 311		**Comment:** The terms “signal evaluation” and” signal assessment” appear to be used interchangeably for the activities to be done after signal confirmation, so it may be difficult to distinguish the evaluation activities during signal validation from those to be done once a signal has been confirmed, which seem to correspond to the term “Evaluation of risks” mentioned by Module VII and E2C R2 (Section 3.16.3) . **Proposed change:** A clarification should be added in section IX.B.3.5. to distinguish the **evaluation of the signal** (to confirm it or refute it) from the **assessment of the risk** after signal confirmation.
335-363		**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')*
		This section only covers “Recommendation for action by competent authorities” and does not take into account the MAHs. **Proposed change:** Line 335: Title of IX.B.3.6 “Recommendation for Action by competent authorities” should read “Recommendation for action”, in line with IM Article 22, par. 1. Line 362: “If there is no evidence of a risk for patients, the competent authority **or marketing authorisation holder** may decide....”
373, 492, 564		**Comment:** The terms “immediately” and “forthwith” for MAHs to communicate validated signals to authorities and for the Agency to communicate PRAC conclusions to the MAH are prone to differing interpretations. **Proposed change:** Clarify the meaning of the terms “forthwith/immediately communicate”, so that they are interpreted in a consistent manner by all parties.
428 & 434		**Comment:** The wordings "Products authorised in accordance with Regulation (EC) No 726/2004", and "with Directive 2001/83/EC" would be better understandable if specified as CAP (like line 462) and non-CAP. **Proposed change:** Add "centrally authorised products (CAP)" and "non- centrally authorised products (non-CAP)" in row 428 and 434 respectively.
465-466		**Comment:** The content and expected use of the “*list of medical events that have to be taken into account for the detection of a signal”* is not clear and could be confused with the existing IME list.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Add additional clarification on the type of events included in this list and its expected use for signal detection purposes.
467-475		**Comment:** It is unclear if the Agency shall support the monitoring of the data in the EV database by providing the specified accesses also for MAHs, as stated by IMP Art 24. **Proposed change:** The sentence “shall support the monitoring of the Eudravigilance database by providing access to...” should be replaced with the IMP wording, i.e. “shall support the monitoring of the Eudravigilance database by providing **national competent authorities and marketing authorization holders**, as appropriate, with access to...”.
480-487, 503-510, 532-539		**Comment:** There should be a process in place ensuring that concerned MAHs are informed about all signals sent to the PRAC, whether they were initially detected by the MAH or by the Agency, the lead/co-lead MS or the NCA. **Proposed change:** Add in the respective paragraphs that the Agency, lead/co-lead MS, NCA should communicate to the concerned MAH/s all validated/confirmed signals within 15 days after sending them to the PRAC.
555		**Comment:** The wording “all available data” is somewhat imprecise and can in its widest interpretation not be considered either rational or motivated for routine signalling. The starting point for any regular, routine signalling activity for all MAHs is reasonably the data in their own possession. If a potential signal is identified in the Detection step, then other available data sources (e.g. external databases) may be tapped into during 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')*
		Analysis for prioritisation or Assessment. **Proposed change:** The sentence "– shall monitor all available data and information for signals;" should be replaced with "- **shall monitor all available data and information in its possession for signals**;".
558-560		**Comment:** To monitor EudraVigilance at least once monthly seems disproportionate for many products (e.g. old products with a well-known safety profile and few reported reactions) and is unlikely to add additional value. Furthermore the opportunity to apply a "proportionate to risk" monitoring frequency seems very limited if monthly is defined as a minimum. **Proposed change:** The sentence "The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information" should be replaced with "**The frequency of monitoring shall be proportionate to the identified risks, the potential risks and the need for additional information**".
Lines 564-565		**Comment:** The sentence *"...shall forthwith inform the responsible competent authority in line with the list as published by the Agency (referred to in lines 463-464) [IM Art 25(4)]"* is not fully clear and seems to include the wrong reference since this list is rather mentioned in lines 458-460.

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		Proposed change: Replace the above sentence with *"...shall forthwith inform the competent authority* ***responsible for signal detection, as specified in the list published by the Agency (referred to in lines 458-460)".***
Lines 564-567		**Comment:** It remains unclear how the communication of validated safety signals addressed in Lines 564-565 is different from that of 'Emerging Safety Issues' addressed in Lines 566-567. **Proposed change:** Provide clarification on the difference in intention and/or way of communication required by the two statements.
566-567		**Comment:** The term "Emergency Safety Issue" seems to be a typographical error since it differs from the terminology used in chapter VI where "Emerging Safety Issue" is used. Furthermore, in Chapter VI the term seems to only include safety issues which may lead to a change in the known benefit-risk balance whereas here it includes any safety issue arising from the MAHs signal detection activity. **Proposed change:** This paragraph should be replaced with "-should notify as an **Emerging Safety Issue** (see Module VI) any safety issue arising from its signal detection activity which **could have a significant impact on the benefit-risk balance** for a medicinal product **and/or have implications for 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')*
		In addition, the term "**Emerging Safety Issue**" should be defined and added to the Definitions module (GVP Annex I).
572		**Comment:** It is unclear if the periodicity of monitoring outlined in this section is only applicable to the Agency and CA, or is also applicable for the MAHs. If the baseline frequency is changed by the Agency or CA and is also applicable to the MAHs, this should be communicated to MAHs. **Proposed change:** Replace "The PRAC should be informed of the decision and its justification" with "The PRAC **and the Marketing Authorisation Holder** should be informed of the decision and its justification"

17 April 2012

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

Comments from:

Name of organisation or individual
EGA – European Generic Medicines Association

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Once all generics companies can access EudraVigilance to pull data, what will be the point in everyone analysing exactly the same information? Should MAH look to work-share schemes or will agencies be taking the lead with generic and well-established 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')*
Line 124		Comment: Marketing authorisation holders and competent authorities should try to gain further information related to reactions they become aware of from such sources (websites and blogs). This wording is not clear and does not explain how MAHs could "become aware" without actively surfing internet, blogs etc. Moreover, it is not clear how safety information could be collected without breaching of privacy of bloggers.
Line 171		Would it be possible to add a quantification range for “small data set”
Line 465		Comment: following consultation with the PRAC may publish a list of medical events that have to be taken into account for the detection of a signal [IM Art 23(3)]; Proposed Change: This text is obscure and should be amended to clarify process and responsibilities.
Line 492		Comment: shall forthwith communicate to the concerned marketing authorisation holder(s) the conclusions of the assessment of the signal by the PRAC1 [IM Art 25(9)]; Proposal: It seems that the signal detection processes conducted by the Agency/PRAC and those conducted by the MAH are completely separate and communicate only conclusions. Instead, they should be more integrated and allow the ongoing sharing of information and opinions eventually LEADING to better and earlier signal detection.
Lines 556-568		Comment: According to guideline the MAHs shall monitor the data in EudraVigilance to the extent of their accessibility. However the same data shall also be monitored by lead/co-lead member state or the Agency. Monitoring of the same data with the same methods by two stakeholders is not expected to reveal additional new safety

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		information and is regarded as duplication of work without clear benefits. Proposed change (if any): This text requires clarifications - as it stands, it suggests that MAHs should perform a second signal detection process, on top of what done based on their own safety databases, with obvious cost and time implications in front of doubtful benefits. Also the frequency of monitoring (once monthly) couldn't be appropriate for generics companies that have small data, usually not significantly changing month-by-month.
Lines 566-567		Comment: ....should notify as an Emergency Safety Issue (see Module VI)…… In module VI Emergency Safety Issue does not appear as an entity. Term "emerging safety issues" is used. An 'Emergency Safety Issue' should be notified only in case of safety issue with potential major public health impact. Proposed change (if any): terminology should be harmonised. A template for reporting of emerging safety issue will be appreciated.
Lines 667-670		Comment: Signals validated by the Agency or a national competent authority will be entered in EPITT. Will MAHs get access to EPITT?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: This Module advises (line 408-11) Signal Management Training of staff *"not only within safety department but also staff who may become aware of potential signals or support signal management" (includes MedDRA and potential signal source databases)".* It is unclear that this guidance reflects the actual practice of signal management activities within Marketing Authorisation Holders where these activities are undertaken by properly qualified safety staff and not by staff generally. This is distinct from the potential for staff in general to become aware of possible product ADRs. The staff outside PV and data management will not benefit from MedDRA training unless they will have an opportunity to regularly use MedDRA.
	Recommendation regarding Comment 1: Remove references to training of staff who are not part of safety functions and/or do not support signal management activities. It should also be sufficient to continue training staff operating outside the safety departments/functions about adverse events/reactions (definition, standards, special reporting obligations), technical complaints, sources of safety data, availability/ accessibility of reference safety information, internal communication, data privacy etc.
	Comment 2: The timelines for PV Risk Assessment Committees' signal analysis, prioritization and assessment validation are unclear.
	Recommendation regarding Comment 2: Add specific timelines for these PV Risk Assessment Committee activities and associated interactions with Committee for Medicinal Products for Human Use and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human.
	Comment 3: The Module states that; "The Agency and the national competent authorities will keep an audit trail of all their signal management activities relating to Eudravigilance "using EPITT. It does not address what happens with signals identified from sources other than Eudravigilance.

Stakeholder number *(To be completed by the Agency)*	General comment
	Recommendation regarding Comment 3: Expand the advice provided in the Module to address signals arising from other sources outside of Eudravigilance.
	Comment 4: With regard to transparency related to Signal Management, it is unclear in the Module IX C 6 (line 678-686) what Competent Authorities will make available to the public and when.
	Recommendation regarding Comment 4: Add text specifying what information will be communicated to Marketing Authorisation Holders as well to the public, when and in what form.
	Comment 5: The operational flow related to signal management between Marketing Authorisation Holders, PV Risk Assessment Committees, Committee for Medicinal Products for Human Use, Coordination Group for Mutual Recognition and Decentralised Procedures - Human, Competent Authorities, lead and co-lead Member States appear quite complex with some lack of clarity of who is doing what, and when.
	Recommendation regarding Comment 5: The inclusion of a flow chart in the Module IX to show the overall process inter-relationships and timeframe.
	Comment 6: In relation to the process of signal validation (section IXB.3.3), the guidance lacks detail as to what is expected of a Marketing Authorisation Holder in relation to communication of a detected/“validated signal” to a Competent Authority.

Stakeholder number *(To be completed by the Agency)*	General comment
	Recommendation regarding Comment 6: Add a section to the Module setting out details as to the expectations as to notification of potential signals to the Competent Authorities by Marketing Authorisation Holders e.g in section IX B.3.7 (line 370 onwards) and/or IX.C.1.5 (line 564).

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 408-411		Comment: Signal management raining of staff outside PV should not be required Proposed change (if any): Remove references to training of staff who are not part of safety functions and/or do not support signal management activities.
line 678-686		Comment: It is unclear in the Module IX C 6 what Competent Authorities will make available to the public and when. Proposed change (if any): Add text specifying what information will be communicated to Marketing Authorisation Holders as well to the public, when and in what form.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The most important prerequisite of signal management is the well-founded individual management of single cases by PV-experts with medical and scientific expertise. A clearer distinction between companies with large amounts of safety data and such with small amounts of safety data would be desirable. In this context it should be noted that complex quantitative methods based on "drug-event" combinations are very important, but they are only useful for extremely large safety data amounts. MAH´s with relatively small safety data amounts need to acquire a pragmatic approach for signal detection. While the new PV legislation and the guideline on signal management provide a clear description of structures, processes and requirements to detect new risks or changes in known risks of human medicinal products, there is heavy focus on the risk side of the equation and little guidance on the Agency's expectations regarding how benefits are taken into account within the context of a benefit-risk scale. The sections on signal validation, analysis, prioritization and assessment may have considerable overlapping in practice. Consideration should be given on combining these sections under one general heading of Signal Validation and Assessment. It is not clear which signal detection methods the EMA would employ for MAH products. Since no single system or process yields a perfect result, an appropriate level of diversity in signal detection methods must be communicated in the guidelines. Additionally, it would be helpful to the global community if the Agency publishes an analysis of the impacts (potential economic, public health and safety, distributive impact, equity, etc.) of the new rule/guidance to ensure that the selected regulatory approach maximizes the net benefits. An area of concern would be if the new rule would have significant or disproportionate impact on small entities.

