8 March 2017
EMA/164711/2017

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

Module V – Risk management systems (EMA/838713/2011 Rev 2)

The draft of this module was released for public consultation between 29 February 2016 and 31 May 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

1 June 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

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

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

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
	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world (including more than 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually. ACRO welcomes and supports the draft Revision 2 of the GVP Module V – Risk Management Systems guideline. ACRO especially welcomes the focus on implementing the principles of the ICH E2C (R2) Question and Answer document on the Periodic Benefit-Risk Evaluation Report and the ICH E2E guideline on Pharmacovigilance Planning in recognising that risk management planning should be proportionate and targeted to adverse reactions that have an impact on the benefit-risk balance of the product when further characterised and/or if not managed appropriately in clinical practice. The consultation document requested feedback on four specific questions, and ACRO is pleased to answer these as follows: 1. *The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?* It is ACRO's view that the RMP should focus on risks that are important because of their medically significant outcomes for patients or public health. Not all adverse reactions pose important risks, and therefore ACRO considers that the RMP should address a focused list of safety concerns, which will be a sub-set of the product safety concerns defined in the PSUR. 2. *Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as*

Stakeholder number *(To be completed by the Agency)*	General comment
	category 4 studies) be included, for information, in the RMP annex 2? ACRO recommends that these studies should be included, for information, in the RMP Annex 2 so that the tabulated information in Annex provides a complete summary of the pharmacoepidemiological study programme, whether or not individual studies are mandated. 3. *Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?* 4. *Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?* ACRO considers section V.B.10 to be helpful in explaining the relationship between the RMP and the PSUR, and therefore recommends the section is maintained. ACRO further recommends that the section is strengthened by emphasising that not all adverse reactions pose important risks, and therefore the RMP should address a focused list of safety concerns, which will be a sub-set of the product safety concerns defined in the PSUR.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
155 - 216		Comment: Rather than "Without prejudice to the definition of terminology provided in GVP Annex 1", ACRO recommends that, to avoid confusion, the guideline should state clearly that the basic definition of terms is as stated in GVP Annex 1 and that the purpose of section V.A.1 is to further clarify the terminology within the context of risk management planning. Proposed change (if any): State clearly that GVP Annex 1 definitions apply and that the purpose of section V.A.1 is to further clarify the terminology within the context of risk management planning.
251 - 269		Comment: The text correctly states that "The principal organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the competent authorities". However, the section describes only the relevant responsibilities of the marketing authorisation applicant/holder. ACRO recommends that the responsibilities of the competent authorities are also described. Proposed change (if any): Add text to explain the relevant responsibilities of the competent authorities.
271 - 276		Comment: In explaining the advantages of the modular format of the RMP, ACRO recommends retaining the text of the current (R1) version of the guideline that allows for modules to be effectively "locked" until new data needs to be added. ACRO considers this an important point that is missing from the R2 draft. Proposed change (if any): Add the text of the current (R1) version of the guideline that allows for modules to be effectively "locked" until new data needs to be added.
327		Comment: Given that the RMP should consider important risks associated with off-label use (line 186), ACRO recommends that it is made clear whether the term "indications" as used here means only those indications applied for/authorised or also potential off-label indications.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Make clear whether "indications" as used here means only those indications applied for/authorised or also potential off-label indications.
410 - 416		Comment: ACRO recommends that the list of important non-clinical safety findings should also include a summary of any important drug interactions identified in non-clinical studies. Proposed change (if any): Add important drug interactions identified in non-clinical studies to the list of important non-clinical safety findings that should be summarised.
440 – 441 and 449		Comment: The text in line 449 refers to "age/gender/ethnic origin tables" but there is nothing otherwise to indicate that ethnic origin may be an important factor in risk management planning. ACRO recommends that the statement in lines 440 – 441 that "other stratifications should be provided where this adds meaningful information for risk management planning purposes" should be accompanied by appropriate examples (e.g., ethnic origin). Proposed change (if any): Add examples (including ethnic origin) to the statement "other stratifications should be provided where this adds meaningful information for risk management planning purposes".
454 - 468		Comment: The current (R1) version of the guideline includes the statement "Any experience of patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity." ACRO considers this an important point that should also be included in the new version of the guideline. Proposed change (if any): Add the statement "Any experience of patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
775		Comment: ACRO recommends adding "Non-imposed PASS" to table V.3 so that it provides a complete overview of additional pharmacovigilance activities, whether or not individual studies are mandated. Proposed change (if any): Add "Non-imposed PASS" to table V.3.
824		Comment: There is an incorrect reference to "see V.B.7" within section V.B.7. Proposed change (if any): Correct the reference.
1087 - 1100		Comment: ACRO recommends that this section, which explains the relationship between the RMP and the PSUR, is strengthened by emphasising that not all adverse reactions pose important risks, and therefore the RMP should address a focused list of safety concerns, which will be a sub-set of the product safety concerns defined in the PSUR. Proposed change (if any): Add a statement to explain that not all adverse reactions pose important risks and therefore the RMP should address a focused list of safety concerns, which will be a sub-set of the product safety concerns defined in the PSUR.
		ACRO thanks the Agency for this comment opportunity. Please do not hesitate to contact ACRO if we can provide additional information [redacted]

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31st May, 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
AEFI

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	
	Questions on which the Agency seeks specific feedback by means of the public consultation: 1) The priority of the GPV module V should be a focused list of safety concerns and ideally can be cross-linked if applicable with the PSUR. 2) Studies conducted by the MAH but not required or imposed by the competent authority should be included for information in the RMP Annex 2 to have all information compiled and avoid possible risks. 3) The additional risk minimization materials as they were distributed in the member states should be included in the annexes of the RMP to ensure traceability and periodic distribution of versions if necesary. 4) Section V.B.10 should be maintained as PSUR is a source of safety concerns.	

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')*	
1409		Comment: Taking into account information collected into: [**359 V.B.4.1 General considerations for generic products and advanced therapy 360 medicinal products** ***361 V.B.4.1.1. Generics*** 365 RMP summaries for most recently approved 366 centrally authorised medicinal products (CAPs) are published on EMA website[3]. The CMDh has 367 published the summary of safety concerns for selected medicinal products for which an RMP is in place, 368 on the CMDh website[4].] And the importance the role of national competent authorities to implement DIR Art 106, we consider very useful if it could be confirmed or specified that the implementation will be performed before Module V should be effective or timelines to implement DIR Art 106 should be specified, because transparency is very important and it will have a great repercussion. Proposed change (if any):	
		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')*	
		Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

