29 September 2017
EMA/647795/2017

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

Module IX Addendum I –Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions

The draft of this module was released for public consultation between 8 August 2016 and 14 October 2016. The module has been revised, taking the comments received into account.

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

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

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

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

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

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

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1. General comments

Stakeholder number	General comment
	AESGP would ask for a clarification as to 'section IX. Add I.2.2 Increased ICSR reporting frequency' as further detailed below.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
194 - 224		**Comment**: This section IX. Add I.2.2 Increased ICSR reporting fr address the requirement of Module IX on detecting signals related including change in the frequency, duration, severity or outcome c methodology related to these aspects would be welcome.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14SEP2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

Name of organisation or individual
CSL Behring

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	
	Whilst the analysis and recommendations proposed appear sensible for products with large datasets, no guidance is proposed for what may or may not be appropriate for products with small datasets and small numbers of adverse event reports per year. Many of the proposed recommendations for listings and analysis in the report are not necessary, and could constitute a significant burden in circumstances where report numbers are sufficiently low that they can be reviewed individually. Whilst this is acknowledged in the section on statistical methods, it is not acknowledged in further sections such as those for specific patient populations etc. Some guidance as to the volume of reports required for certain analyses to produce meaningful results, such as subset analyses, would be helpful.	

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')*
39-43		Comment: We appreciate the complexity of the tasks to evaluate and implement signal detection algorithms that are suitable for a given database. We would, however, support the recommendation of the IMI PROTECT to 'a framework for selecting the best quantitative signal detection algorithm to suit the organisational goals and resource available within a pharmacovigilance group'. Proposed change (if any): We suggest EMA to consider providing more guidance on such a framework. Such a generic framework approach would provide a number of potential benefits such as: - Increased comparability for approaches across industry due to better standardization - Increased comparability of signal detection results - Greater clarity for small to medium size companies with spontaneous report databases that may be a order of magnitude smaller than any database that has been used so far to develop the existing recommendations. Small and medium companies most likely to not have the skills and resources to conduct the expected research within the short implementation timelines, especially in a situation where there is little to no public experience with small databases available. Specific guidance by the agency for small databases, therefore, would be highly appreciated.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	
156-157		Comment: This statement contradicts earlier advice that setting a threshold too low will result in large, potentially unmanageable, numbers of SDRs to investigate. Proposed change (if any): Remove the statement that a threshold above 1 might lead to missing an adverse reaction, as it is not helpful.	
169-170		Comment: Similar statements in earlier text have been referenced. Proposed change (if any): Provide a reference for this statement.	
307-307		Comment: Displaying each DEC in the signal detection listing with counts for each category is a very data-dense solution, and not very useful for products that receive very few of these types of reports. Proposed change (if any): Suggest separate listings of cases that contain one of these circumstances, or PT counts of all events in cases that report one of these special circumstances. For products where there are known issues, or where the consequences of misuse/medication error are serious may warrant additional listings/counts, but this judgement should be made on a product specific basis.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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14 October 2016

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

Comments from:

Name of organisation or individual
EFPIA [redacted]

Summary of contents of the EFPIA response

1. General comments on **GVP Module IX**
2. EFPIA responses to the questions raised by the EMA on **GVP Module IX**
    a. Response to question 1
    b. Response to question 2
    c. Response to question 3
3. Specific comments on **GVP module IX**
4. General comments on GVP Module IX **Addendum I**
5. Specific comments on GVP Module IX **Addendum I**