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 61 - 62		**Comment**: Since marketing authorization holders should collect also safety information arising from use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors, and suspected adverse events associated with occupational exposure, this information is not necessarily associated with an adverse event.
Line 122-127		**Comment:** Inclusion of internet and digital media as a data sources for signal management needs to include a statement regarding validation of reliability of these sources. **Proposed change (if any):** Insert after line 125: Reliability of these sources (e.g., the availability of an identifiable patient or reporter) should be validated and taken into account when using them as information sources for signal detection.
Line 183 - 192		**Comment**: It should be added that especially an accumulation of listed and non-serious adverse events (e.g. allergic reactions) should be intensively monitored since such an accumulation could be associated with possible issues regarding the product quality.
Line 193		**Comment**: According to the EMA Guidance on signal detection, the following aspects should be also considered: a) Grouping of substances (e.g. API with a similar action profile);

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		b) Class effect detection; c) For the MAH it should be apparent, how big EMAs database is and what the variables are and what the analysis is referring to, e.g.: “MAH’s signals versus all cases in the database”; c) Exclusion of cases without causality; d) Exclusion of cases from off label use; e) A relation to incidences/estimations of signal of disproportionate reporting from originator. Furthermore, EMA should generate an option to detect possible class effects (directly in the EMA database).
Line 207 - 210		**Comment**: According to statistical assumptions or methods, the approximate number of cases needed at least to yield a possible signal (e.g. Gaussian distribution etc.) should be provided (minimum number of cases for detecting a signal of disproportionate reporting is provided in the EMA 2008 guideline with N=3. The minimal number of reference cases for a mathematically acceptable approach should be also provided).
Line 211 - 212		**Comment**: Different EU competent authorities require various intervals in which a signal detection assessment report (SDAR) should be done (weekly, monthly, quarterly, annually). Clarification is needed, who should do signal detection in what intervals (e.g. when a product is under intensified monitoring versus regular surveillance).
Line 224 - 225		**Comment:** The guidance stipulates that “where signal detection uses an automated screening of database, corresponding ICSRs should be individually reviewed.” Caveats need to be stated here as an automated screening can result in many false positives which do not need individual review of ICSRs.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Insert after line 224: It is recognized that automated screening of spontaneous databases suffer from important biases and limitations. These limitations must be kept in mind when interpreting signal detection algorithms which may result in false positives.
Line 226 - 227		**Comment**: A clear support on which statistical methods may be applicable in what situations would be advantageous. Examples would be helpful.
Line 229 - 276		**Comment**: When a signal has been detected, the workflow for signal validation should include: (1) How to deal with double reports? (2) How to deal with off-label use? (3) What kind of sources should be used (studies/ post marketing safety/ epidemiological analysis/single literature review)? (4) Are prospective versus retrospective data analysis to be weighted differently? Note: In this section only signals from post marketing ADR data are concerned at first stage.
Line 254		**Comment**: Availability of other relevant sources of information providing a richer set of data on class effects should be detectable; therefore a (sub-) group-analysis of classes of active pharmaceutical ingredients (APIs) would be necessary. Potential class effects would very much precede late-detected effects in certain APIs, e.g. such with low patient exposures.
Line 289 - 294		**Comment**: Attention should also be given to biological plausibility as defined by medical history, age related effects, genetic disposition (acetylation) etc..

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 311 - 329		**Comment**: A signal evidenced in one country, can be no signal in another, as the SPCs of different MAHs are usually not identical, e.g. with respect to expectedness, contraindications, and warnings etc. This should be assessable. Alternatively, an MAH should be able to indicate, whether he is originator of a product or not. As during signal detection also the number of own cases is a variable in the equation, the whole equation can depend on the number of cases that one has in the database. The number of these, however, might be negligible compared to those of the originator. Therefore, signals from an originator might have a higher impact than signals coming from generics with low number of cases overall.
Line 324 - 329		**Comment**: The popular abbreviation SMQ for standardized MedDRA queries should be used/mentioned – this makes a search for a keyword within the document easier.
Line 325 - 330		**Comment:** The guidance states that “Signals sometimes need to be assessed at the therapeutic or system organ class level or at the level of standardized MedDRA query.” It should also be noted that an important stratification of signals is at the patient or patient group level where quantitative methods may have a role in monitoring 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')*
		safety of medicines in special populations. **Proposed change (if any):** Insert after line 329: Signals may also need to be assessed based on patient groups or levels such as conducting focused signal detection in narrow age groups or identification of new safety signals arising from numerator/denominator-based methods of collecting safety data such as in clinical trials. Quantitative methods may have a role in monitoring the safety of medicines in special populations.
Line 368		**Comment**: It would be preferable that the Agency publishes a form or spreadsheet, which refers to the necessary points to be considered electronically, for that signals can be easily reported (e.g. as xml-File). Reporting of signals e.g. into a certain gateway in Eudravigilance would be advantageous => generating a third gate: 1. clinical trials gateway 2. other studies gateway 3. detected signals gateway Would it be also possible to refer to existing tools of risk communication, such as defined by the Rapid alert or non emergency information system?
Line 378 - 383		**Comment**:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The quality of signal detection strictly depends on the quality of reports in the database. One important issue has not been described, which is 'data-cleaning', redundancy and double reports within the EMA-database. This should be addressed.
Line 518 - 539		**Comment**: When assessing a signal, it should be taken into consideration, how many marketing authorizations in a certain country versus EU exist, and whether the situation/signal detected at company level refers to how many countries. A procedure is needed, that a detected signal at EU level could be validated by national competent authority.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<17 April 2012>

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

Comments from:

Name of organisation or individual
EuropaBio Manager, Healthcare Biotechnology

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the first wave of draft GVP modules. EuropaBio's mission is to promote an innovative and dynamic biotechnology based industry in Europe. EuropaBio, has 62 corporate and 7 associate members operating worldwide, 2 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises. EuropaBio broadly supports the comments provided by EFPIA, the European Federation of Pharmaceutical Industries and Associations, and would like to provide some additional general comments of specific importance to its members. Our comments focus on important aspects related to the expected business impact for small and medium-sized enterprises, as well as to advanced therapy medicinal products. EuropaBio welcomes the alignment with existing ATMP-specific guidance (e.g. guideline on safety and efficacy follow-up – Risk management of ATMPs – EMEA/149995/2008), which brings a certain level of stability in the legal framework for companies operating in the field.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	We would like to highlight that specifically for SMEs adequate transitional periods and proportionate implementation of the significant system changes are necessary while avoiding unnecessary administrative burden.	
Module II PSMF – Transition from the DDPS	We strongly welcome the introduction of the PSMF independent from a specific marketing authorisation and we recommend a simple and pragmatic transition process for products with existing DDPS. As a PSMF is required for any new MAA and for all renewals due after the implementation date, we believe that many MAHs would have an interest in moving to PSMF for all authorised products at once to avoid maintaining both a PSMF and a DDPS in parallel as well as reducing the number of variations to be submitted. The change-over is currently proposed to occur for each product including a DDPS via a Type IB Variation. In order to reduce administrative burden for Industry and Regulators, we recommend using a Type IB worksharing procedure per group of MAHs sharing the same PSMF and including a list of all affected products authorised in the EEA regardless of their specific registration route covering one Type IB fee. We strongly encourage the national competent authorities to immediately implement the outcome of the worksharing procedure into all national authorisations without any further national process. This will ensure a consistent and pragmatic phasing in of the new PSMF	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	across EEA without unnecessary administrative burden. The management of changes to the PSMF should completely be delinked from the Variation regulation and any specific MAAs. The summary of the PSMF covering location and contact details of the EU QPPV person should solely be managed through notification of required updates to the EVMPD and not trigger any variation process.	
Module II PSMF – Co-licensing/Co-marketing scope	The scope of description and documentation of co-licensing and co-marketing arrangements in the PSMF is unclear. However, the expectations for inspections need to be explicit. Within the current Volume 9A it has until now been applicable to arrangements within the EEA. Please clarify that the scope is being limited to commercial arrangements applicable to markets within the European Economic Area.	
Module V RMP – ATMP section	Duration of exposure to the medicinal product may be a challenging subject to describe for ATMPs, as the kinetics of cells and genes are different as compared to classical molecules. E.g. Manipulated cells can be used in a single administration to initiate a biological repair process. It is however unknown what proportion of these cells will actually become an intrinsic component of the repair tissue and for how long these cells will be retained. Please specify how exposure duration should be calculated and how relevant is this parameter is in such case.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
Module V RMP vs Module VII PSUR - document structure and interchangeable modules	The scope and purpose of PSUR and RMP are not always clear, because of the focus and the overlap in some modules of both documents. Although the PSUR is considered to be mainly used for post-authorisation information reporting, it is also expected to capture pre-market experience. This applies vice versa to the RMP where post-authorisation data are reported. We propose to clarify and simplify both document purposes and structures. The RMP should focus on the pre-authorisation strategy including the binding commitments for post-authorisation development, while the PSUR should focus on the post-authorisation phase reporting the results or the development activity and monitoring of the adverse events. Emerging post-authorisation data should not require updating of both documents, but rather require only one document update. A specific section for risks associated with a Medical Device is necessary for the use of Drug Delivery Systems and better linkage with the Risk Management Systems of such devices that follow different methodologies. For the sake of clarity, we propose that all post-authorisation studies, whether they are PASS or PAES, are included into one Annex to the RMP. Both	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	study types usually include safety parameters and may not easily be distinguishable. The significant expansion of the RMP content and the administrative burden of producing an updated RMP document should be taken into account by the Regulators. We discourage establishing a practice of "routine" updates to an RMP in the absence of any new information that materially affects the product's benefit-risk balance and, consequently, the absence of any need for modifications to the pharmacovigilance and risk minimisation activities.	
Module V RMP – comprehensive review process including local inputs	A comprehensive process to include additional national risk minimisation activities or drug utilisation studies within the RMP needs to be thought through in detail as multiple ongoing parallel discussions in the post-authorisation phase might unnecessarily slow down market access for innovative products and can prove to be especially challenging for SMEs. The PRAC is responsible for assessing the overall RMP and as such involves representatives from all Member States. We recommend that this process should ensure that any specific local requirements are included during the PRAC assessment process. In addition, drug utilisation studies to be recorded within the RMP should be strictly limited to the EEA region.	
Module V RMP and Module VII PSUR –	The schedule for submissions of RMP updates is not well defined, and may differ from the schedule for submission	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
submission schedule for updates and document life-cycle management	of PSURs. The data intervals under review may therefore differ between the 2 documents, limiting the "interchangeability" of the overlapping content. A clear co-ordination and document life-cycle management process needs to be established for both documents to maximise their value and avoid any confusion or redundancy. To ensure consistency, the same rapporteur should be utilised for the assessment of PSURs and RMPs as well as any product related PASS. The assessment process for PSURs may last beyond 6 months. This will pose challenges for products requiring very short PSUR submission cycles and taking into account the data lock points and adequate time to analyse and prepare the following PSURs. We strongly welcome the new proposal that any changes recommended as a consequence of a PSUR review are implemented into the product information without any subsequent variation submissions.	
Module VI ICSR - webmonitoring	In support of a proportionate implementation of the new requirements, we propose that the monitoring of ICSRs from websites should be focused on company-sponsored sites. Active screening of non-sponsored websites for adverse reactions is a resource consuming and challenging task, especially for SMEs. In addition, the scientific validity of such sources is often not quantifiable. The added value of such reports over scientific publications is questioned in relation to the	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	additional effort required to capture, analyse and assess the information from blogs, forums, etc.	
Module VI ICSR – Validation of reports	Under the new requirements patient or consumer reports should be handled as spontaneous reports irrespective of any subsequent 'medical conformation'. The only requirement for a reporter to be considered identifiable is the availability of contact details in order to confirm or follow-up the case. We are concerned that a MAH or Regulatory Agency may not be able to distinguish genuine, authentic adverse reactions reported by a patient/consumer from fake reports that may have been submitted under a fake email address (identifiable reporter with contact details). Some clarification regarding the confirmation of the existence of a reporter needs to be established.	
Transitional periods	As a general rule, new processes or templates should become mandatory for use 6 months after they have been finalised to allow companies adapting their internal processes and documents. Changes involving adaptations to IT systems should be phased in with at least 18 month transitional periods as significant re-programming, validation and company investment are required for their implementation.	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases (Eurordis)

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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')*
675-689		Comment: When the opinion of the PRAC differs from the opinion of a national competent authority, or when the some PRAC members express a divergent opinion, is it foreseen to add a document commenting on these divergences? Proposed change (if any):
682-683		Comment: A detailed description of the adverse reaction or concern or signal should be available, in lay language, understandable, illustrated when applicable, so that the public can understand what the concern/reaction/signal is about. The role of the patients in the PRAC will help, and contact persons in relevant patients' organisations who volunteer to be involved in risk communication should be highlighted in the document. Proposed change: Article 26(j) of Regulation (EC) No 726/2004 states that by means of that portal, the Agency shall make public at least the following: description of the adverse drug reaction or new signal in question in lay language, conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees. These documents should be available in all EU languages.
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 17th, 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EVM is in agreement with general comments of EFPIA
	In the guidance, public access and requirement for MAH to do data explorations for their products on monthly basis is mentioned. However, the timelines and extent to which MAH will be able to use Eudravigilance is not provided. Implementation of this process requires access to Eudravigilance.
	Signal tracking system is mentioned. Are their any recommendations for types of signal tracking system to be used by MAH?
	There is no mention of observed to expected analysis in signal detection. Will EMA primarily use disproportionality analyses? Should the methods be specified under statistical signal detection methods? Which one would EMA use (PRR)?