<30 May 2016>

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	AESGP overall appreciates this second revision of the guideline on good pharmacovigilance practices "Module V – Risk management systems" and believes that the document is more pragmatic than its previous version. However, **guidance on implementation of the new template will be required**. Indeed, it is proposed that the new template will be mandated prospectively for new and updated risk management plans (RMPs) from a certain date with an appropriate transition period. During the transition period, adoption may be optional and may be partial for RMP updates, such as move to new tables whilst leaving other sections unchanged. Its **impact on the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh) initiative to publish the list of safety concerns per approved RMP of active substance per product should be considered**. Marketing Authorisation Holders (MAHs) would hence welcome the opportunity to discuss this as part of the CMDh ad hoc group on RMP initiatives. There **will be a period of misalignment as MAHs refocus their safety concerns**; it is these refocused safety concerns that should be published and used for harmonisation across MAHs and for use by generic companies for their RMPs. There may be a period where generic companies only have access to the previously published safety concerns of an innovator which may not be aligned to the clarification as provided in the revised GVP module. The **increased emphasis on life cycle management for the RMP, with removal of safety concerns and omission of modules for certain products is welcomed**. However, clarification is required as to the RMP modules which can be omitted for established actives on market for more than 10 years and not approved by the legal routes specified in the GVP template – this is not clearly stated in the GVP module, but is referred to in the template. Furthermore, there may be 'new' or 'initial' MAAs for established actives on market for more than 10 years. Lines 1192 to 1198 of the GVP module V (Section V.C.1.1. 'Risk management plans with initial marketing authorisation applications') should be further clarified to state that submission of all parts of an RMP would not be required for actives on the market for more than 10 years. A simplified RMP for these product types was an important part of industry proposals for this GVP revision. **Allowance for**

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	omission of modules and for reduced or, in certain cases, no content in other modules as appropriate to stage in life-cycle is an important clarification to make in line with risk proportionality. The acceptance of the concept of proportionate information in the RMP in line with the stage in the product lifecycle is welcome. **Clarity that an RMP can cover multiple products should be provided in the introduction to the GVP module**. Lines 630, 817 to 822, 986-987, and 1009 suggest this is allowed, whereas line 304 refers to the ongoing application only. This allows the MAH to use a single RMP for different applications. **Same simplification should apply to homeopathic medicines under Article 16(2) of Directive 2001/83/EC**. Although the **ability to refer to eCTD sections** is welcome (particularly to the product information - PI) and may be helpful to reduce duplication, **it should be considered that not all products are already transferred into the eCTD format** In addition, this may cause difficulties if the RMP is used for countries outside of the EU, or present other practical issues. **The reference to eCTD sections with use of hyperlinks should, therefore, be optional and not mandatory**. To ease navigation between the GVP module and the template, **AESGP suggests referring to the section number from the template rather than just the part, module and section title**. For instance, in line 602, this would read V.B.4.8.1 RMP Module SVII**.1** 'identification of safety concerns in the initial RMP submission', and **likewise when providing guidance on subsections** such as in line 607, minimise complexity by removing the subheadings number V.B.4.8.1.a and refer to the relevant section number of the template instead i.e. line 607-608 becomes ~~**V.B.4.8.1.a**~~ **RMP Module SVII sections SVII.1.1 and SVII.1.2**. The numbering of the GVP module is quite difficult to follow and errors were noted during review. A **Glossary at the beginning or end of the document with all abbreviations used within the document would be helpful**. For instance, clarification is needed as to meaning of the acronym QRD. **AESGP welcomes reduction of duplication within the RMP**, **but where guidance is duplicated from GVP Module to RMP template, it must always be consistent.** Consideration for reducing the duplication, e.g. by using cross-reference to the

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	template would hence be appreciated. **There is still an unfavourable situation of nationally approved RMPs in parallel procedures as there can only be one current RMP**. Thus the RMP is modified by country, but another submitted or a previous version is approved in other countries and the cycle of resubmissions begins again. Could there be a centrally approved RMP in a similar way to a centrally reviewed PSUR? Even with that, the EU-RMP has additional complications as it may also be used outside of the EU.
	AESGP responses to the four questions on which the EMA seeks specific feedback by means of the public consultation: Question 1: The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? AESGP welcomes the clarification around what constitutes a safety concern in the RMP and accepts the fact that the priority of the RMP should be a focused list of safety concerns, and to that extent may, initially, not always be fully aligned with the PSUR. AESGP considers that the clarification of safety concerns in the revised GVP is a restatement of the intended meaning rather than a new definition. Therefore, the priority should be to introduce the same clarification into the PSUR and hence attain alignment. It is also felt that these clarifications may help with the harmonisation with non-EU countries adopting the EU module and requiring submission of the EU-RMP and minimise instances where safety concerns (not considered so by the company and the Agency) are requested to be added by a non-EU agency. Question 2: Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? This should not be mandatory i.e. be consistent with the legislation. In addition, data from these studies are disclosed via other ways (PAS register for EU voluntary non-interventional trials, PSUR).

Stakeholder number *(To be completed by the Agency)*	General comment
	Question 3: SHOULD THE ADDITIONAL RISK MINIMISATION MATERIALS AS THEY WERE DISTRIBUTED IN THE MEMBER STATES BE INCLUDED IN THE ANNEXES OF THE RMP (I.E. RMP ANNEX 6 – PART B)? No, because they are not part of the RMP assessment per V.B.9.6.2. In addition, presenting additional risk minimisation materials in the RMP annexes as distributed to member states would add unnecessary burden and would not add great value. Furthermore at the time an RMP (or its update) is approved such materials would not be available as they would need to be customised, reviewed by the National Competent Authorities (NCA) before they can be incorporated into the RMP. This would trigger the need for the RMP to be updated even in the absence of other update. Question 4: SHOULD SECTION V.B.10 BE MAINTAINED OR DELETED (I.E. IN THE LIGHT OF THE RMP TERMINOLOGY DESCRIBED IN V.A.1.)? It is useful to keep this section to emphasise the principles of sharing modules between an RMP and PSUR to avoid duplication. However, Table V.4 appears incomplete and it should be recognised that the sections will not always be completely aligned due to difference in time periods.

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')*
159		**Comment**: Any adverse drug reaction (ADR) identified in the clinical programme would meet the definition of identified risk. It should therefore be confirmed that all ADRs which are not considered important i.e. not meeting the definition of safety concern for the RMP should be discussed in SVII.1.2. If confirmed, clarification as to whether this infers that the RMP would need to be updated every time an ADR is added to the Summary of Product Characteristics (SmPC) is warranted. This may also drive consistency worldwide especially for those countries following the EU format or requiring submission of the EU-RMP. **Proposed change**: Please clarify the need or not to discuss all the ADRs, and split them into important versus non important in the RMP in the GVP module SVII or the RMP template (lines 373-381)
162 - 165		**Comment**: Paragraph from line 162 to 165 would only be appropriate in case where the active comparator is within the same drug class. In the case of older active comparators including those from the same class, identified risks may have occurred at a different threshold. Moreover, this does not take into account the severity of an adverse event, which may be more or less for the new product, and as such may impact its importance i.e. as an important identified risk. **Proposed changes**: "In general, a two arm clinical trial~~, the~~ may have a comparator ~~may~~ that can either be a placebo, an ~~–~~active substance or non-exposure. ~~Where~~ If an adverse event which is an identified risk for an active comparator within the same drug class occurs at a similar ~~(active comparator)~~ or higher frequency with a new product, this could suggest~~s~~ that the adverse event should also be an identified risk for the new product."
167 - 169		**Comment**: Wording should be aligned with that of the 'guideline on summary of product characteristics (SmPC)' for consistency (see first paragraph under point 4.8 'Undesirable effects').