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1. General comments

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

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

2. EFPIA responses to the questions raised by the EMA

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

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

3. Specific comments on GVP Module IX

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
100		**Comment:** Changes in population distribution should be included as a possible cause for raising a signal and as the text refers to known association, this should be adverse reaction, rather than adverse event **Proposed change:** New aspects of a known association may include changes in **distribution (e.g. gender, age and country),** frequency, duration, severity or outcome of the adverse ~~event~~ **reaction**.
112		**Comment:** The EU signal management process described is that of the EMA and Competent authorities, it should be noted that MAHs processes may differ. **Proposed change:** The EU signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR Art 21(1)]. **MAHs may have an alternative process but should encompass the general principles of the EU signal management process.**
128		**Comment**: Confirmation of a new aspect of a known association should be included. **Proposed change:** Add: "nor a new aspect of a known association" i.e. "The fact that a signal is confirmed does not imply that a causal relationship **nor a new aspect of a known association** has been established, but that the signal should be discussed at EU level and further investigated by PRAC (see IX.C.4.)."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
147-152		**Comment:** In this definition, Emerging safety issue applies to authorised medicinal products and GVP Module VI is referenced. However, in GVP Module VI (Rev 2) Section VI.C.2.2.7., the notification of emerging safety issues is also applicable in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, when information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the medicinal product under evaluation may become available to the applicant. **Proposed change**: A safety issue considered by a marketing authorisation holder in relation to an authorised medicinal product **(or product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation**) under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit balance of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals.
161-172		**Comment:** Although implied with current text consider to make clear that sources for identifying signals can also stem from information within a drug class and in addition may not be limited to drugs used for one indication. **Proposed change**: Add: "information on class effects" and "information from use in other indication(s)".
163		**Comment:** This text is tailored to the process at the NCA/Agency level. However, as the MAH also performs signal detection, the sources for signals should apply to the MAH as well. **Proposed change:** "... provided ~~by marketing authorisation holders~~ in the context of regulatory procedures (e.g. Risk..."
173-175		**Comment:** Signal detection is generally based on periodic monitoring within the MAHs safety database, with supplementary information being derived from the larger databases.

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
263		**Comment**: How a signal is managed depends on the prioritisation and this defines the timelines, add reference to these. **Proposed change:** Add "For timelines refer to IX.C.3"
IX.B.5 Lines 269-294		**Comment**: This section only refers to MAHs being required to provide documented evidence of appropriate signal management practices but can the Agency confirm that these quality system requirements will apply across all MS who are delegated signal detection responsibilities in EV for NAPs and medicinal products authorised via MRP/ DCP? How will the HMA or the Agency ensure that all MS staff are performing signal management activities consistently and are trained appropriately? Signal detection responsibilities should follow the same expectations as the MAHs. **Proposed change**: Through the HMA, MS will ensure that any signal detection delegated to a MS for e.g. nationally authorised or MRP/ DCP authorised products is subject to quality management principles.
299		**Comment:** In order to avoid any uncertainties, please mention that both MAHs and CAs should monitor the safety of medicinal products in the EudraVigilance database. **Proposed change**: Just below the heading, please add: "Marketing Authorisation Holders and Competent Authorities should monitor the safety of medicinal products in the EudraVigilance database."
331-333		**Comment:** It is stated that monitoring of EV should be performed to determine new or changed risks. It is not mentioned that it should be performed to detect signals. Recommend adding clearer intention for EV monitoring by stakeholders. **Proposed change:** Add "Monitoring of EudraVigilance is a mandated signal detection activity according to the DIR."
Lines 338-340		**Comment:** There is no timeline provided for the Agency to grant narrative access for the MAH. **Proposed change:** Please consider addition of a timeline for narrative access for MAH.
341		**Comment:** "The review of the electronic reaction monitoring report suggests a signal (see IX.A.); " First time the electronic reaction monitoring report is mentioned in the document – this report should be more clearly defined.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Define earlier in document.
347-348		**Comment:** The wording confuses the concept of a signal before and after validation. Furthermore, the case narratives may be relevant for signal assessment, as well as validation. **Proposed change:** Move the following statement to the start of Section IX.C.2.1: "When validation or assessment of a signal is supported by data from EudraVigilance, marketing authorisation holders should take information from the case narratives into account, as applicable."
368		**Comment:** Term "Active substance" does not specify the brand for the MAH. Is the expectation that all products with the same active substances must be reviewed by all MAHs? **Proposed change**: Can it be clarified that each MAH reviews their own products.
IX.C.3.2. and IX.C.3.4.		**Comment:** The concepts signal validation and assessment are mixed up. Variations are required to be submitted within 3 months after signal validation. But, at signal validation it is not clear yet if a label variation is anticipated. This can only be recommended after full assessment of the signal. After the signal validation step the MAH needs to carry out further work on assessing the signal, determine causality, agree core labelling impact and prepare and submit SmPC. Depending on the issue, its priority and complexity, three months for the full assessment may be challenging. **Proposed change:** Change the timeframe to 6 months (or Day 180 of signal).
416-421		**Comment:** First sentence of paragraph is too complex and needs editing because the criteria for notification should be simple and immediately understandable. **Proposed change:** Change wording to "If a validated signal is discussed in the frame of a PSUR within 3 months, a standalone notification is not necessary."
439		**Comment:** Signal notification as soon as possible and no later than 30 days: depending on the complexity of the signal this timeline may be too tight for MAHs to come to a sound conclusion whether a variation is required because this needs a thorough signal assessment and not just signal validation. **Proposed change:** The module should describe how to handle situations in which the MAH concludes that a