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 119		Comment: Regarding the sentence “national competent authorities should put in place a system encouraging the early reporting, as soon as possible after the acceptance of the manuscript”, it remains unclear to whom this early reporting of the manuscript is aimed. Indeed, usually the study report is prepared before the manuscript is ready for publication. Proposed change: There is confusion throughout the text between “manuscript” and “study protocol”
Lines 104-107		Comment: Active surveillance should stimulated and reporting be promoted. This should be clarified.
Lines 122-124		Comment: In module VI it is mentioned that only sponsored web sites should be screened. Data sources that are not company sponsored (social networks, blogs) should not be considered as scientifically valid as those foreseen in Module VI. Proposed change: Delete this paragraph as signal detection should not be in social media.
Line 235		Comment: Editorial comment “..., the following should be taken account:” Proposed change: Insert word in italic letters “..., the following should be taken *into* account:”
Lines 375-376 & 482-487		Comment: The competent authorities / EMA / lead or co-lead MS should also communicate their results within specific timelines

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Add specific timelines for the competent authorities / EMA / lead or co-lead MS, e.g. As soon as possible and within 15 days at the latest
Line 576-579		Comment: Please specify whether signal detection will be done at MedDRA PT level or higher level and which method and threshold will be used. Will there be any restriction or stratification used? For vaccines, will only vaccine data be used in denominator or all drugs + biologics? Proposed change (if any): Please address the raised points
Line 580-581		Comment: How the baseline frequency will be determined? Will it be determined separately for vaccines on vaccine AE dataset? Does the baseline frequency imply that observed to expected analysis will be used? Proposed change (if any): Please make clarifications in this paragraph
Line 645		Comment: Please clarify whether the ad-hoc PSUR refers to PBRER or other reports.

Please add more rows if needed.

14/08/12

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

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 4 – line 95		Comment: Change “of” to “on” before “periodic monitoring” Proposed change (if any): based on periodic monitoring of large databases such as the EudraVigilance database
Page 4 – line 100		Comment: What is “adverse reaction databases” referring to? Proposed change (if any): Clarify examples of such databases
Page 4 – line 120		Comment: Remove the semi-colon Proposed change (if any): as possible after the acceptance of the manuscript of the results of post-authorisation
Page 5 – line 132		Comment: Change “that” to “than” Proposed change (if any): require other methodological strategies than other medicinal products.
Page 5 – line 133		Comment: Clarification or removal of the word structured Proposed change (if any): In order to determine the evidence supporting a signal, a recognised methodology shall……..
136		Comment: This line and others in the guideline refer to the Implementing Measures. It is confusing to have two documents to describe the same processes. Proposed change (if any): Incorporate all relevant information from the Implementing Measures into this and other GVP guidelines, as applicable.
Page 5 – line 139		Comment: Severity of the event should also be considered

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Different factors may be taken into account for the prioritisation of signals, namely the fact whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness or severity of the reaction involved and factors related to the documentation of the reports in the EudraVigilance database
Page 6 – ***IX.B.3.2.1***		Comment: Why do non-valid (inadequately documented) AEs have to be collected for signal detection, but then this text says to remove them from the signal detection process Proposed change (if any): clarifiation
185		Comment: Module VI makes it clear that literature reports relating to other brands, formulations and routes of administration or from countries where the MAH has never marketed the product do not need to be expedited. However it is not clear if these should be used for signal detection. Proposed change (if any): Clarification is required on exactly what literature cases should be considered for signal detection purposes.
Page 7 – line 224		Comment: Correct used to uses Proposed change (if any): Where signal detection uses an automated screening of a database
Page 8 – line 250		Comment: Refer to the two bullets Proposed change (if any): In principle only signals not falling under the above two categories should be validated
Page 8 – line 261		Comment: Add an A at the start of the sentence Proposed change (if any): A signal becomes a validated signal if the verification process of all relevant documentation
Page 9 – line 283		Comment: Why are only valid cases being considered? There may be circumstances where a non-valid case

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		e.g. non-identifiable reporter, may be an indicator of a potential signal Proposed change (if any): …a high number of cases reported in a short period of time,
Page 9 – line 312		Comment: Do not understand the meaning in the first sentence of this paragraph Proposed change (if any): Clarify the wording
Page 10 – **IX.B.3.6**		Comment: This sections includes recommendations for other parties than just the CAs. Remove CA from the title of this section Proposed change (if any): **IX.B.3.6. Recommendation for action**
Page 14 – line 495		Comment: Change “to” to “with” Proposed change (if any): should collaborate with the signal validation performed by a national competent authority
556 - 560		Comment: This section states that the MAH shall monitor the EV database at least monthly proportionate to the identified and potential risk. For a product with few ICSRs and with small risk, monthly monitoring seems rather excessive. Proposed change (if any): Clarification is required as to how the MAH will monitor the EV database. Also the timelines for monitoring the database should allow for more flexibility depending on the product and its identified and potential risks.
564 - 565		Comment: The MAH is supposed to inform the CA of any signal in line with a list published by the Agency. This list is said to be referred to in lines 463 and 464, but this is not the case. Proposed change (if any): Please provide the correct reference and further clarification regarding this list (what is it and where will be found?).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 16 – line 566		Comment: should “emergency” be “emerging”? Proposed change (if any): Clarification

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 18th 2012

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

Comments from:

Name of organisation or individual
French Association of Regional Pharmacovigilance Centres

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 164-182		Comment: This guideline should provide all different methods used for signal detection in databases, their condition of use and their validity. Otherwise why write such a guideline ? Proposed change (if any):
Line 434		Comment: For national authorised products, the signal detection within Eudravigilance database is performed by the national competent authority, but conditions should be precised: on the whole database ? or only on the national data ? If the proportional reporting ratios method is used, this may lead to highly variable results. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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

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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')*
91-92		Comment: How will NCAs ensure they are informed of signals in a timely manner?
101		Comment: PSURs are not signal detection tools, and in line with other modules are an evaluation tool for effective risk management/minimisation.
122		Comment: Please provide guidance regarding how frequently the internet and digital media should be monitored as well as how broad the scope of the search should be. Recommendation to monitor special internet sites or digital media such as support or disease groups to check if they describe significant safety issues which may necessitate reporting seems unnecessarily burdensome and should be limited to those sponsored by the MAH.
126-127		Comment: Please clarify what is meant by confirming suspected SADRs from other sources.
161-162		Comment: What is meant by “spontaneous reporting systems are considered as the starting point of the signal management process”?
221		Comment: Is the intention to move to thresholds for signals?
305		Comment: Results of signal evaluation to be communicated publically- please confirm extent and nature of what will be included.
331		Comment: Please provide further guidance on what is meant by a staged approach to 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')*
		temporary measures?
335		Comment: Do all signals require submission to EMA or NCAs – also see 566-567.
346		Comment: Please define active monitoring and provide examples.
349		Comment: In the absence of a PSUR how will periodicity be defined and what format should the update take?
353		Comment: What is the likely trigger to require a PASS here?
365-367 and 422		Comment: Please clarify the meaning of sharing information on signals between stakeholders and shared responsibility.
369		Comment: Please clarify the meaning of “only communicate validated signals”.
373		Comment: Please define timelines of “immediately communicated”.
412		Comment: Why should training to non-safety personnel extend to MedDRA? Some groups are commercial in nature and this would be unnecessarily burdensome.
556		Comment: When will the extent of access be known to take into account?
566-567		Comment: Please clarify whether it is appropriate to notify all safety issues arising from signal detection activities as Emergency Safety Issues, as the bullet suggests. Also, please clarify if the MAH should notify as an Emergency Safety Issue only those signals that have been confirmed, rather than those that have been detected and are still under investigation or those that have been evaluated and did not suggest a new causal

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment: Review of the new guidelines created some confusion regarding the processing and communication of signals. More definitions and examples would be very helpful to guide the MAH on how to correctly implement the guidelines. Points of most confusion: The numerous uses of the term 'signal'. It was difficult to determine how to treat a data aberration or signal of disproportional reporting, which in the FDA definition would be considered a signal, and whether this type of signal needed the same type of evaluation/validation as a signal defined by the Report of CIOMS Working Group VIII (CIOMS, Geneva 2010). Additionally, there was confusion on the process of validating, verifying, evaluating, analysis, assessing or confirming a signal. There appeared to be considerable overlap in these processes. Proposed change (if any): Provide definitions for 'signal of disproportional reporting', 'confirmed signal', 'verified signal', as well as practical examples of each with descriptions of their appropriate management, e.g. what type of signal needs entry into the signal tracking system, what type of signal needs to be reported to health authorities.
	Comment: Proposed change (if any):

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 83-84 and 107-108		Comment: There is no mention of pharmacoepidemiology data (e.g. claims databases, EHR) as sources for signals. Are these included in "other sources" or are they not suggested data sources for signal detection? Proposed change (if any): Suggest adding specific text on expectations on pharmacoepidemiology data sources Comment: 'Quality' (in addition to non-clinical, clinical and PV data, 83-84 and in addition to non-clinical, interventional, non-interventional, systemic reviews and meta-analysis studies, 107-108) indicated as the source for identifying new signals. Proposed change (if any): Clarification is needed on quality data or studies as the source for identifying new signals.
Lines 95, 160, 194		Comment: '...monitoring of large databases' (95), 'monitoring of data from spontaneous reporting systems' (160), 'periodic monitoring of large databases' (194), Proposed change (if any): Specifics for 'monitoring' are needed in each case. Does monitoring refer to routinely review of aggregate data, periodically performed statistical data mining or any other methods?
Lines 122-123		Comment: Will there be future guidance on methods to perform surveillance on social media and clarifications on 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')*
		expectations of MAHs? Are MAHs obligated to actively look at these sources? Proposed change (if any): Please clarify expectations on surveillance of social media
Line 137		Comment: Will there be guidance on levels of 'prioritization', e.g. will there be standardized definitions (categories) or will they follow MAH determined definitions? Proposed change (if any): Please clarify whether there will be additional guidance on levels of prioritization or whether MAHs may determine their own definitions.
Line 151		Comment: "exchange of information" Proposed change (if any): Replace with "communication" or "communication of findings"
Line 156		Comment: " ...when a signal is detected from aggregated results of a study" Proposed change: Delete 'aggregated' as it is not applicable term to the results from one study