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed changes: "An undesirable outcome for which there is a scientific basis for supposition of a causal relationship with the medicinal product (e.g. a signal, a class effect plausible also for the new product, findings from (non-) clinical studies) but where there is insufficient support to conclude that there is no reasonable evidence of a causal association.
178 - 184		**Comment**: Routine risk minimisation is applicable to all risks. **Proposed changes**: "Typically, a potential risk will not be considered 'important' if it has minimal impact on patients or, upon further characterisation, does not require ~~at least routine~~additional risk minimisation activities that are intended to affect clinical practice, even if a strong causal relationship ~~were~~ was found. For example, if a potential risk, once confirmed, requires dose reduction or more frequent monitoring in certain populations, then that would qualify the potential risk as 'important'. If a confirmation of the potential risk as an identified risk would not result on any changes of the monitoring requirements, then such a potential risk would not usually be considered 'important'. Potential risks may be removed from the safety specification in the RMP (see V.B.1). "
214 – 216		**Comment**: This paragraph is confusing. The definitions of safety concern, important identified risk, important potential risk, missing information and safety concern are not different from other GVP modules but merely a restatement of the original intention.
229 - 239		**Comment**: Good that focuses on reducing the list of safety concerns over time. However it is not clear how MAH goes about removing risks such as risks that were required by Competent(s) Authority(ies) when assessing previous RMP; also how CMDh list will be updated with these more focused safety concerns.
236 – 239		**Comment**: Clarification is needed as to what is meant by "long time" (line 237) and whether this is a regulatory timeline, based on scientific evidence or both? Same goes for the term "required risk minimisation measures" (lines 237-238) which is rather vague, as well as the term "standard clinical practice" (line 238). Indeed, there are different "standards" of clinical practice

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		within the EU, which amongst other things justify why risk minimisation plans must be adapted to risk minimisation programs, where additional risk minimisation tools are adapted accordingly. **Proposed changes**: "In certain circumstances, important identified risks may need to be removed from the safety specification ~~(~~e.g. for products marketed for ~~a long~~sufficient enough time (based on scientific evidence) for which the given important risks ~~and the~~with required additional risk minimisation measures have become fully integrated into standard accepted clinical ~~practice~~ standard of care, thereby changing their category to not important.~~us reducing the risk to a level when is no longer considered an important risk)~~."
249 - 250		**Comment**: 'Routine' practice does not necessarily correlate with accepted clinical standard of care. Routine practice in some regions might not be considered *clinically acceptable standard of care* by medical and scientific societies. **Proposed changes**: "The ~~need to continue~~continuation of additional risk minimisation activities may ~~change~~not be needed once accepted as part of clinical standard of care~~; as they become part of the routine practice~~."
264 - 269		**Comment**: The list of safety concerns should also be reviewed if a change in legal status is being proposed, e.g. switch from prescription to non-prescription. **Proposed changes**: "In addition, there are ~~two~~ three specific moments when the MAHs are advised to reflect on the need to review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimisation activities: with the 5-year renewal, ~~and~~ around the submission of the first PSUR following the (first) renewal (usually 8-9 years following the granting of the marketing authorisation – when the assessment of the generic products for the active substance commences) and when a change in legal status (switch from prescription to non-prescription) is being proposed."
270		**Comment**: This paragraph is important and particularly appreciated for non-prescription medicinal products, as

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Nationally Authorised Products with limited information in dossier can put information in RMP to support the risks.
275 - 276		**Comment**: Wrong cross-reference is noted. **Proposed change**: In addition, in specific circumstances certain RMP modules may have reduced content requirements (see V.C.~~2~~1.1).
283 - 287		**Comment**: Not all (nationally) products dossiers have been yet transferred into an eCTD dossier, whether all dossiers irrespective of regulatory activities use the CTD format. **Proposed change** : "However, the safety specifications in the RMP should not be a duplication of data submitted elsewhere; where applicable, the information in the RMP should provide an integrated overview/discussion focusing on the most important risks that have been identified or are anticipated based on pre-clinical, clinical and post-marketing data presented in other modules of the ~~e~~CTD."
292 – 294 (including Table V.2)		**Comment**: Table V.2. is only relevant for initial marketing authorisation applications and/or major updates (extension application or major type II variation). **Proposed change**: "To aid consistency between the information provided in the eCTD and the RMP, Table V.2 indicates where information from the eCTD for initial marketing authorisation applications or major updates is likely to be discussed in the RMP:
295		**Comment**: The inclusion of literature references in Annex 7 should be limited to key references only, with others being provided on request, as it is currently in practice. **Proposed changes**: "Only key ~~l~~literature referenced in the RMP should be included in RMP annex 7".
295 - 296		**Comment**: Reference should be made to the exact section of relevance.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: "This should be in the format of links if already included elsewhere in eCTD (see V.B.9.7)."
300 - 301		**Comment**: Science should be replaced by scientifically **Proposed change**: "The RMP is part of the scientific dossier of a product and as such should be scientificallyee based and not promotional."
308 - 318		**Comment**: The description of the RMP Part I "product(s) overview" is not fully aligned with the corresponding section in the RMP template (see page 9/45). Items described in the module listed from line 308 to 318 (i.e. active substance information and administrative information on the RMP) are not written in table part I.1 in the RMP template. Similarly not all items described in the RMP template (e.g. details of the currently approved RMP) are written in the GVP module. **Proposed change**: A full alignment between the GVP module V and the RMP template should be ensured.
326		**Comment**: The GVP module only refer to the currently approved product information while the RMP may in situations where changes to the approved product information are proposed include a link to the proposed product information in the eCTD sequence. In addition, not all (nationally) products dossiers have been yet transferred into an eCTD dossier, whether all dossiers irrespective of regulatory activities use the CTD format. **Proposed changes**: "eCTD link to the currently approved or newly proposed PI where applicable; in other cases, reference to respective CTD knot either as a hyperlink or in written form should be accepted."
336 – 337		**Comment**: The safety specification is not a formatted presentation of scientific evidence. **Proposed changes**:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 purpose of the safety specification is to provide ~~an~~ adequate ~~discussion~~ scientific evidence on the safety profile of the medicinal product(s), with focus on those aspects that need further risk management activities."
387 - 389		**Comment**: The terms 'racial' and 'ethnic' bear the risk to be understood differently. It would therefore be necessary to make a reference to a scientifically sound document which would clarify what is meant by these; similarly to the FDA guidance for industry 'collection of race and ethnicity data in clinical trials' available and specific to the US population. (same goes to the term 'ethnic' used on lines 449 and 466) **Proposed change**: "The RMP module should include incidence, prevalence, outcome of the target disease (i.e. indications) and relevant co-morbidity, and should when relevant for assessment of safety and risk management be stratified by age, gender, and racial and/or ethnic origin[1] ." (same comment goes to the term 'ethnic' which is used on lines 449 and 466)
423 - 425		**Comment**: It should be clarified that the type of safety concern (explained on lines 423-425) is considered to be a *potential* risk. **Proposed change**: "Where the non-clinical safety finding could constitute as important potential risk to target population, it should be included as a safety concern in RMP module SVIII."
430		**Comment**: It would be useful to have some guidance on when updates to this section may be expected throughout lifecycle as new data become available. **Proposed changes**: "Final conclusions on this section should be aligned with content of module SVII and any safety concerns should be carried forward to module SVIII. This section would only be expected to be updated when new non-clinical data impact the safety specification and/or the benefit/risk of the product."