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		variation is needed after the signal notification was sent out.
447		**Comment**: For a generic drug, if a signal was confirmed by a generic company and the PRAC decides that it will undergo PRAC analysis and prioritization we request that the originator MAH will be informed promptly. **Proposed changes:** Include text that provides for prompt notification of the originator MAH for confirmed signals with generic medicines. EFPIA seeks clarification of what action(s) are required by the originator MAH following this notification.
Lines 477-478 Lines 553-554		**Comment:** Some instances occurred in which additional MAH(s) were requested to comment on an adopted PRAC recommendation, which already included additional data requested from MAH(s). **Proposed change:** To prevent this unwarranted situation it is suggested to either improve the identification of MAH(s) needing to provide additional data or to indicate in Figure IX.4 that there can be multiple rounds of need for additional data and MAH(s) submitting additional data to all PRAC members (NAPs) and EMA (CAPs and NAPs).
Lines 541-555 (end) Appendix 1, Figures 1-		**Comment:** We refer to the General comment on the Role of the MAH. The contributions of MAHs should be acknowledged and clarified in the process flow diagrams. **Proposed change:** Add a macro-flow diagram with timeframes as requested under 'General Comments'. All four diagrams should be modified to acknowledge the contribution of MAHs to signal detection. EFPIA PVEG will offer to assist, if this is considered acceptable.

4. General comment on GVP Module IX Addendum I

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

5. Specific comments on GVP Module IX Addendum I

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

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

Name of organisation or individual

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
FARMAINDUSTRIA	It seems that the GVP Module IX Addendum I covers and suggests some methodology that can be applicable to big companies with big safety databases. However, there is no method explained for small-medium companies who cannot perform disproportionate reporting or other statistical analyses because its database does not contain enough data. Could it be possible that the Addendum I contained also a description or some examples of methods that could be used by small-medium companies?
FARMAINDUSTRIA	We would like to make a comment on the signal detection process that all the MAHs will have to perform in Eudravigilance database. As the data that will be analysed by all the stakeholders will be the same and proportion ratios are going to be provided in reports generated by EMA, it could be useful to define some common rules in order that data are analysed in the same way. In this sense, could it be possible to establish a specific threshold(s) in order to define if we have a signal of disproportionate reporting or not?

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

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

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

The Guild of Healthcare Pharmacists (GHP) supports the proposed changes made in this Addendum to GVP Module IX as it adequately describes the components of an effective system for routine scanning of accumulating data, and adequately lists the methodological aspects that should be considered in detecting potential signals.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 295		**Comment:** The list of examples should include falsified medicinal products as these are now mentioned in GVP Module VI **Proposed change:** Line 295 should read: "adverse reaction, e.g. abuse, misuse, overdose, medication error, occupational exposure, or **falsified medicinal product**.
Line 296-297		**Comment:** Following on from the above comment, falsified medicinal products should be included **Proposed change:** Line should read: "IX. Add I.5.1 Abuse, misuse, overdose, medication error, occupational exposure or falsified medicinal product"
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<October 11th, 2016>

Draft guideline on good pharmacovigilance practices GVP - Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	This document should be renamed "use of disproportionality statistics methods for signal detection" The title for section I3 and I4 should consequently be changed to take into account that the methods used for those items are also disproportionality methods. It would be good to have an idea of the minimal size of the database allowing using disproportionality statistics methods. It would also be good to give some practical aspects for others signal detection methods.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