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 172		Comment: “data from all appropriate sources should be considered” Proposed changes: Add ‘with a consistent approach in safety data management across all sources (e.g. search strategies, dictionary etc)’ at the end of this line
Lines 175-176		Comment: Please provide more information on what is considered an ‘appropriate qualified’ reviewer. Does "appropriately qualified" mean a healthcare professional? Does it mean a physician? Proposed change (if any): Reviewer credentials should be described (MD, PharmD, Biostats?)
Lines 177-178		Comment: Timeframe within which urgent action should be taken to avoid major public health issue needs to be specified. Proposed change (if any): Please provide some general guidance on what would be appropriate time frames for action in these circumstances
Lines 201-202		Comment: Does ‘automatically’ mean computer assisted? Proposed change (if any): Please clarify what is meant by ‘automatically’

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 212-213		Comment: 'Product lifecycle' should also be added as criteria for determining periodicity of statistical report generation – will affect how an established product's safety profile is determined Proposed change (if any): Add 'lifecycle' or similar wording to text – "...may vary according to the active substance / medicinal product, its indication and potential or identified risks as well as the lifecycle of the product"
230-233 and 255-260		Comment: It is not clear how extensive a signal should be evaluated for (1) validation versus (2) analysis/assessment. In many ways, the evaluations appear to overlap. The suggested evaluation for signal validation may involve the same data sources, and methods as the formal signal analysis and assessment. Proposed change (if any): It may be clearer to refer to the validation step as a type of triage for identifying signal/topics that need to be further assessed in a formal manner (e.g. via ADR assessment/causality assessment).
Lines 274-277		Comment: Does every finding from signal detection activities need to be entered into the signal tracking system for documentation/tracking of validation? For some types of signalling activities, this would not be practical or valuable. Typically, there is a triage step before further assessment (validation) of initial findings. It was noted (205-207) "signal of disproportionate reporting does not necessarily indicate that there is a signal to be further investigated or that a causal association is present". Does this mean that only those signals of disproportionality that have been triaged for further review need to be entered into a signal tracking system for documentation/tracking of validation. Would that same approach apply signals identified through other signal detection methods?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Please clarify what types of signals need to be tracked in a signal tracking system.
Line 333		Comment: '...that there is a potential risk that needs to be prevented.' It is unlikely that all potential risks can be prevented absolutely. Potential risks should be prevented or minimised. Proposed change: Amend text accordingly "...that there is a potential risk that needs to be prevented or minimised."
Lines 370-372		Comment: Will there be additional guidance on what validated signals need to be communicated to CA? For non-urgent signals, will communication in the PSUR be sufficient? Should signals routinely be 'confirmed' before communicated to the Agency except for when the potential impact on the risk-benefit profile requires urgent action? Communication of signals before they are confirmed will generate many false alarms and may be a resource drain for the MAH/CA. Proposed change (if any): Please provide additional clarity in this guidance as to what should be communicated to competent authorities and how such communication should be conducted.
Line 379		Comment: "Tracking systems need to be documented and should include also signals, for which the verification process conducted was not suggestive..."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Text should be amended to clarify the purpose of tracking systems - 'Tracking systems ~~need to be documented~~ should be used for documentation and should include also signals, for which the verification process conducted was not suggestive of a new potentially causal association....
Line 399		Comment: "Information received, searches, searches outputs, assessments and decisions" Proposed change: Replace 'searches' with 'search methodologies'' to provide more clarity on what is meant by 'searches' as opposed to 'search outputs'
Line 404		Comment: 'Documentation by the MAH demonstrating compliance with these provisions may be requested and reviewed before and after authorization...' Proposed change (if any): Amend text for clarity – "...before and after marketing authorisation"
Line 555		Comment: Will there be any additional guidance on expectations for MAHs regarding the PV responsibility to "monitor all available data and information for signals"? Is the MAH required to seek out "all" potentially helpful data sources? Does holding a data source for other reasons require a MAH to monitor the data source for signals? 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')*
		A pragmatic and reasonable approach should be applied to selection of data sources and this should be further clarified in the guidance.
558-560		Comment: In response to the commitment “The frequency of the monitoring should be at least once monthly” for EudraVigilance, what is meant by 'monitoring' and does the frequency apply to all products? Monthly monitoring of EV with disproportionality (statistical) analysis seems excessive as the signal scores are unlikely to change significantly over such as small time period. Monitoring quarterly in the first 2 years after launch of a new product seems more reasonable approach. Frequency of monitoring after that can be adjusted accordingly. By monitoring, are other methods than disproportionality analysis suggested? Does the review include for all products and/or events, even products with little activity or safety risk? Monthly monitoring of EudraVigilance is felt to be too frequent for more established products that have low patient exposure. Periodicity of monitoring should be linked to product factors such as lifecycle, identified/potential risks etc. Could monitoring be targeted to higher risk products (newly approved) or events of special medical concern (Designated medical events or medically important events? Will there be guidance on what is meant by "proportionate to the identified risk" e.g., example review schedules (monthly for 2 years...) Proposed change (if any): Please clarify what is meant by ‘monitoring’ and consideration should be given to a more risk-based frequency rather than ‘monthly’ for all products.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
556-558		Comment: There is considerable overlap in the spontaneous AE reports in the Company safety database, AERS, EudraVigilance, and Vigibase, especially for products marketed globally. The MAH should have flexibility to decide to monitor one or more of these data sources if it is determined to be the best safety source for a particular product. Proposed change (if any): Please clarify that the MAH is responsible for choosing the best safety data source for a particular product.
556-558		Comment: Will the MAH have any responsibility to monitor what will be made available to the public in the first phase of opening EudraVigilance access or will the MAH only need to begin monitoring EV when full MAH access it provide through EVDAS (2015)? Proposed change (if any): Clarification required.
566-567		Comment: Timeline for notification of emergency safety issues needs to be explicitly specified. Proposed change (if any): Specify the timeframe explicitly.
585-588		Comment: Is the expectation that the MAH performs the same reviews (should perform the same signal detection activities) as those mentioned for the Agency/CA?

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19.04.2012

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

Comments from:

Name of organisation or individual
F.Hoffmann – la Roche

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Roche supports the comments EFPIA has sent in. The modules are in general well written but would benefit from consistency checks across in terms of definitions and requirements for the quality system. In particular Module I describes that, in each module, particular quality aspects will be discussed, and as this is clearly the case in a number of modules, it is less obvious in other modules. A few additional comments are provided here as well as questions for clarification that were raised while reviewing the draft modules. Overall the EFPIA finds GVP Module 9 on Signal Management is well structured and a comprehensive description of both signalling routines and how the interaction and communication between stakeholders should work in a European environment. The two main concerns from EFPIA regard the requirements for MAHs to search routinely in **all available data** and the specification of **a frequency of monthly searches** by MAHs in EudraVigilance. **All available data** risk creating a too broad requirement for routine signalling and **a fixed monthly frequency** will be neither risk proportionate nor necessarily add any value in addition to the authorities searches. Both points are further developed in the Specific Comments below. Regarding **transitional measures** the EFPIA considers that the requirements to devise, document and implement detailed quality system procedures, including a potential IT tool for a tracking system with an audit trail, for all signal management processes will necessitate **an 18 months transitional period** for these requirements. The Agency is urged to consider earlier communication with the MAH than that following the conclusion of signal assessment by the PRAC, in order that the MAH can contribute all available data to the assessment. The Agency should consider that, when a signal is communicated to a Market Authorization Holder (MAH) as a result of statistical signal detection activities, a primary task for the MAH in formulating a response will be to perform a reconciliation of cases. It will be necessary for the MAH to determine which individual cases related to the signal are common to both the EudraVigilance

Stakeholder number *(To be completed by the Agency)*	General comment
	database and the MAH's own safety database, which are uniquely held in EudraVigilance, and which are uniquely held in the MAH's safety database. To permit meaningful and expeditious evaluation of signals, the initial communication of a signal to an MAH should not be simply a numerical summary, but should include sufficiently detailed information to at least allow the reconciliation process to begin. With regard to requirements for urgent notification of the Agency and/or Competent Authorities for emerging safety issues, changes to benefit-risk, etc. we urge harmonization of the requirements between EMA and other Health Authorities, including the FDA

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')*
83-86		Comment: Pharmacoepidemiology data is an important source of signals, which is not mentioned. Proposed change: Add in line 84 “and pharmacoepidemiology data”
113		Comment: A precise definition of a “registry” should be provided. Proposed change (if any): Align definitions and only have one source for them (Annex I)
115		Comment: Results of registries or studies initiated by the MAH is covered by Module VIII. Proposed change: The reference in parenthesis “(see Module VI)” should be replaced with “(see Module VIII)”.
119-121		Comment: PASS results must be communicated to NCA within 12 months from the end of data collection according to Module VIII, regardless of manuscript acceptance. Introducing different requirements in different GVP Chapters does not simplify and as stated here it risks create inconsistency between countries/NCAs. Proposed change: Replace this whole paragraph with: “MAHs shall submit the study report of all PASS to competent authorities within 12 months from the end of data collection or where required completion of data validation (see Module VIII).
126-127		Comment: There is very little additional value in requesting that MAHs should try to verify “social media” reports in EV over and beyond routine duplicate check in their own data base, otherwise this represents unnecessary duplicate activity for marketing authorisation holders and national competent authorities. Proposed change: Remove last sentence or make it exclusive for the Agency and NCAs for the time being.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
177-178		EFPIA has already addressed the issue that the recommendation for urgent and appropriate action should be specified in terms of a time period. However, they did not address the question of how “Day 0” for assessing the period should be determined. Proposed change (if any): "Day 0" should be defined as the date that the sponsor determines that the suspected adverse reaction or other information qualifies for reporting.
259-260		The Agency should note that “screening of databases with larger datasets” as a means of signal validation can only be properly conducted when the datasets are independent of one another (i.e. non-overlapping), or when the extent of overlap is well known and characterized. Otherwise, the appearance of cases in both datasets may lead to a false indication that a signal is valid. Proposed change (if any): Line 259 to read “…screening of additional **independent** datasets.”
261 + 268		Comment: Stringency in terminology will improve understanding. The term “verification” seems to be used as synonym for “validation”. Proposed change: Change from “verification” to “validation”.
308		Comment: Stringency in terminology will improve understanding. The term “evaluation” seems to be used as synonym for “assessment”. Proposed change: Change from “evaluation” to “assessment”.
373, 492, 564		Comment: The terms “immediately” and “forthwith” for MAHs to communicate validated signals to authorities and for the Agency to communicate PRAC conclusions to the MAH are prone to differing interpretations.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Specify the intended timeframes for these communications in clear wording, e.g. within 15 days.
401		Comment: The term “Potential signals” risk being subject to varying interpretation. Proposed change: The term “Potential Signal” should be defined and added to the Definitions module.
458-460		Comment: MAHs should be informed about the initial frequency of monitoring of their products applied by the Agency and the NCAs. Proposed change: The list published by the Agency should also include the initially intended frequency of monitoring if other than monthly.
467-475		Comment: It is unclear if the Agency shall support the monitoring of the data in the EV database by providing the specified accesses also for MAHs. Proposed change: Specify if the Agency will support the specified accesses also for MAHs or only for the authorities.
482-487, 506-510, 532-536		Comment: MAHs need to be informed about the result of the activity that the Agency, the lead/co-lead MS or the NCA undertake to confirm any validated signals communicated by the MAH (whether the validity is confirmed or not) within 15 days. Proposed change: Add in the respective paragraphs, that the Agency, lead/co-lead MS, NCA should communicate back to the MAH whether the signal has been confirmed or not within 15 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')*
488		At what stage of validation or assessment will the MAH be informed about signal communication received by the Agency or its delegates from third parties?
555		Comment: The wording “all available data” is somewhat imprecise and can in its widest interpretation not be considered either rational or motivated for routine signalling. The starting point for any regular, routine signalling activity for all MAHs is reasonably the data in their own possession. If a potential signal is identified in the Detection step then other available data sources may be tapped into during Validation, Analysis and prioritisation or Assessment. Proposed change: The sentence “– shall monitor all available data and information for signals;” should be replaced with “- shall monitor all available data and information in its possession for signals;”.
558-560		Comment: To monitor EudraVigilance at least once monthly seems excessive for many products with a well known safety profile and few reported reactions. At this point it is not to rationalise the system to specify a monthly frequency in EV for MAHs. To what extent this will make sense for the total breadth of all MAHs product portfolios is very much dependent on the tools that will be made available. It must also be considered what a monthly monitoring by MAHs with the likely more limited access (i.e. only identified own products) can add to the authorities broader monthly monitoring. Furthermore the opportunity to apply a “proportionate to risk” monitoring frequency seems very limited if monthly is defined as a minimum. Proposed change: The sentence “The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information” should be replaced with “The frequency of monitoring shall be proportionate to the identified risks, the potential risks and the need for additional information”.
566-567		Comment: The term “Emergency Safety Issue” seems erratic in that it differs from the one used in chapter VI