[1] A reference should be included here

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432 - 435		**Comment**: It should be clarified that this section is of relevance for initial RMP and/or major updates associated with new clinical data. This would not need to be updated for other updates even though the clinical trial exposure is evolving. **Proposed changes**: "In this RMP module, in order to assess the limitations of the human safety database, summary information on the patients studied in clinical trials should be provided in an appropriate format (e.g. tables/graphs) at time of submission of the initial RMP or updated RMM with data from new clinical studies. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time exposed to the medicinal product."
469 - 482		**Comment**: Section SV "Post-authorisation experience" is much reduced and leaves to the discretion of the MAH what to include, i.e. relevant/helpful for risk management planning, which is an improvement.
470 – 472		**Comment**: The new guidance states that "important" risks in the safety specification are not a long list of all events in 4.4 and 4.8, but should focus on those that have an action in the pharmacovigilance plan, or risk minimisation plan. Does this mean that in the new section, "risks not considered important for the safety specification" now requires in section SVII 1.2 description of events in 4.4/4.8 of the label, a statement that routine pharmacovigilance is sufficient? Or does this also include other serious events, which were e.g. seen in clinical trials, but e.g. "confounded by indication"? What would be the threshold for listing an event in this section; state that it is not a concern or not including it in the document?
483 - 489		**Comment**: Please confirm that in section SVI, the additional EU requirements from the safety specification only comprise misuse for illegal purposes and that the other sections in the existing template are not now required to be discussed in this section.
487 - 489		**Comment**: This are straightforward risk minimisation activities (Controlled distribution is an additional risk minimisation strategy, limited pack size and special medical prescription are other risk minimisation tools) designed specifically for risk prevention. (See the practical approaches to risk minimisation for medicinal products from the Council for international organisations of medical sciences (CIOMS) Working Group IX) **Proposed changes**:

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		"● the potential for misuse for illegal purposes, and, where appropriate, the proposed means of limiting this with additional risk minimisation when necessary; e.g. limited pack size, controlled distribution, special medical prescription (see also V.B.7.)."
493 - 494		**Comment**: Please clarify whether safety topics derived from specific situations/data sources should be discussed in this section even if they are not considered to be safety concerns for the RMP (particularly for established products).
493 - 537		**Comment**: It would be clearer and less confusing if the list of safety topics in the GVP module and in the RMP template were consistent.
501 - 511		**Comment**: It would be helpful if the expectations of the Good Practice Guide on risk minimisation and prevention of medication errors could be reflected in the RMP template. The guide requires a stand-alone summary of aggregated data on medication errors in the clinical trials and post-marketing period so it would be good if the two documents were harmonised.
502 - 504		**Comment**: 'Remedies' (line 504) appear to mean risk minimisation measures; this term should therefore be used for consistency. **Proposed change**: "Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible ~~remedies given~~risk minimisation measures provided."
532 - 534		**Comment**: The Good Pharmacovigilance Practices (GVP) on pregnancy and breast-feeding (P.III) is not available yet, so consideration for a revised wording should depend on whether the updated GVP module V will available before the new GVP P.III.
604 - 606		**Comment**: This RMP section refers to 'initial' RMPs and reads as if referring to new products e.g. new chemical entities. It should therefore be clarified as to whether this section would be needed for a first RMP for an established product or for a switch in legal status.

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607 title		**Comment**: The subheading makes it complicated, especially as it is not used in the RMP template. For ease of reference between the GVP module V and the RMP template, it would be better to use the sections' numbers. **Proposed changes**: ~~**V.B.4.8.1.a**~~ **RMP module SVII sections** SVII.1.1 ~~**"Risk considered important for inclusion in the safety specification"**~~ **and** SVII.1.2 ~~**"Risk not considered important for inclusion in the safety specification"**~~
609 – 616		**Comment**: What is the criterion for events to be described? The new guidance seems to clarify, that "important" risks in the safety specification are not a long list of all events in 4.4 and 4.8, but focuses on those that have an action in the PV plan, or risk minimisation plan. Does this mean that in this new section, "risks not considered important for the safety specification", now require a description of events in 4.4/4.8 of the label with a statement that routine PV is sufficient? Or does this also include other serious events, e.g. observed in the clinical trials, but, e.g. "confounded by indication"? What would be the threshold for listing an event in this section; state that it is not a concern or not including it in the document? The expected content or an example for risks that would typically be expected in this section should be given (reference also to line 469-472 of the RMP template). Please clarify. **Proposed change**: "In this RMP section, for each risk, the following information should be summarised and discussed: • [for risks taken forward as safety concerns (include an example of risks that would typically be expected in this section)] the level of scientific evidence of an association (including when relevant a causality assessment); • Seriousness; • Frequency; • Clinical and benefit-risk impact; • [for risks not taken forward as safety concerns (include an example)] the justification for not including

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		them as safety concern."
612 - 614		**Comment**: The information requested here for each risk on scientific evidence for the risk, seriousness, frequency and clinical and benefit-risk impact is asked for again in SVII.3. Can this duplication be eliminated?
615		**Comment**: Regarding risks not taken forward as safety concerns, a justification is required for each. Can additional guidance be included as to what is expected here? This could amount to a very long list of AEs which are not considered to meet the definition of important. This is not considered of value, particularly for products (such as non-prescription medicines) which have been on the market for many years.
617 title		**Comment**: The subheading makes it complicated, especially as it is not used in the RMP template. For ease of reference between the GVP module V and the RMP template, would it better to use the sections' numbers. **Proposed changes**: **V.B.4.8.2. RMP module SVII.2 ~~section "Identification of safety concerns with a submission of an updated RMP"~~**
619		**Comment**: Regarding newly identified risks considered important, can additional guidance be given as to what the expectation is here? Signals evaluated? AEs added to the SmPC?
621 - 624		**Proposed changes: ~~V.B.4.8.2.a RMP module SVII section "Newly identified risks of the product"~~** Data presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1.~~1~~ **~~V.B.4.8.2.b Justification on the safety concerns re-classification (deletion, addition, downgrade and/or upgrade)~~** In addition, ~~W~~when an important risk or missing information is re-classified, added or removed, a justification should be provided in ~~this RMP~~ section SVII.2.2.
633		**Comment**: "This RMP section applies to all stages of the product's life cycle". Clarification as to whether this implies that other RMP sections do not. Otherwise, this sentence should be deleted.