Name of organisation or individual
Medicines for Europe
[redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Medicines for Europe welcomes this opportunity to provide comments. As revised module and its addendum are released together for consultation, they are being compared for their clarity, structure and appropriateness of guidance they provide. Unfortunately the addendum is very general and does not provide required clarity as revised GVP module IX does. The addendum discusses various principles with their pros and cons but fails to convey the expectation of agency. The addendum is coming across as theoretical notes than a guidance from agency. Absence of any table, figures or flowcharts makes it difficult to follow and not user friendly.
	Moreover, the provision of a guidance on methodological aspects of signal detection is acknowledged. However, it remains unclear if this guidance should be applied to proprietary databases of each MAH or if it is a general guidance for EV data. The addendum gives general information and describes different considerations but **lacks for concrete thresholds, comparisons of concretized criteria (values, thresholds) leading to a statistical threshold and conclusion on a real signal.** Exact guidance on how MAH have to look at EV data including recommended thresholds is missing. A threshold of 1 in disproportionality analysis seems to be low and there is former evidence of higher thresholds being adequately appropriate to increase sensitivity (Evans et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.) as a threshold of 1 raises the possibility that a large number of false positive results may be generated for a given drug. Using thresholds of PRR>2, Hauben et al. showed that PRR produced more signals, thus increasing sensitivity (Hauben et al.). Statistical analysis and methods discussed strictly refer to spontaneously reported suspected adverse reactions (ICSRs). For statistical signal detection in MAH database, it is not clear if solicited cases (especially those rated as not related) and cases from interventional studies should be excluded from the analysis? The methodological aspects outlined within the current guidance on signal detection may not be applicable for smaller databases, or medium databases. Also the fact that statistical tools and programs may not be available for all MAHs should be taken into consideration. With regard to this, can it be considered that signal detection in EudraVigilance covers this type of analysis within

Stakeholder number *(To be completed by the Agency)*	General comment
	the MAH´s database and MAHs are not requested to further perform signal detection on their own data?

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 69		Comment: Guidance on what is considered as 'too large' a dataset would be welcome.
Lines 69-75		Comment & proposed change: In terms of statistics, we suggest that a statement is added that the review of small databases and/or products may not require numerical / statistical methods but that individual scrutiny of all incoming ICSRs will suffice to fulfil applicable regulation.
Lines 97-98		Comment: "In particular the impact *(94-95: of statistics across whole database or based on subgrouping)* on the false positive rate should be considered." Proposed change: State suggestions of case numbers and other criteria which would result in a not acceptable high number of false positive results.
Lines 119-120		Comment: If the granularity is increased, we have the low level terms, i.e. the finest level of granularity of MedDRA. We would recommend inclusion of the option for terms which are in a higher MedDRA hierarchy, e.g. High level terms or High level group terms etc. Proposed change: "Screening at the second finest level of granularity, i.e. Preferred Term (PT), has **mostly** been shown to be a good choice in terms of sensitivity and positive predictive values**, however, dependent on the specific signal, higher levels of granularity can be more meaningful.**"
Lines 122 - 124		Comment: We suggest that the clarification is added as a practical advice to stakeholders. We agree that in the routine disproportionality analysis (no targeted monitoring), stakeholders may decide to focus their efforts on SDRs from IME origin.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: A subset of MedDRA terms judged to be important medical events (IMEs) is thus considered a useful tool in statistical signal detection **when filtering results for medical review.**
Lines 134 – 161 (especially 146-161) (Thresholds)		Comment: Different threshold influencing items are explained, i.e. lower confidence bound, number of ICSRs, time of the product on the market, but no numbers or thresholds for these items or value of disproportionality statistic or relative risk; Proposed change: Some suggestions for numbers/thresholds of above items subject to each other and finally statistical thresholds for being a relevant medically assessable signal would be very helpful.
Lines 157-158		Comment: As threshold of 1 means everything which occurs more often for one drug than for all others (but is maybe a well-known AE for the former) would be a signal leading to inadmissible, not meaningful high signal numbers, the sentence should be deleted. Please see as well the "general comment" section. Proposed change: Please delete the sentence.
Lines 163-167		Comment: The reference should be more detailed / targeted. Proposed change: The appropriate frequency of monitoring may vary with the accumulation of knowledge of the risk profile of a specific active substance/medicinal product (see IX.C.2**.2. Periodicity of monitoring of GVP Module IX – Signal management (Rev 1)).**
Lines 208-212		Comment: Suggest numbers for ICSRs and related time periods, DEC numbers related to ICSR numbers for the conclusion of a significant change, especially when receiving only limited numbers of ICSRs. Also the threshold for statistical signal detection methods should be provided.
Lines 254-258		Comment: Shall separate pediatric SD become a routine? If so, which age threshold would 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')*
		recommend?
Lines 265-267		Comment: Which statistical thresholds the Agency would recommend for different ranges of numbers of ICSRs?
Lines 268-269		Comment: *'An additional aid to focusing on paediatric safety issues can be provided by a list of adverse events that tend to have more serious outcomes in children than adults[10].'* - Should this be seen as a requirement or only a suggestion? For each way more clarification would be helpful.
Lines 276-279		Comment: Shall separate geriatric SD become a routine? If so, which age threshold would the Agency recommend? The GVP Module PIV – Geriatric Population – to which the paragraph in this addendum refers in this regard is planned for Q4 2016.
Lines 296-308		Comment: Please note that Abuse, misuse, overdose, medication error and occupational exposure are already included in the general SD and can be easily searched there with definition of individual SD criteria. Therefore we would NOT support the routine separated screening of respective terms. Proposed change: Kindly revise the text accordingly.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 September 2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