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		where “Emerging Safety Issue” is used. Furthermore, in Chapter VI the term seems to only include safety issues which may lead to a change in the known benefit-risk balance whereas here it includes any safety issue arising from the MAHs signal detection activity. Proposed change: This paragraph should be replaced with: “-should notify as an Emerging Safety Issue (see Module VI) any safety issue arising from its signal detection activity which may lead to changes in the known benefit-risk balance for a medicinal product.”
566-567		Comment: The term “Emergency Safety Issue” seems erratic in that it differs from the one used in chapter VI where “Emerging Safety Issue” is used. Proposed change: The terms “Safety Issue” and “Emerging Safety Issue” should be defined and added to the Definitions module.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The scope of this module is rather broad. The question is however, if the requirements as described in this module can be fulfilled. Since the module aims at providing guidance in the signal management process, it might be more efficient providing clear information where possible and asking for maximum transparency about the signal detection and management processes as conducted by the parties involved.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
147		Comment: the definition of signal validation is not clear. Proposed change: Please provide a clear definition of the validation process.	
164		In this section, the identified risks in the RMPs are missing. It seems obvious however, that special attention should be paid at these potential risks in the signal detection process. It has been mentioned in the signal validation section, but for signal detection it is valuable too.	
169		Comment: Whichever methods are employed for the detection of signals… This sentence suggests that parties involved are free to use any approach as long as the criteria that are mentioned are fulfilled. However, the criteria that are mentioned are not very well defined in this stage. There is a lot of room for interpretation. It is well possible that in this stage the consequences of conducting signal detection and evaluation are not clear yet. Therefore an evaluation of this process should be agreed upon.	
194		Statistical analysis in large databases. Also in this section, no clear guidance is provided. When using disproportionality analysis, it is clear that performance is not optimal. We should be aware however to aim for a maximum sensitivity and thereby getting large numbers of false positive signals. This is	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		simply not feasible. It is obvious that given the large differences between databases it is not possible giving any suggestions for cut off values or even the choice of the statistical approach. A solution might be asking for a clear standard operating procedures including a description of the database and specification of the thresholds that are being used in order to make te process more transparent. The workload could be limited as long as it is clear which criteria have been applied for limiting the amount of work.	
311		Signal assessment is a very time consuming and costly process. It is not clear under what circumstances signal validation does not has to be followed by signal assessment. Some guidance should be given, otherwise the amount of work would be too large and the quality would be jeopardized just like the feasibility of the system.	
498		Since the time for validation is limited, it is important to give a clear definition of the (minimal) requirement for the validation stage.	
571		The frequency of monitoring is specified, but not the way how it should be carried out. Large differences may occur between the member states. Also for this point some guidance is needed.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 April 2012

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

Comments from:

Name of organisation or individual
Medicines Evaluation Board – the Netherlands

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')*
Line 128		Comment: Heading refers to signal management, whereas the text describes signal detection methods. Proposed change (if any): change header to “Methodology for signal detection’
Line 133		Comment: some of Bradford-Hill criteria are missing Proposed change (if any): include ‘temporal relationship, specificity’ after ‘exposure-response relationship’
Line 138		Comment: public health impact is missing here Proposed change (if any): add public health impact
Line 171-172		Comment: not only data set is important, but also the actual numbers underlying the statistics. Methods might be still corrupt if small numbers of adverse event-drug combination
Line 187-188		Comment: It should be documented how many cases are being excluded from analysis because of duplicates and/or inadequate documentation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 190		Comment: positive/ negative rechallenge and dechallenge is missing here Proposed change (if any): Add ‘positive/ negative rechallenge and dechallenge’

Please add more rows if needed.

17 April 2012

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

Comments from:

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

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1. General comments

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

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')*
324-325		Comment: The MSSO believes the highlighted text below may better suggest how to use the different groups of MedDRA to produce a meaningful data output in order to facilitate signal detection. Proposed change (if any): Signals sometimes need to be assessed at the most appropriate group level of the MedDRA hierarchy to warrant a meaningful aggregation of data. Standardised MedDRA Queries (SMQs) may be used for signal detection in order to retrieve and review cases of interest where signals identified from adverse reaction databases ~~the therapeutic or system organ class level or at the level of a standardised MedDRA query~~ and the search for information may need to be extended to other products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of the reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Medical Products Agency, Sweden

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Regarding the chapter Structures and Processes, some of the sub-processes (e.g. the role and responsibilities when there is no lead member state; validation of a signal) are still not completely clear on how to translate the process into practical routines. We consider that the Module would benefit from more practical guidance in this context. All identified signals should be entered into the EPITT database and an audit trail should be made of all signal detection activities. However, while the EPITT database is in use currently, it would be helpful if clarification can be given on how an audit trail should be managed.

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 572-586		Comment: It is suggested in the module that the NCAs shall ensure the monitoring of data in the EudraVigilance database once per month and for products where additional monitoring is requested the database should be monitored every second week. Without knowing how the information will be presented (methods are under testing) and how the tools to keep track of the audit trails for the signal detection sub-processes are made, it is difficult to overview the amount of work required from the NCA. The workload could become significant given the number of products on the market. We agree that the monitoring frequency should be proportionate to the identified risk, the potential risks and the need for additional information and suggest to modify lines 572-580 and 584-585 in line with the following: Proposed change (if any): NCAs shall ensure the monitoring frequency should be proportionate to the identified risk, the potential risks and the need for additional information, and may consider the monitoring of data in the EudraVigilance database once per month and for products where additional monitoring is requested the database should be monitored every second week.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 08 Jun 2012 15:20:00

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

Comments from:

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

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In general, Novartis finds the GVP module on signal management a comprehensive description of signal detection and evaluation activities and how the interaction and communication between stakeholders should work in a European environment. One aspect of the GVP which requires further clarification is the target of the signalling activities. Are the activities and expectations outlined directed at the active medical product or the active moiety? This is particularly relevant for combination products. Novartis would also like to highlight the apparent inconsistency between the undefined risk-based periodicity approach specified in section IX.B.3.3.3 for large databases and the defined, non risk-based approach to periodicity for monitoring in Eudravigilance. Monthly monitoring for products with infrequent reporting and a well established safety profile is excessive, unlikely to generate new validated signals, and pulls resources from those products which truly require frequent monitoring. Regarding transition time for implementation, the requirement to develop systems for a fully compliant signal management system, including a tracking tool with audit trail, is quite extensive and will require 18 months.

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 82		Comment: The term "all" is very broad and could be interpreted to extend to data beyond the capability of the MAH to access. Proposed change (if any): Propose to change phrase to "relevant scientific information accessible to the MAH concerning the use of…… and other sources of information."
121-126		Comment: It is unclear why social media is highlighted in this section separately from other sources of signals. More clarity is needed on the requirements for MAHs to review social media sites but this is more appropriately discussed in Module VI. Furthermore, there is very little added value in requesting that MAHs should try to verify "social media" reports in EV over and beyond routine duplicate check in their own data base. If already being assessed by national competent authorities in Eudravigilance, this is unnecessary duplication for MAHs. Proposed change (if any): Relocate lines 121-126 to Module VI. Provide further clarification on requirements and expectations of MAHs with regard to social media. Delete last sentence (lines 125-126) of paragraph.
187		Comment: Please define "inadequately documented cases". Is this the same as non-valid cases? Also, the direction to exclude these is inconsistent with lines 372 – 374 in Module VI and with previous inspection experience where it was made clear that non-valid cases were expected to be reviewed and included in on-going safety evaluation activities. Proposed change (if any):
186-192		Comment: The information on these lines is better placed in Module VI and does not need to be duplicated in this section.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): End paragraph at line 186 with sentence "Even a single report……and taking further action."
211		Comment: The periodicity for this section on statistical analyses in large databases is inconsistent with that expected for Eudravigilance. This risk-based approach is the most reasonable. If EMA expects a minimum periodicity (monthly is excessive and unlikely to yield new signals for old products with an established safety profile), it should be stated. Also there is no discussion in this module of review of clinical trial databases. Proposed change (if any):
224		Comment: It is unclear from a documentation perspective what the expectation around individual review of ICSRs is. Proposed change (if any): Rephrase to say "Where signal detection used an automated screening of a database, the underlying data should be evaluated to understand the context of the signal."
261		Comment: It is not clear what is meant by verification and validation Proposed change (if any): Definitions of verification and validation should be added to the Glossary
277		Comment: Content of this section IX.B.3.4 is inconsistent with the title. The section only discusses prioritisation. Proposed change (if any): Change title to: Signal prioritisation. Line 146 is also then impacted and should be changed to say signal prioritisation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
306		Comment: The terms "evaluation" and "assessment" seem to be used interchangeably but are not defined. Proposed change (if any): Use consistent terminology throughout document and add relevant definitions to Glossary
320		Comment: If possible, replication of a signal should be performed in separate data sources from those that generated the signal. Proposed change (if any): Add this sentence to the paragraph
372		Comment: Which signals need to be communicated and in what time frame is not clear. Immediately is not defined. Also, what is the mode of reporting and timeframe expected for signals that may not have implications for public health, i.e. non-important signals. Should these be communicated in the next PSUR? Proposed change (if any): Clarify what is meant by "immediately". Provide guidance on expected timeframes and mode of reporting for all signal types, important and non-important.
374-375		Comment: Communication from MAH to competent authorities and from competent authorities to MAH should be defined in both directions. Details on timeframe and mode of reporting are not provided Proposed change (if any): Provide details of communication (timeframe and mode of reporting) from competent authorities to MAH.
400		Comment: Use of the term "Potential" signal is redundant as a signal requires further evaluation before it is validated in accordance with CIOMS VIII. Proposed change (if any): Delete word "potential".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
373, 492, 564		Comment: Need consistent use of terminology. Please clarify differences, if any, between "immediately" and "forthwith". Proposed change (if any): Specify timeframe using number of days rather than these words which could be interpreted differently; e.g. within 15 calendar days.
410-411		Comment: Since the sources for identifying signals comprise also clinical data and signal detection and evaluation both belong to the signal management process also statisticians should be involved into the training. Proposed change (if any): Add statisticians to the staff to be trained.
457-459		Comment: EMA should publish the list of products and include the frequency of monitoring so that MAHs are informed of the intended frequency for their products. Proposed change (if any): Modify sentence to state the frequency of monitoring will also be included in the published list.
		Comment: Proposed change (if any):
467-475		Comment: Please clarify whether MAHs will have access to these data outputs and statistical reports to support monitoring by the MAH in Eudravigilance 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')*
482-492, 506-510, 532-536		Comment: EMA should inform MAHs of the results of all signal detection activities and not only those signals which are validated. A time frame should be clearly specified. Proposed change (if any): State in the appropriate paragraphs that the MAH should be informed within 15 calendar days whether the signal has been validated or not.
532-536		Comment: It is unclear why a signal notified by MAH would not be validated. Please clarify any circumstances under which this might occur. Proposed change (if any):
540-561		Comment: If a validated signal is sent to the PRAC, the MAH should be notified of who is the rapporteur and time frame for assessment. Proposed change (if any): Add a bullet to this section stating, "The MAH shall be notified of the rapporteur and timeframe for assessment."
555		Comment: The phrase "all available information" is not clear and excessive if for routine signalling it goes beyond the data the MAH has in its possession. Proposed change (if any): Revise sentence to read, "….shall monitor all available data and information in its possession for signals".
555		Comment: It is unclear from this sentence what will be available to MAH from Eudravigilance. Please clarify. 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')*
558-560		Comment: Monthly monitoring of Eudravigilance is neither rational nor reasonable and is not proportionate with risk. For well established products with few safety reports, monthly monitoring is highly unlikely to yield a signal. The language provided is also inconsistent with that provided with section IX.B.3.2.2 (lines 211-212). In addition, if MAHs have limited access to Eudravigilance (only own products), monitoring by MAHs in Eudravigilance is not going to yield anything beyond that resulting from monitoring the MAHs own database. Proposed change (if any): Replace sentence with "the frequency of monitoring shall be proportionate to the identified risks, potential risks, and need for additional information." Consider removing requirement for Eudravigilance monitoring by MAHs if only limited access to own data will be provided.
565-566		Comment: The term "Emergency Safety Signal" refers to the Module VI, which uses the term "Emerging Safety Issue". In addition to the inconsistent terminology, how these terms are used is also inconsistent. In Module VI, emerging safety issue is defined as one which may lead to a change in the benefit-risk balance. In the Signal Management module, Emergency Safety Issue refers to any safety signal arising from signal detection activity. Proposed change: The language should be revised to read, "…should notify as an Emerging Safety Issue (see Module VI) any safety issue arising from its signal detection activity which may lead to a change in the known benefit-risk balance for a medicinal product."
567		Comment: As stated earlier, "assessment" and "evaluation" seem to be used interchangeably and are not defined. Proposed change (if any): Use consistent terminology and add term to Glossary
569		Comment: Please clarify what is expected to be captured in the audit trail. 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')*
584 - 601		Comment: Reviewing statistical outputs every 2 weeks seems excessive as it is unlikely the volume of additional reports will change substantially in such a short time frame for most products. Also, the criteria for 2 week monitoring is quite broad. What will be the basis for the decision? Proposed change (if any):
617-619		Comment: It is not stated when the MAH will be notified of the decision. Proposed change (if any): Provide clear timelines for notification of MAH
629		Comment: No time frame is provided for notification of MAH. Also there is no opportunity for consultation with MAH in advance of final outcome, which prohibits discussion in advance of a final determination. Proposed change (if any): Add in a consultation step with MAH before the final determination is made.
680-688		Comment: The MAH should receive notification of assessments, decisions, etc. prior to public notification. Since other health authorities and individuals access the EMA website at a time zone prior to Europe, the MAH should not be surprise by information it was not previously made aware of. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module IX – Signal management) is very comprehensive and provides helpful guidance on the set of activities performed to manage safety signals related to medicinal products authorised for human use in the EU. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.
	The development timeframe for a fit-for-purpose tracking system (and personnel training) may be at least 18 months following publication of the finalised GVP Module IX.
	If it is considered that spontaneous reporting generates SUSPECTED adverse reactions, the relevant qualifier should be consistently introduced throughout the text, as appropriate, in this and in all other GVP modules.
	It appears that the definition and use of "*signal management*" in Module IX is not entirely consistent with the international consensus definition, i.e., the definition and use of the term that appears in the Overview of Signal Management (pages 87-97 and page 115 of Practical Aspects of Signal Detection in Pharmacovigilance from CIOMS Working Group VIII). If the intention is to be consistent with the international consensus definition, then the CIOMS Working Group VIII definition of "*signal management*" should be included in GVP Annex I (Definitions) for use in the revised Module IX (page 87). Signal management consists of a set of activities including signal prioritization and evaluation to determine whether a signal represents a risk, which may warrant further assessment, communication or other risk minimization actions in accordance with the public health importance of the issue. Following signal evaluation, a signal either becomes an identified risk, a potential risk (which implies that closer monitoring and/or further investigation is necessary), or does not constitute a risk and does not warrant further action at that time.