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636		**Comment**: Since it is not possible to provide actual incidence rates of Adverse Events post-authorisation, this item should state "e.g. reporting rates" since it does not appear to only refer to clinical trial data. **Proposed changes**: " frequency (e.g. ~~incidence~~ reporting rates with confidence intervals)"
658		**Proposed changes for clarity**: **V.B.4.9. Part II RMP module SVIII "Summary of the safety concerns"**
664 - 670		**Comment**: The term 'real' should be replaced by 'scientifically substantiated'. **Proposed changes**: "The purpose of the pharmacovigilance plan in part III of the RMP is to present an overview and discuss how the applicant/marketing authorisation holder plans to further characterise the important risks identified in the safety specification. It provides a structured plan for: • the investigation of whether a potential risk is ~~real~~ scientifically substantiated or not • further characterisation of safety concerns including severity, frequency and risks factors; • how missing information will be sought; • measuring the effectiveness or risk minimisation measures."
673 - 674		**Comment**: 'Part II' should be added for consistency. **Proposed change**: "The pharmacovigilance plan should focus on the safety concerns summarised in RMP Part II module SVIII of the safety specifications and should be proportionate to the benefits and risks of the product."
679		**Proposed changes**: **V.B.5.1. RMP part III section III.1 "Routine pharmacovigilance activities"**
715		**Proposed changes**: **V.B.5.2. RMP part III section III.2 "Additional pharmacovigilance activities"**
729 - 730		**Comment**: It needs to be clearer that this piece is referring to PASS studies.
731 - 732		**Comment**: MAAs is usually used as an abbreviation for 'Marketing Authorisation Applications' and not for companies. Therefore would suggest replacing MAAs by applicants, also in line with line 701. **Proposed changes**:

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		"~~MAAs~~ Applicants and MAHs may submit to EMA or national competent authorities PASS protocols for Scientific Advice."
733 - 740		**Comment**: Clarification as to whether an updated RMP, incorporating the draft protocols for part A and B is expected to be submitted when the protocol is submitted for review (which is not the current understanding) or whether the process should continue to follow the same process and consist of a submission of the cover letter/protocol with the protocol to be added once final to the RMP at the earliest opportunity. Furthermore, for those submitted for information only (Part C) – it should be confirmed that such submission of initial protocol and protocol amendments can be done as part of the earliest opportunity and not necessarily prior to study start/implementation would be welcome. **Proposed changes**: "Until completion of the study and submission to the competent authorities of the final study report; protocols for studies in the pharmacovigilance plan should be provided in RMP annex 3. RMP annex 3 – part A should contain protocols ~~submitted for assessment~~ that had been agreed, when the protocol submission has been requested by the competent authority; RMP annex 3 – part B should contain protocol~~s~~ amendments that have been agreed with competent authorities ~~and are being submitted with the RMP for amendment~~, when the protocol submission has been requested by the competent authority i.e. previously in part A; RMP annex 3 – part C should protocols already approved and other category m studies protocols, submitted for information only when available (see V.B.10).
741		**Comment**: Clarify that the final report submission milestone is mandated for all studies, while other are to be agreed on a study by study basis. **Proposed changes**: "~~Milestones, including a~~ The time point for the final study report submission to the competent authority~~,~~ should be included for each study. Additional milestones if requested may need to be added."

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757 - 759		**Comment**: Module V says "Studies not required by the EU or national competent authority should not be included in the pharmacovigilance plan (...)". This should be clarified and clearly stated in the text as proposed below. **Proposed changes**: "Studies required in jurisdictions outside the EU should not be included in the RMP unless they are also imposed, as a condition to the MA or as a specific obligation, or required by the Agency or a national competent authority in EU Member States. Studies required in jurisdictions outside the EU and not imposed or required by the ~~EU~~ Agency or a national competent authority in EU Member States should not be included in the pharmacovigilance plan in the RMP."
757 - 761		**Comment**: Consideration for transitioning of existing RMPs, e.g. removal of studies which no longer need to be in the RMP would be welcome.
789 - 790		**Comment**: Clarification that only studies imposed or included as specific obligations are required to be included is welcome. However, as per the Cat 4 studies, a guidance on transitioning arrangements for removing voluntary studies from this section in approved RMPs via a pragmatic way (i.e. as part of a routine update) would be welcomed.
823		**Comment**: There should be guidance on what is meant by 'regular intervals' in the sentence "The need for continuing risk minimisation measures should be reviewed at *regular intervals*" (line 823). Is it a case-by-case basis or on collective evidence acquired already on the use of particular tools, such as patient alert cards? The term "required risk minimisation measures" is vague. All products have "required" (routine) risk minimisation measures. Same goes to the term "standard" clinical practice. Even within the EU, there are different "standards" of clinical practice, which is one of the reasons risk minimisation plans must be adapted to risk minimisation programs, where additional risk minimisation tools are adapted accordingly.
845 - 848		**Comment:** Could reasons for not including SmPC part 4.3 'Contraindications' be clarified here?
921 - 923		**Comment**: The GVP module seems to refer to the current RMP Annex 6 and this should be corrected. In addition, the text "Protocols for proposed and ongoing studies in categories 1-3 of the section "summary table

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		of additional PV activities" in RMP part III" seems out of place and should be deleted. **Proposed changes**: "Where relevant, details of additional risk minimisation activities should be provided in RMP Annex 6 – ~~Protocols for proposed and on-going studies in~~Details of proposed additional risk minimisation measures (if applicable)~~ categories 1-3 of the section "Summary table of additional pharmacovigilance activities"~~".
926		**Comment**: The acronym of QRD should be spelled out.
941		**Comment**: As the scope of the guidance is EU, the term 'region' should be clarified.
941		**Comment**: Sentence on lines 940-941 seems to call for information on the impact of additional risk minimisation activities to be included when the RMP is updated. Clarity on whether this would be considered for any RMP update (as routine) or whether this should only be associated with specific updates, and trigger of a variation should be provided.
995 - 999		**Comment**: Regarding the summary of the RMP, the agency is clearly taking a different approach with this revision of the Module V. Plain language, rather than lay language, is called for. An example would be helpful, particularly when the intended audience for this section is not specified, even though line 1156 refers to the content, language and format being appropriate to the intended audience.
1012 - 1015		**Comment**: The section V.C.2.'Submission of a risk management plan to competent authorities in the EU' refers to XML file, so does the sentence 'the electronic file should be submitted in accordance to V.C.2.' (line 1014) mean that XML file could also be submitted for products that are still in NeeS or even in paper format? In case where this would only be applicable to centrally authorised products (as noted under V.C.2.), this should also be written and clarified in lines 1014 - 1015.
1025 - 1026		**Comment**: A consistent approach should be proposed and as outlined earlier, there is a risk that such information becomes out-of-date as timelines evolve. It is therefore suggested to remove this as an option, or clarify that this information does not need to be kept up-to-date.
1034 – 1035 & 1042 - 1043		**Comment**: These parts add additional burden and suggest not mandating to update the RMP at time of submission of the draft protocol(s)/protocol amendments as this may require several updates during a