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

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1. General comments

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

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')*
163 - 167		A one-month interval between consecutive data summaries has been investigated in validation studies for signal detection methods. More frequent monitoring has also been used, for instance for medicinal products under additional monitoring or during intensive vaccination programmes. The appropriate frequency of monitoring may vary with the accumulation of knowledge of the risk profile of a specific active substance/medicinal product (see IX.C.2.). Comment: If no minimum interval is obligatory this paragraph could be misleading and should be deleted. Proposed change (if any): ~~A one-month interval between consecutive data summaries has been investigated in validation studies for signal detection methods. More frequent monitoring has also been used, for instance for medicinal products under additional monitoring or during intensive vaccination programmes.~~ The appropriate frequency of monitoring may vary with the accumulation of knowledge of the risk profile of a specific active substance/medicinal product (see IX.C.2.).

Please add more rows if needed.

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<14/10/2016>

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions'

(EMA/209012/2015)

Comments from:

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

Please find below the answer to the 'Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions' by the REGenableMED consortium.

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	All the partners of the REGenableMED project are aware of the existence of this draft Guideline. We welcome the opportunity to review this Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions.

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 46-47		Comment: Could you please clarify what could be these other methods or give an example? Proposed change (if any):
Line 49		Comment: Please refer to any guidance on the classical disproportionality analysis. Proposed change (if any):
Lines 160- 160		Comment: Should it be highlighted that differing thresholds might be used to define an SDR on a case by case basis? However, it may be expected that differing thresholds might be used depending on whether the product is under additional monitoring or not. Proposed change (if any):
Lines 246- 253		Comment: Specific signal detection measures aimed at recipients of orphan medicinal products seem to be of high value given the low number of patients. Similarly, specific signal detection measures aimed at recipients of medicinal products under additional monitoring (as it is often the case for advanced therapies) seem to be a reasonable precaution. Proposed change (if any):
Lines 296- 308		Comment: Signal detection measures may also be used to identify falsified medicines. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14October 2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Section IX. Add I.2.1, Disproportionate reporting, Lines 121-124		Comment: This section of the guidance recommends assessment of a subset of MedDRA terms referred to as "important medical events (IMEs)". However, there is no definition for this terminology provided within this guidance. We request that the Agency provide a definition for the term, IME, in order to minimize any confusion in interpretation by MAHs and any stakeholders. It is should be further clarified whether an event is determined to be an IME by the Sponsor or MAH, investigator or list of MedDRA preferred terms (PT). If the Agency recommends that Sponsors or MAHs follow the MedDRA PT list as IME, it is important to note that this list is exhaustive and would not provide added value in the assessment of signal detection and management. If this is a Sponsor or MAH –derived list, the requested clarification should include some criteria that Agency expects Sponsors or MAHs to follow in order to determine a list of IMEs. Proposed change (if any):
		Comment: Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2016

Submission of comments on GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)

Comments from:

Name of organisation or individual
Seqirus

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
77-90		Comment: The key assumption of a statistical signal detection system based on disproportionality reporting is that the calculation of the expected value is based on the ICSRs that do not contain the specific product and that these ICSRs contain a diverse selection of products most of which will not be associated with the adverse event. Whilst large spontaneous databases may contain multiple products, no comment/guidance is proposed for whether or not disproportionality analyses may be appropriate for databases with one product/product class or very limited products. Proposed change (if any): General guidance on whether a signal detection system based on disproportionality reporting is appropriate for small to medium sized spontaneous databases containing one product class or very limited products would be helpful to MAHs. In addition, recommendations as to how to derive alternative background rate/incidence for such databases would be helpful.
168-170		Comment: The performance of statistical signal detection has been shown to depend on the nature of spontaneous ICSR database and this appears to be related to the mix of medicinal products included in the database. Proposed change (if any): As proposed for line 77-90.

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