Stakeholder number *(To be completed by the Agency)*	General comment
	The terms "*validated signal*" and a "*verified signal*" appear to have been used interchangeably throughout the document. The term "*verified signal*" should be used throughout the document to make it consistent with the Overview of Signal Management chapter in the Report of COIMS Working Group VIII. Also, make it clear whether or not the usage of the term "*verified signal*" is consistent with that in the Report of CIOMS Working Group VIII which defines "*identified risks as those that emerge from verified signals*" (page 94 of the CIOMS VIII report). These concepts should be defined in GVP Annex I, per the international consensus definitions provided in the CIOMS VIII report. **Note**: In addition to providing this general comment, somewhat overlapping comments on these concepts appear with reference to lines 51, 155, 261, and 268.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
51-52		**Comment**: This terminology "*validated signal*" is the first of many examples of terminology that we would suggest using standard definitions for consistency and clarity in this guidance document. Many are consensus definitions adopted by international experts, for example consider using CIOMS VIII terminology "*verified signal*" or in this particular line "*verified*". **Proposed change**: Revise lines 51-52 to read: "*In order to suggest a new potentially causal association or a new aspect of a known association, any signal should be ~~validated~~* ***verified*** *taking into account other relevant sources of information*."
122-127		**Comment**: Experience with focused monitoring of social media is limited and is also the subject of intense research. Thus, it is important for regulatory guidance to clearly indicate that it is inadvisable to require a focused group of programs to monitor this information. This section should be removed from the requirements until consensus guidelines and standards are established. The guidance should clearly indicate, however, that this is a potential future source of information. **Proposed change**: Revise lines 122-127 to read: "*Other sources of information include the internet, digital media (such as public websites, social networks, blogs) or other systems through which patients and consumers may communicate adverse experiences with medicinal products (see Module VI).* ***Until research demonstrates the value of focused monitoring of social media to pharmacovigilance, it remains a potential source of safety information that might be harnessed in the future. Nevertheless,*** *marketing authorisation holders and competent*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		authorities should try to gain further information related to reactions they become aware of from such sources. ***~~If the available information is limited, suspected serious adverse reactions should be confirmed if possible in other data sources such as EudraVigilance~~***.”
155-158		**Comment**: It would seem the common first step when a signal is detected in aggregate data would be to review the individual cases that comprise the signal as well as cases with similar events. There should be clear distinction between the terms such as validation, assessment, and analysis used throughout this document. The definitions in GVP Annex I should support these distinctions. **Proposed change**: Revise lines 155-158 to read: “• *when a signal is detected from aggregated results of a study,* ***if*** *it is* ~~*generally*~~ *not possible or practical to assess each individual case,* ~~*and validation*~~ ***further evaluation*** *may require collection of additional data;*”
171		**Comment**: It is unclear what qualifies as a *complex method*. This should be defined in GVP Annex I in the context of signal management. Also, how small is too small? If one looks at organizations that currently use quantitative methods, the range of data base sizes is quite wide – the range is upwards from tens of thousands of cases (as in the Lareb Center). **Proposed change**: Define complex method in the context of signal management here and in GVP Annex I (Definitions).
187-192		**Comment**: Reference should be made to de-challenge and re-challenge and their definitions reiterated in GVP Annex I instead of “*the clinical outcome in relation to drug continuation or discontinuation*” which can be misleading and result in erroneous evaluation of an event outcome.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Revise lines 187-192 to read: "*The information to be reviewed should include the number of cases (after exclusion of duplicates and inadequately documented cases), the patient's demographics (e.g. age and sex), the suspected medicinal product (e.g. dose administered) and adverse reaction (e.g. signs and symptoms), the temporal association* ***(including well-documented, i.e., high quality / minimally confounded), positive rechallenge / dechallenge information), the presence of potential alternative causes for the adverse event,*** *the clinical outcome in relation to drug continuation or discontinuation, the presence of potential alternative causes for the adverse event, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.*"
234-235		**Comment**: The basis for the requirement that additional information to consider should always be independent of the source of the signal. Very often these factors are evaluated, in part, using the same data in which the signal was detected. **Proposed change**: Revise lines 234-235 to read: "*For this signal validation process, ~~independently from the source of signals,~~ the following should be taken into account:*"
250-254		**Comment**: Is temporal persistence proposed as a requirement to warrant validation (presumably additional)? Real world experience suggests that temporal persistence of quantitative findings (e.g., SDRs) is the norm, so caution should be exercised in suggesting that temporal persistence in effect is a signal based on new information on a known/already evaluated issue. **Proposed change**: Revise lines 250-254 to read: "*However, an already known signal may require validation if its apparent frequency of reporting, ~~its temporal persistence,~~ its severity or a change in the previously reported outcome (such as fatality) suggests new information as compared ~~to~~* ***with*** *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')*
		data included in the SmPC or previously assessed by the competent authority."
261 + 268		**Additional Comment**: This section does not appear to represent the international consensus definitions of signal "*refinement*", "*strengthening*" or "*substantiation*" which really refer, generally, to the process of signal evaluation. This is not limited to the specific aforementioned activities or independent data sources. **Proposed change**: Check that these terms are defined in GVP Annex I (Definitions) and are consistent with the CIOMS VIII report. Use of the terms in this module should be made consistent with these international consensus definitions.
274-277		**Comment**: The following is not clear: "...*the reasons why signals did not suggest a new potentially causal association, or a new aspect of a known association as well as information that would facilitate further retrieval of the cases and assessment of the signal.*" **Proposed change**: Revise lines 274-277 to read: "*Marketing authorisation holders and competent authorities should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals* ***were not verified*** ~~*did not suggest a new potentially causal association*~~*, or a new aspect of a known association as well as information that would facilitate further retrieval of the cases and assessment of the signal."*
309-310		**Comment**: The intended meaning of the following is obscure: "*The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the level of prioritisation attributed to the signal.*"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Revise lines 309-310 to read: *"~~The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the level of prioritisation attributed to the signal~~* ***Summary information on signal prioritisation outcome should be tracked, along with a summary of the rationale for that prioritisation****."*
311-334		**Comment**: The order of activities, validation, analysis and assessment in section IX.B.3.5. are confusing. See comments above. **Proposed change**: Adopt change proposed above, i.e., clarify the terminology, sequence, and logic for each step of the signal management process in accordance with the CIOMS VIII report. Update Annex I with appropriate definitions and include a statement in Module IX that refers readers to the definitions in GVP Annex I. See line 141 (Section IX.B.3.).
316-319		**Comment**: The scope of "*unpublished data*" is not clear. Does this terms include data that are not property of the MAH, e.g., owned by an independent entity (and possibly unknown to the MAH or otherwise unavailable to the MAH)? **Proposed change**: Revise lines 316-319 to read: "*This review should include pharmacological, non-clinical and clinical data when available and be as complete as possible regarding the sources of information, including the application dossier,* ***published*** *literature articles, spontaneous reports and non-published information from ~~the~~ marketing authorisation holders and ~~national~~ competent authorities*."
395		**Comment**:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The intended meaning of "*quality measures*" is vague. **Proposed change**: Define "*quality measures*" in GVP Annex I (definitions) and give examples in this module to enhance clarity as the term is used in this module. The definition and usage should be consistent across all GVP modules.
687-689		**Comment**: The following section on transparency is not clear: "*In this context, several key documents will be made publicly available through the Agency's web- portal. These documents will include the conclusions of the PRAC assessments and recommendations following the evaluation of signals.*" (Lines 687-689). More guidance is needed to provide clarity on how this will be accomplished. How soon after a communication with the MAH will news about the MAH's products be made public via these documents? What will the format of the documents be? Will public disclosure include a verbatim transcript of the PRAC discussion? **Proposed change**: Provide guidance on timing, roles, responsibilities, and related processes.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

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

Comments from:

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

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
	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Module IX – Signal management.
	In general we want to point out that the overall timeframe of the consultation was very short for an in-depth analysis and commenting on this comprehensive guidance documentation.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
409 - 412		Comment: This concerns not only staff within the safety departments but also staff who may become aware of potential signals or support signal management, such as staff within regulatory, non-clinical research, medical, pharmacoepidemiology and market research departments. The training should include MedDRA and available signal source databases, as applicable. Proposed change (if any): Detailed training on MedDRA and signal detection seems to be excessive for staff which is not included in the actual signal detection process.
558 - 560		Comment: The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information [IM Art 25(2)]; Proposed change (if any): A risk based approach does not necessarily require a monthly signal detection, e.g. in case of APIs with very few or no ICSRs.
631		Comment: risk-benefit balance Proposed change (if any): Benefit-risk balance
687 - 689		Comment: In this context, several key documents will be made publicly available through the Agency's web-portal. These