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		procedure to align with the latest drafts and add unnecessary burden to companies/Agency as well non-EU agencies that require all RMP versions to be submitted. The protocol submission should be handled as a standalone post-authorisation measure (cover letter + protocol) and only when the protocol/protocol amendment is considered final, the RMP should be updated.
1047 title		**Comment**: In order to be consistent with the other header which includes further wording, it is proposed to clarify what is under annex 3 – part C. **Proposed changes**: **V.B.9.3.3. RMP annex 3 – part C – approved protocols**
1048 - 1049		**Comment**: based on the previous feedback that Part A and B should contain final agreed protocols, see suggested changes. **Proposed changes**: "~~Previously agreed protocols for on-going studies and p~~Protocols not ~~reviewed~~ previously agreed by the competent authority should be included in this part C of RMP annex 3, as follows:"
1051 - 1052		**Comment**: A clarification is needed as to what is meant by 'the name of the procedure' (lines 1051 – 1052) Does this refer to the general description or a specific procedure number?
1060 - 1061		**Comment**: Confirmation of what needs to be done when follow-up forms are updated is warranted, e.g. this section can be updated at the next earliest opportunity unless the change is significant enough to warrant a review.
1075 - 1082		**Comment**: As per our response to question 3 (here above in the general comments), the additional risk minimisation materials as they were distributed in the Member States should not be part of the RMP, considering that they are not part of the RMP assessment per V.B.9.6.2. Indeed, this will only result in an increase of the overall size of the RMP and will not be of any added value. For example the educational materials for 28 Member States could easily contain 300 pages. We would therefore suggest a deletion of this paragraph.

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		Proposed change : "~~Should include, for information only, the additional risk minimisation materials as they were distributed in the Member States. Materials included in this annex are not assessed and are not considered endorsed as part of the RMP assessment. The content and distribution plan of the additional risk minimisation activities included in the RMP will only be assessed and agreed at national level (e.g. educational materials messages, brevity, target audience,; paper brochure, electronic document; distribution: by MAH representatives, on national competent authority website, with each pack of the product).~~"
1083 - 1084 title		**Comment**: Clarify that not all reference materials need to be provided, but key references only while other should be provided upon request. **Proposed change**:"**V.B.9.7. RMP annex 7: Other supporting data (including key referenced material)**"
1106		**Comment**: Table V.4 appears incomplete. Indeed, the table should include all areas of commonality RMP/PSUR. Otherwise, there should be an acknowledgment that the information will not always be aligned between PSUR and RMP due to differences in time periods and data lock points. In addition, the table seems to indicate that the RMP part II module SV should include "actions taken for safety reasons" (equivalent to section 3 in PSUR) but this is not clear in the description in V.B.4.6 or in the RMP format guidance (template) for part II module SV (lines 318 – 349 of the template). **Proposed change**: Deletion of table V.4
1180 - 1188		**Proposed changes**: 3rd bullet point: "situation where milestones for studies in the pharmacovigilance plan need to change and when their final study report is submitted for which an updated RMP would be expected."
1194		**Comment**: There may be 'new' or 'initial' MAAs for established actives on market for >10yrs. Clarify to state that submission of all parts of an RMP would not be required in such situations. There is no mention of established actives on market for >10 years in Section V.C.1.1 and no clarification of

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		modules of the RMP that can be omitted. However, such information is provided in the template. This is potentially confusing. **Proposed changes**: For established actives on the market for > 10 years, allowing for omission of modules as stated in the template and for reduced/no content in other module as appropriate to stage in life cycle.
1212 - 1213		**Comment**: It should be recognised that, in the period of transition to this GVP module, the safety concerns published on the CMDh website for the originator product may not be aligned to the clarified definitions. Marketing Authorisation Holders should be able to justify non-inclusion on these grounds.
1256 - 1264		**Comment**: There is a need for clarification on how to handle a fixed combination consisting of one new substance and an old one, as the current wording (below) would mean that the new active substance follows bullet point 1, and that the old substance follows bullet point 2 in the paragraph below. "For new applications for fixed dose combinations, there are two situations: 1. The combination contains a new active substance: A full RMP, following the elements as for full initial MAA, should be submitted. RMP modules SI-SVI should focus on the new active substance. 2. The combination does not contain a new active substance: The RMP should follow the elements for a generic product. For the purpose of establishing the elements of RMP part II, "the originator" should be read as "any/all authorised products containing the same active substances included in the new product."
1265 - 1271		**Comment**: Homeopathic medicines should have reduced RMP content requirements similarly to medicinal products of well-established use. Accordingly, Part II "safety specification", Modules SI to SVI should not be required for these products. **Proposed change:** "**V.C.1.1.5. New applications under Article 10a, i.e. "well-established medicinal use" and under Article 16 (2) i.e. homeopathic medicines**

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		For new applications under DIR Art 10a and DIR Art 16(2), RMP elements are as follows: • RMP part I: The elements are the same as for a full initial MAA, • RMP part II: Only RMP modules SVII and SVIII are required. The applicant is required to justify the proposed safety concerns, or the lack of any thereof, using available evidence from published scientific literature (information available in the public domain). • RMP parts III-VII: The elements are the same as for a full initial MAA".
1291		**Comment**: The wording infers the RMP should be submitted as multiple pdf files, this should be changed to singular. **Proposed change**: "For centrally authorised products, the RMP should be submitted as PDF file~~s~~ within the eCTD submission."
1292 - 1294		**Comment**: It should be clarified whether the Commission Decision is always the trigger. There are procedures where a Commission Decision is not issued within 2 months. Meaning for practical reasons the outcomes /positive opinions/acknowledgements will be collected/bundled and later on published in one single decision.
1308		**Comment**: It is acknowledged that an updated RMP would be expected when a due date changes. However, in case where the change in due date of final report for a Cat 3 study (Annex 3 Part C) is due to a change in the protocol not mentioned in the RMP body or reviewed by the Agency, e.g. extension of follow up period, it should be confirmed that such submission would be expected prior to the initial due date, but not necessarily prior to the implementation of the amended protocol (extended follow-up period) is warranted.
1308 - 1310		**Comment**: For clarification, wording should be modified as follows. **Proposed changes**: "For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP ~~with~~ as part of the procedure triggering those changes."
1322 - 1324		**Comment**: It should be clarified what is meant by 'changes introduced in the last update (as applicable)'. In

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		other words, is it suggesting that when an updated RMP is already under review upon submission of the new RMP, companies will not be expected by default to take the unapproved "updated RMP under review" as the baseline? Currently this is not necessarily the default position.
1329 - 1330		**Comment**: Clarity on what is considered the timepoint of approval for an updated RMP when the procedure includes the commission decision making steps is warranted, i.e. would the RMP be considered approved at CHMP opinion or Commission decision. Following form that, when should the Annex I be submitted- currently the default was to submit Annex 1 post CHMP opinion except for initial RMPs.
1358 - 1360		**Comment**: The PRAC is not involved in the RMP assessment for nationally authorised products and it only reviews by default RMP for centralised products. The second part of the sentence on line 1360 should be deleted. **Proposed change**: "For the RMP assessment, the PRAC appoints a PRAC rapporteur who works closely with the (Co-) Rapporteur(s) appointed by the CHMP ~~or with the Reference Member State as appropriate~~."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from: Baxalta Inc US

Name of organisation or individual

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

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

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment for question 1 The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Answer The priority of the RMP should be a focused list of safety concerns. Full alignment is not needed as the documents are complementary. Comment for question 2 Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Answer Category 4 studies which are not adding relevant information should not be included in the RMP. Comment for question 3 Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Answer The EU RMP contains information on key elements. Materials as approved in the Member States can differ per country. Inclusion of these different materials in the EU RMP has no additional value. Comment for question 4 Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?

Stakeholder number *(To be completed by the Agency)*	General comment
	Answer Section 10 on post authorization studies can be deleted, relevant information from these studies can be added to the specific paragraphs associated with the described risks.
	Page 31, lines 1030-1031; Page 32, line 1067-1068; Page 32, line 1085-1086: Annexes may include the links to other modules of the eCTD dossier **Comment:** Based on the preference for hyperlinks, it would appear that the RMP is no longer a stand alone document. Please confirm.
	Pag 19, line 615-616: [for risks not taken forward as safety concerns] the justification for not including them as a safety concern. **Comment:** Please be more specific. For example, is the MAH expected to justify why each risk identified in the prescribing information but is not included as a safety concern>

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 314		Comment: Data Lock Point is not clearly defined Proposed change (if any): Please define data lock point (e.g., data of latest safety information, data of latest received source document, etc).
Line 340 – 343 SV.1.2		Comment: These instructions are not clear as whether only one table should be presented in this section Proposed change (if any): Please clarify whether should only be one table presented for this section.
Line 491		Comment: Referencing V.B.4.8. RMP module SVII "Identified and potential risks", there is an error in spelling Proposed change (if any): This RMP module should provide a focussed discussion…

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Baxter Healthcare

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Response: The definitions of a safety concern should be consistent within the PSUR and RMP, therefore there should be consistency with the safety concerns and there should not be a difference in this identification, otherwise there would be a lot of confusion with respect to the definitions.
	Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Response: In order to have a full understanding of exposure etc. we believe these should be included in annex 2.
	Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Response: We believe that the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP should not be included. Many times there are a lot of discussions and negotiations among different member states that take place after the approval of the RMP. If we were to wait for these conversations to be completed there would be a long delay.
	In order to know which sections to complete in a generic RMP, will MAHs now have access to originator RMPs – will they be publicly available?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
170-189		Comment: Description of important no longer has the guidance previously provided, that “important” risks would likely be in W&P section of the SmPC. Given the “important” risks have potential impact on public health should this guidance not remain? Especially since the SmPC guideline description of what should be in W&P is also similar to what is described as “important” risks. Proposed change (if any): Would add back in “Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.” The new definitions appear to be somewhat more confusing. Line 176: beyond routine risk communication (see V.B.7.). – the risk minimization measure should allow for routine risk minimization in the form of section 4.4 even when there might not be a direct action to be taken, such as warning a HCP of the risk of anaphylaxis and what may occur. The previous definition left this open to things in section 4.4. Per the SPC guidelines, ARs that are mentioned in 4.4 already meet this higher definition and in order to remain consistent with the SPC, we should not have a distinction between routine risk communication and “beyond routine risk communication” In line 178 it is stated “upon further characterisation, does not require at least routine risk minimisation activities” – again we are stating routine risk minimization activites as a general term, which we agree with, rather than then dividing this into routine risk communication and beyond routine risk communication
840-850		Comment: This section on routine RMM describes the SmPC as a RMM however there is a distinction with “routine risk communication” and “routine RMM beyond routine risk communication”. Why is there this distinction if we are all under the umbrella of RMM? As stated above, to meet the criteria of “important” risk, it should be only those risks that can change the B-R balance of the product and should therefore normally be in sections such as 4.4 Proposed change (if any): would remove this distinction since we need to remain consistent with the SPC guidelines for what is in section 4.4
936-954		Comment: Module XVI solely focuses on effectiveness checks (EC) for additional RMM. Would request 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')*
		clarification here, that routine RMM do not necessarily require ECs. Proposed change (if any): add a sentence in such as : As described in Module XVI, effectiveness checks must be described for additional risk minimisation measures; however only in specific circumstances would the effectiveness evaluation also apply to routine risk minimisation measures associated with safety concern(s) which are described in the SmPC/PIL (e.g. the SmPC provides guidance for clinical actions beyond routine standards of clinical care for either the risk itself or management of the target population).
Section starting with line 1192		Comment: The understanding of when to utilize which sections appears to be more confusing now. Especially with the need to check many different areas to see if things had previously been completed by the originator. Proposed change (if any): need to have the table that was in the previous module added back in, to help understand when to utilize which sections.

Please add more rows if needed.

Date of submission>

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Federal Institute for Drugs and Medical Devices (BfArM)

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
	General comments: New definition of important identified and potential risks: We highly appreciate that efforts are being made in order to improve the content of the existing GVP module. Whilst we support the overall aim to update the existing guidance taking into account experience gained so far we consider further improvements necessary to provide more clarity. In this regard we wish to highlight that we prefer the “old” definition as per GVP V rev.1 over this new definition. Acknowledging however that the definition is to be revised we believe that the “new” definition is too long and complicated. A sentence with 3 conditional parts (and/or, and, or) and a cross reference is difficult to read and understand. In addition, the term “*when further characterised*” is too vague and is, in our view, sufficiently described by “*would usually lead to further evaluation as part of the pharmacovigilance plan within the RMP (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use; which populations are particularly at risk)”*. We would therefore propose the following version, which in our view is easier to read and understand: *“An important identified or important potential risk is a risk that could have an impact on the product’s benefit-risk balance when at least one of the following criteria are fulfilled:* • *It is not managed appropriately in daily clinical practice.* • *It would usually lead to further evaluation as part of the pharmacovigilance plan within the RMP (e.g. to investigate or monitor frequency, severity, seriousness and outcome of this risk under normal conditions of use; which populations are particularly at risk).* • *It requires risk minimisation activities beyond routine risk communication (V.B.7).”* However we want to highlight that also the term “if not managed appropriately in daily clinical practice” is subject to

Stakeholder number *(To be completed by the Agency)*	General comment
	interpretation by MAHs and NCAs especially since daily clinical practice may vary greatly among different Member States and health care systems. A safety concern may be managed appropriately in daily clinical practice in one Member State but not in another. <u>Important parts of the RMP have been deleted as per GVP V rev.2, but we consider it necessary and helpful to maintain this information in the RMP:</u> 1. Summary of changes to the Risk Management Plan over time (VI.2.7) In our view, there is a need for a “history” of important risks in the RMP. In the current section VI.2.7 “Summary of changes to the Risk Management Plan over time” changes/addition/deletion of important risks are tracked and brief explanation is included why these risks were deleted from the RMP. We believe that this is particularly important considering the background that one intention of this GVP V revision is too decrease the number of important risks in the RMP. We are concerned that with deletion of section VI.2.7, this information might be lost over time. As per the new approach with a focus on the RMP as planning instrument, initially available information on safety aspects may be deleted over time and we consider it helpful to have a clear and transparent record of these changes. In addition, we believe that this information should be available to the public, too, as it might be important to explain why safety concerns are removed from the RMP despite the risk as such still being a risk associated with the use of the concerned product. It might therefore be helpful to include a respective section for changes in the RMP summary for the public. 2. It is a legal requirement from IR Art 30 (1)(c) that the RMP contains an evaluation of the effectiveness of interventions to minimise the risks without any restriction to additional risk minimisation measures only. Especially in cases of restricted indications due to safety concerns it is essential to monitor continuously the number of ICSRs reported for the relevant risk and the prescription data stratified for indication to evaluate whether this routine risk minimisation measure is effective in daily clinical practice. Therefore, evaluation of the effectiveness of risk minimisation measures is crucial also for routine risk minimization measures and should not be restricted in part V of the RMP to additional risk minimisation measures only. Additionally, such restriction would also not allow for an interchange of this section of the RMP with the respective section 16.5 of