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		documents will include the conclusions of the PRAC assessments and recommendations following the evaluation of signals. Proposed change (if any): The language of the assessments should be appropriate to the target population to avoid causing uncertainty.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Procter & Gamble

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 4 – line 95		Comment: Change “of” to “on” before “periodic monitoring” Proposed change (if any): based on periodic monitoring of large databases such as the EudraVigilance database
Page 4 – line 100		Comment: What is “adverse reaction databases” referring to? Proposed change (if any): Clarify examples of such databases
Page 4 – line 120		Comment: Remove the semi-colon Proposed change (if any): as possible after the acceptance of the manuscript of the results of post-authorisation
Page 5 – line 132		Comment: Change “that” to “than” Proposed change (if any): require other methodological strategies than other medicinal products.
Page 5 – line 133		Comment: Clarification or removal of the word structured Proposed change (if any): In order to determine the evidence supporting a signal, a recognised methodology shall……..
Page 5 – line 139		Comment: Severity of the event should also be considered Proposed change (if any): Different factors may be taken into account for the prioritisation of signals, namely the fact whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness or severity of the reaction involved and factors related to the documentation of the reports in the EudraVigilance database
Page 6 –		Comment: Why do non-valid (inadequately documented) AEs have to be collected for signal detection, but then

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To 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.B.3.2.1		this text says to remove them from the signal detection process Proposed change (if any): clarifiation
Page 7 – line 224		Comment: Correct used to uses Proposed change (if any): Where signal detection uses an automated screening of a database
Page 8 – line 250		Comment: Refer to the two bullets Proposed change (if any): In principle only signals not falling under the above two categories should be validated
Page 8 – line 261		Comment: Add an A at the start of the sentence Proposed change (if any): A signal becomes a validated signal if the verification process of all relevant documentation
Page 9 – line 283		Comment: Why are only valid cases being considered? There may be circumstances where a non-valid case e.g. non-identifiable reporter, may be an indicator of a potential signal Proposed change (if any): …a high number of cases reported in a short period of time,
Page 9 – line 312		Comment: Do not understand the meaning in the first sentence of this paragraph Proposed change (if any): Clarify the wording
Page 10 – **IX.B.3.6**		Comment: This sections includes recommendations for other parties than just the CAs. Remove CA from the title of this section Proposed change (if any): **IX.B.3.6. Recommendation for action**
Page 14 – line 495		Comment: Change “to” to “with” Proposed change (if any): should collaborate with the signal validation performed by a national competent

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		authority
Page 16 – line 566		Comment: should “emergency” be “emerging”? Proposed change (if any): Clarification

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 Apr 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
General aspect	Signals should follow a structured and recognized methodology, which amy vary depending on the type of medicinal product it is intended to cover.
187	Inadaequately documented cases- to be defined
223	The corresponding ICSRs should be individually reviewed: To have a look at every case?
410	Which staff to train? Market research departments?
540	MAH should be informed by the PRAC
554	Available data-to which database does the MAH have access to?
557	Monthly doesn't make sense for every molecule!
584	Every 2 weeks is excessive
619	When and how is the MAH notified?
676	MAH to be notifed

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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Submission of comments on 'GVP Module IX – Signal management' (EMA/827661/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	When there is access to the EV database it means that specific data sets are available to the Marketing Authorisation Holders. CA are implementing a worksharing process to divide actives over the different countries. It then seems not sensible for MAH to do exactly the same review of the actives. Such a scenario does not seem to fulfil the intentions of the new legislation which were reduction of duplication of effort, bureaucracy and simplification. Therefore MA holders should complete signal detection on their own data only and not include the third party eudravigilance data in their review. The signal management program could indicate that in case of a possible signal the EV database should be researched for additional data.
	Signal communication (timelines, format, prioritisation of signal communication) might be defined in more detail

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 - 124		Comment: We do acknowledge the fact that other sources of information include the internet, digital media (such as public websites, social networks, blogs) or other systems through which patients and consumers may communicate adverse experiences with medicinal products. These blogs/internet for a are places where patients communicate with and assist each other and help each other coping with their diseases. It is questionable whether the content of such internet fora represents a body of data of sufficient quality and reliability to trigger signal communication in and of them. Proposed change (if any): Limit the search to media for which the MAH sponsors or controls a site. If a MAH becomes aware of a potential signal relevant internetfora could be used to support the finding.
235		Comment: grammar correction Proposed change: Add "*into*" (taken into account)
299-302		Comment: One ICSR from a non EU country does not by definition" fall under the definition of "signal" and should therefore not be discussed as such. If it is identified as a signal it will be prioritised as written. Furthermore detection of cases in Eudravigilance for products not authorised in EU by the MA holder is are not accessible to all MA holders – so the requirement is impossible Proposal:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Delete the sentences 299-302 and replace by: *Signals for products still under first authorisation in EU by the MAH should get prioritised.*
316 - 319		Comment: The application dossier, literature articles and spontaneous reports are usually available to the MAH but non-published information from third party MAHsand national competent authorities are not available. Standard requests for up to 100 signals each month at the authorities is not practical. Proposed change (if any): Specify other information from marketing authorisation holders and national competent authorities should be used if available.
322-324		Comment: Signal assessment: “Summarising information from different data sources also requires the choice of an internationally agreed definition of the medical issue. If no such definition exists, an operational definition should be developed.” This statement seems too general and it is not entirely clear what is the expectation from the MAHs in this respect. Proposal: Clarification is needed
359 - 361		Comment: Temporary measures to ensure the safe and effective use of the medicinal product or to eliminate the risk should be considered, including the possibility of temporarily suspending the marketing authorisation of the medicinal product. Products on the market have a positive risk benefit ratio. A temporarily suspension of the marketing authorisation as a precaution and withholding the product from patients should also be regarded as a risk to the health of of patients receiving the proposed-suspended medication. This should be also taken into

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		consideration. Proposed change (if any): Temporary measures to ensure the safe and effective use of the medicinal product or to eliminate the risk should be considered, including the possibility of temporarily suspending the marketing authorisation of the medicinal product *"but always balanced against the risk inherent in denying patient access to medication*.".
375 - 376		Comment: The PRAC will do the majority of signal assessments and therefore signal assessments should be released immediately by the PRAC. Proposed change (if any): *The PRAC, CHMP, CMD(h) and* Competent authorities should …
386 – 406, 570		Comment: The description of the quality systems and documentation described in this chapter is clearly focused on electronic systems including tracking system, audit trail etc. This guidance should also apply for small and medium sized pharmaceutical companies where only a limited number of case reports maybe collected. This depends also on the risk of the marketed products (e.g. vitamins). Such a sophisticated system is disproportional for SMEs. Proposed change (if any): the quality system used for signal management should be designed appropriate to the anticipated risks of the products.
411 - 412		Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The training should include MedDRA and available signal source databases, as applicable. Training of market research departments in MedDRA or other staff with no medical background is disproportionate since there is no need for such staff to use or understand MedDRA. Training is necessary and should be appropriate to the asks undertaken by each employee Proposal: This combination of training systems for GxP and non-GxP sectors should be deleted from an official guidance.
556 - 560		Comment: "[The marketing authorisation holder:] • shall monitor the data in EudraVigilance to the extent of their accessibility [IM Art 22(2)]... The frequency of the monitoring should be at least once monthly…" The search in Eudravigilance is performed per active substance, so it does not seem realistic for companies with a large portfolio of products such as generics. CA are dividing the actives over the countries in a worksharing process. It does not make sense for MAH to do duplicate the actions. It is not consistent with the intentions of the new legislation which were reduction of duplication, bureaucracy and simplification. MAH should therefore be required to perform signal detection on their own data only and not include the third party eudravigilance data in their review. The signal management SOPscould indicate that in case of a possible signal from the company data, the EV database should be researched support or disprove the signal.
566 - 567		Comment: "[The marketing authorisation holder:] should notify as an **Emergency** Safety Issue (see Module VI) **any** safety issue arising from its signal detection activity;" (1) Is this section referring to "VI.C.2.2.6. **Emerging** safety issues" in Module VI" (rather than "Emergency")? (2) It will be helpful if more examples were provided as to what is the meaning of "**any** safety issue"? -- If, 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')*
		example, a need to update the product's labelling was recommended during the signal management process – is that something the MAH is expected to notify forthwith as Emerging Safety Issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (as per Module VI, section VI.C.2.2.6.)? Proposal: Clarification and correction of "Emergency" into "emerging" is needed. "shall validate any detected signal and shall forthwith inform the responsible competent authority *in the timing appropriate to the signal possible public health impact and impact on the risk/benefit profile of the medicinal product*"

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
MHRA Pharmacovigilance Inspectorate

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Section IX.B.1, Lines 91-92: "Competent authorities should ensure they are informed in a timely manner of adverse reactions notified to reporting systems managed by other institutions or organisations". What is the expectation with respect to NCAs obtaining information from registries or other organised data collection systems managed by non-commercial, non-governmental organisations? If there is no legal basis for NCAs to request this information, then this objective may be difficult to achieve.	
	In this GVP the terms benefit-risk and risk-benefit are both used. There should be consistency within the GVP and across different GVPs.	

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)*
99-103		***IX.B.1. Data sources for signal management*** Comment: suggested text improvement. "Signals from spontaneous reports may be detected from individual case safety reports (ICSRs), included in adverse reaction databases, articles from the scientific literature, periodic safety update reports (PSURs) or other information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments) or the on-going benefit-risk monitoring of medicinal products". Proposed change: "Signals from spontaneous reports may be detected from individual case safety reports (ICSRs), ~~included in~~ adverse reaction databases, articles from the scientific literature, periodic safety update reports (PSURs) or other information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments, Risk Management Plan updates) or from the on-going benefit-risk monitoring of medicinal products".	
115-117		***X.B.1. Data sources for signal management*** Comment:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		"Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific and medical literature for those journals/active substances not included in the list screened by the Agency". Proposed change: We believe that the text "for those journals/active substances not included in the list screened by the Agency" is incorrect in this context and should be deleted. The purpose of the Agency literature screening is to identify ICSRs. MAHs are still expected to screen literature (including publications on the list screened by the Agency), for the purpose of ongoing signal evaluation i.e. this may include identifying articles that do not contain ICSRs, but which contain important new safety information. Without this amendment, there could be an important gap in literature monitoring.	
137		***IX.B.2. Methodology for signal management*** Suggested text improvement. Comment: "Different factors may be taken into account for the prioritisation of signals, namely the fact whether…". Proposed change:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		"Different factors may be taken into account for the prioritisation of signals, namely ~~the fact~~ whether…".	
157-158		**IX.B.3.1. Introduction** Comment: "when a signal is detected from aggregated results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data". Proposed change: The meaning of this sentence is unclear. Does it actually refer to aggregated results from multiple studies? MAHs are generally expected to review and assess individual cases from studies that they sponsor and this text appears to suggest that they do not need to do this. In addition, the meaning of "may require collection of additional data" is unclear. Perhaps an example would be useful.	
205-207		***IX.B.3.2.2. Statistical analyses in large databases*** Comment: "Given the limitations of these methods, a signal of disproportionate reporting does not necessarily indicate that there is a signal to be further investigated or that a causal association is present".	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: This sentence seems incomplete. Suggested update to: "Given the limitations of these methods, a signal of disproportionate reporting does not necessarily indicate that there is a signal to be further investigated or that a casual association is present and so potential signals identified via these methods should be reviewed for appropriateness prior to full signal validation".	
224-225		***IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports*** Comment: "Where signal detection used an automated screening of a database, the corresponding ICSRs should be individually reviewed". Proposed change: text improvement - Where signal detection uses an automated screening of a database, the corresponding ICSRs should be individually reviewed".	
230-233		**IX.B.3.3. Signal validation** Comment: "When a signal has been detected, an evaluation of the data supporting the signal should be performed to verify that the	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, and therefore to justify further assessment of the signal [IM Art 25(1)]". Proposed change: While it may not be appropriate to include a timeline for the evaluation of a detected signal, it may be useful to include the word promptly i.e. "When a signal has been detected, an evaluation of the data supporting the signal should promptly be performed to verify that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, and therefore to justify further assessment of the signal [IM Art 25(1)]". We have observed instances where MAHs have failed to investigate in a prompt manner identified signals.	
237-239		**IX.B.3.3. Signal validation** Comment: "Strength of evidence for a causal effect (e.g. number of reports, taking into account exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders)".	

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		Proposed change: We think it is important to state that the absence of this detailed information should not result in the signal being automatically dismissed. For example, it is not often with spontaneous data that you will have all those data elements within all the cases, but the absence of the information does not imply that the risk is not real.	
261-263		**IX.B.3.3. Signal validation** Comment: “Signal becomes a validated signal if the verification process of all relevant documentation is suggestive of a new potentially causal association, or a new aspect of a known association, and therefore justifies further assessment”. Proposed change: text improvement – “A signal becomes a validated signal if the verification process of all relevant documentation is suggestive of a new potentially causal association, or a new aspect of a known association, and therefore justifies further assessment”.	
268-273		**IX.B.3.3. Signal validation** Comment: “Signals for which the verification process is not suggestive of a new potentially causal association or a new aspect of a	

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		known association are not-confirmed but may deserve special attention in subsequent analyses. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at adequate time intervals to ensure that all relevant cases are considered". Proposed change: This paragraph could be clearer and could confirm that when there is not enough evidence to confirm the potential signal at the initial verification stage it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm or refute the signal. "Signals for which the verification process is not suggestive of a new potentially causal association or a new aspect of a known association is not confirmed, ~~but~~ may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm or refute the signal. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered".	
299-302		**IX.B.3.4. Signal analysis and prioritisation** Comment: "If the marketing authorisation application for a new active	

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		substance is still under evaluation by a national competent authority and a safety signal is reported from a third country where the substance is already authorised, or a severe adverse reaction arising from that third country is detected in EudraVigilance, this signal should also be prioritised". Proposed change: If application is a national one, then safety signals from other Member States where the substance is already authorised (e.g. by a different MAH) may also be important. Perhaps a change should be made to address this e.g. remove the reference to third country.	
278-310		**IX.B.3.4. Signal analysis and prioritisation** Comment: This section describes that signals can be/should be prioritised and what information should be considered when prioritising. However, there is no guidance or examples relating to what types of action could be taken based on the priority outcome. For example, if a signal is given a "high priority" what does that mean?	
311-334		**IX.B.3.5. Signal assessment** Comment:	

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		Elements in this section appear to duplicate some of the requirements/processes that occur at the signal validation step. Proposed change: We recommend that this section should clearly describe what is required during the signal assessment stage that is not required at the validation or prioritisation stage. At the moment both steps seem very similar. In addition, a clarification could be included in line 149 that some activities that are suggested at the signal assessment stage may have already been completed at the signal validation stage.	
332-334		**IX.B.3.5. Signal assessment** Comment: "For a new signal of a severe adverse reaction, temporary measures could be taken if the first stage of the assessment based on information already available concludes that there is a potential risk that needs to be prevented". Proposed change: strengthening of text – "For a new signal of a serious or severe adverse reaction,	

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		appropriate temporary measures should be taken in a timely manner if the first stage of the assessment (based on information already available) concludes that there is a potential risk that needs to be prevented".	
359-361		**IX.B.3.6. Recommendation for action by competent authorities** Comment: "Temporary measures to ensure the safe and effective use of the medicinal product or to eliminate the risk should be considered, including the possibility of temporarily suspending the marketing authorisation of the medicinal product". Proposed change: There is no mention in this section of updates to product information, which is one of the most common outcomes of signalling activities. We suggest that this should be added.	
372-374		**IX.B.3.7. Exchange of information** Comment: "Validated signals that may have implications for public health and the benefit-risk profile of the product in treated patients should be immediately communicated to the competent	

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		authorities, and when appropriate this should include proposals for action". We understand the desire for NCAs/EMA to receive only validated signals. However, on some occasions it may take an MAH considerable time to validate a signal. There may be some occasions where it would be appropriate for an MAH to have an early discussion with authorities about a potential high priority signal (even if not fully validated), in order to allow the MAH and authorities to work together on the validation exercise e.g. authorities may have access to EudraVigilance data that is not accessible to MAHs (e.g. in the first couple of years after implementation of the new legislation).	
381		**IX.B.4.1. Tracking** Comment: "Tracking systems need to be documented and should include also signals…". Proposed change: "Tracking systems need to be documented and should also include ~~also~~ signals…".	

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397		**IX.B.4.2. Quality systems and documentation** Comment: "(including integrity when transferred)" – the meaning of this phrase should be clarified. What transfer does this refer to?	
403		**IX.B.4.2. Quality systems and documentation** Comment: "Audit trail should also allow traceability of how validated signals have been investigated". Proposed change: text improvement - "Audit trails should also allow traceability of how validated signals have been investigated".	
437		***IX.C.1. Roles and responsibilities*** Comment: "a work sharing may be introduced". Proposed change: text improvement - "~~a~~ work-sharing may be introduced".	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
465-466		**IX.C.1.1. Roles and responsibilities of the Agency** Comment: "following consultation with the PRAC may publish a list of medical events that have to be taken into account for the detection of a signal [IM Art 23(3)]". Proposed action: We assume that this refers to a list of 'Alert' terms that on the receipt of a new case would always flag the case as a potential signal in both automated and manual signal detection activities. If that is the case then it should be made clearer as there is room for misinterpretation.	
476-477		**IX.C.1.1. Roles and responsibilities of the Agency** Comment: "should prepare a technical document establishing common triggers for signal detection and describing EudraVigilance data outputs and statistical reports". Proposed action:	

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		Our understanding is that routine signal detection should be ongoing at all times and should not be initiated based on certain triggers. Does the first part of this sentence actually refer to scenarios that would trigger signal review/validation? Please clarify.	
486-487		**IX.C.1.1. Roles and responsibilities of the Agency** Comment: "where the validity of the signal is not confirmed within 15 days, no further action shall be required". Proposed action: If new information is received at a later date, then further action may be required after further analysis. The Implementing Measure states, "However, non-validated signals may merit special attention in the case of subsequent signals". In addition, even if the signal is not validated at this stage, EMA and NCAs may request the MAH to provide additional information or perform additional analyses, if considered appropriate. Should text to indicate this be included?	
494-496		**IX.C.1.1. Roles and responsibilities of the Agency** Comment:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		"should collaborate to the signal validation performed by a national competent authority that detected a signal involving a centrally authorised products or an active substance for which the EudraVigilance data monitoring is performed by the Agency". Proposed change: English usage - "collaborate" should be changed to "contribute", or to "should collaborate with the NCA that detected a signal with regards to the signal validation…".	
509-510		**IX.C.1.2. Roles and responsibilities of the lead/co-lead Member State** Comment: "where the validity of the signal is not confirmed within 15 days, no further action shall be required". Proposed action: If new information is received at a later date, then further action may be required after further analysis. The Implementing Measure states, "However, non-validated signals may merit special attention in the case of subsequent signals". In addition, even if the signal is not validated at this stage, NCAs may request the MAH to provide additional information or perform additional analyses, if considered appropriate. Should text to indicate this be included?	

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514-516		Comment: "should collaborate to the signal validation performed by a national competent authority that detected a signal involving an active substances/medicinal products for which it has been appointed the lead or a co-lead Member State". Proposed change: English usage - "collaborate" should be changed to "contribute", or to "should collaborate with the NCA that detected a signal with regards to the signal validation…".	
535-536		**IX.C.1.3. Roles and responsibilities of the national competent authorities** Comment: "where the validity of the signal is not confirmed within 15 days, no further action shall be required". Proposed action: If new information is received at a later date, then further action may be required after further analysis. The Implementing Measure states, "However, non-validated signals may merit special attention in the case of subsequent signals". In addition, even if the signal is not validated at this stage, NCAs may request the MAH to provide additional information or perform additional analyses, if considered appropriate. Should text to indicate this be included?	

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558-560		**IX.C.1.5. Roles and responsibilities of marketing authorisation holder** Comment: "The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information". It appears inconsistent that MAHs will be required to monitor EV on a monthly basis (when this is possible), but no periodicity for signal detection activities is recommended for the MAH's analysis of other data available to it (in earlier sections of the GVP). Flexibility is desirable, because what is appropriate for a well-established generic product for which there are no current safety concerns, and for which the MAH receives very few ICSRs, is different from what may be appropriate for other types of products.	

Please add more rows if needed.

<18 April 2012>

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

Comments from:

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

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

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
98-102		Comment: The inclusion of "PSURs" in this paragraph contradicts with the content from Module VII (Periodic safety update report) which states that: "The PSUR should not be used to provide the initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted" (lines 201-203 from Module VII). Proposed change: Therefore, we propose to remove "periodic safety update reports (PSURs)" from this paragraph.
121-126		Comment: Reference is made to the second and third sentence in the paragraph referring to "other sources of information (such as internet, digital media etc) that reads as follows: "Marketing authorisation holders and competent authorities should try to gain further information related to reactions they become aware of from such sources. If the available information is limited, suspected serious adverse reactions should be confirmed if possible in other data sources such as EudraVigilance." Proposed changes: 1. Delete the second sentence (starting in line 123: Marketing authorisation holders and competent...) from Module IX, as this is a repetition of the requirements outlined in greater detail in Module VI (Management and reporting of adverse reactions to medicinal products). 2. The third sentence (starting in line 125: If the available information is limited...) should be rephrased to allow for a balanced risk-based approach. The clause "but despite this potentially indicative of an impact on the risk-benefit balance of the product or have implications on public health" should be inserted into this sentence to than read as follows: "If the available information is limited but despite this potentially indicative of an impact on the risk-benefit

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		balance of the product or implications on public health, suspected serious adverse reactions should be confirmed if possible in other data sources such as EudraVigilance."
464 - 465		[The Agency] following consultation with the PRAC may publish a list of medical events that have to be taken into account for the detection of a signal [IM Art 23(3)]; Comment: It is unclear what this refers to. Is this: • A list similar to the IME spreadsheet from EMA which is already available? • A list of terms to search for a specific signal (e.g. a listing similar to and possibly duplicating MedDRA SMQs)? • A list of specific signals that must be regularly monitored with signal detection activities for all active substances? Proposed change: Additional clarification is needed.
466-474		Comment: It is unclear if the Agency shall support the monitoring of the data in the EudraVigilance database by providing the specified accesses also for MAHs. Proposed change: Specify if the Agency will support the specified accesses also for MAHs or only for the authorities. In case more meaningful reports cannot be supported in time, a monthly routine review of data in the format alone as specified in Annex 2 of the EudraVigilance access policy document by the MAH is far more an administrative task than a useful monitoring activity in the interest of pharmacovigilance. A transitional period may be appropriate.
471-473		[The Agency ... shall support the monitoring of the data in the EV database by providing access to] customised

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		grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction; Comment: Would any of the stratification of data by at risk patient groups allow for clear differentiation of non-therapeutic usage of company products (overdose, abuse, misuse, off-label use) opposed to therapeutic use? It would be useful to have a tool to discriminate in such way.
557 - 559		"…The frequency of the (EudraVigilance) monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information [IM Art 25(2)]" Comment: • This needs clarification as "…shall be proportionate…" could only mean more frequent than monthly not to be conflicting with "…at least once monthly…" • Does "EV monitoring" mean as of 2012 via Webportal access or as of 2014/15 via Data warehouse and monitoring including the use of the analysis functionalities provided.
584-585		For products subject to additional monitoring (see Module X), the frequency for reviewing the statistical outputs should be every 2 weeks... Comment: see comment above concerning frequency for reviewing.

Please add more rows if needed.