Stakeholder number *(To be completed by the Agency)*	General comment
	the PSUR. 3. Figure V.3. Requirements for new marketing applications In GVP V rev.1 a table was included which parts are needed for which type of application (Figure V.3. Requirements for new marketing applications). We believe this table was/will be very helpful. We would therefore like to strongly recommend updating this table in line with the revisions made and (re-)including this updated table “requirements for new marketing applications” (analogue of figure V.3 from GVP V rev.1). We consider such an overview important to provide clarity and quick reference for both NCAs and industry. 4. SmPC (old: Annex 2) We believe that the SmPC should be attached to the RMP (Annex 8?). It simplifies the assessment of an RMP, and allows to directly check the wording regarding warning of important risks. When the SmPC is no longer integrated into the RMP or directly linked with eCTD module 1.3, RMP variations might result into the challenging situation to retrieve the latest version of a current SmPC -especially for nationally authorized products. Moreover, as the definition of an important risk includes the requirement of risk minimisation activities beyond routine risk communication (i.e. information beyond those provided in section 4.8; line 842, GVP V rev.2), the SmPC in the Annex or link to eCTD Module 1.3 allows to directly access warnings in section 4.4 in order to check whether they fulfill criteria of V.B.7. --- <u>Questions on which the Agency seeks specific feedback:</u> 1. *The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?* In our view there should be a full alignment with the PSUR content for the following reasons: 1. Problems of two parallel definitions of “important risks”

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	It will not add clarity if the term “important risk” is defined differently in the context of a PSUR or a RMP. Each reference will have to specify which definition of an important risk applies - as per GVP V or as per GVP VII. There is also only one definition in the “Guideline of pharmacovigilance practice Annex I – Definitions Rev3”. This module would have to be updated in parallel. Moreover, there is a need to provide sufficient information that this difference in definition actually will exist once GVP V rev.2 comes into effect. Apart from this cover note question there is no statement within GVP V rev.2 that informs the reader about the essential difference in the definition of an important risk between the two documents. Corresponding information would need to be added to GVP module VII and GVP Annex I. 2. Changes of the definition of an important risk (safety concern) also affects other GVP modules The updated risk definition of an important risk does not only affect GVP VII. The term “safety concern” is defined as an important identified risk, important potential risk or missing information (see “Guideline of pharmacovigilance practice Annex I – Definitions Rev3”). All GVP modules, not only GVP VII, use the term “safety concern”. In consequence, in parallel of revision of GVP V, there will be a need for clarification which definition of an important risk (= safety concern) applies to the other GVP modules. Alternatively, we propose to use other terms than “important risk” and “safety concern” for GVP V to reduce the potential confusion. Instead of the terms “important risk” and “safety concern”, new terms such as “risks to be followed up”, “summary of risks with additional PhV activities” could be defined and used in GVP V rev.2 to make it clear that these differ from the definition of “important risk” and “safety concern” used in other GVP modules. 3. Direct reference of GVP VII to safety specification of the RMP (ICH-E2E). In regard to important risks, there is direct reference of GVP VII to the safety specification of the RMP. GVP module VII outlines in PSUR sub-section VII.B.5.16.1. PSUR sub-section “Summary of safety concerns”: “*The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary[18] that is current at the start of the reporting interval of*

Stakeholder number *(To be completed by the Agency)*	General comment
	the PSUR." [18] ICH-E2E – Pharmacovigilance planning ICH-E2E forms the basis for GVP V. Hence, GVP VII directly links the summary of safety concerns, which, throughout the current structuring of the PSUR, forms the basis for B/R assessment, within the PSUR to the safety specification, which is part of the RMP. Moreover, the "safety specification", defined within the RMP (=part II) of a product is explicitly mentioned in the introductory note on GVP VII.A (see below). *"The "modular approach" of the PSUR described in VII.B.5. aims to minimise duplication and improve efficiency during the preparation and review of PSURs along with other regulatory documents such as the development safety update report (DSUR)[1] or the safety specification in the Risk Management Plan (RMP)… ."* In consequence, any change in the safety specification of an RMP (e.g. by changing the definition of an important risk in GVP V rev.2) will directly affect the summary of safety concerns displayed in the PSUR as per current GVP module VII. It is therefore unclear on which basis the safety specification of the RMP should be a subset of the list of product safety concerns. This is not evident when reading GVP V rev.2 and GVP VII. As outlined above, GVP VII gives advice that upon preparation of the PSUR reference to the RMP should be made to populate the summary of safety concerns. Hence, B/R assessment in PSURs would only be based on a subset of clinically relevant risks. Therefore, a revision of GVP V would warrant a corresponding update of GVP VII. In our view, it might be important to highlight that former parts of the summary of safety concerns might still be important for an overall benefit-risk assessment in the PSUR. Therefore, we would like to suggest including specific guidance in GVP Module VII that the evaluation of new information with respect to previously recognized identified and potential risks (VII.B.5.16.3) should also include prior safety issues that have been deleted from the actual summary of safety concerns of the RMP. It might also be helpful to include a respective subsection in the RMP that might facilitate accommodation of safety aspects that do not or do no longer form part of the RMP summary of safety concerns, but are considered important to be evaluated and followed up within the PSUR. 4. New definition difficult to understand for lay people The term "important risk" is also used in the public summary of the RMP. However, the term "important risk" is not defined within

Stakeholder number *(To be completed by the Agency)*	General comment
	part VI of the RMP template (Draft guidance on format…). We believe the newly proposed definition of important risk is not self-evident for lay people. The new approach of defining an important risk as part of the RMP focusses on planning aspects and does not necessarily reflect the totality of important key safety aspects of a medicinal product. Consequently, lay people are likely to misunderstand the concept of an “important risk”. For lay people, the term “important risk” carries a certain expectation, which in our view comes close to the definition of an important risk being clinically important or relevant for B/R. The new definition of an “important risk” would also contradict the recommendation to present the public summary (part VI) in plain-language approach. We would therefore like to suggest to including more explanation in the template for the public summary highlighting that the provided set of safety concerns has a specific focus on planning aspects and should not be taken as a set of key safety aspects of a medicinal product. 5. Reduction of interchangeability As per introductory note of GVP VII.A, the purpose of modular format of PSUR and RMP was to minimise duplication and improve efficiency. However, the proposed update of GVP V rev.2 decreases the number of common modules between PSUR and RMP from 5 common modules in the current GVP V rev.1 to only 1 common module in GVP V rev.2 (compare section V.B14.1 GVP V rev. 1 to section V.B.10.1 GVP V rev.2 and taken into account that the modules of effectiveness measures are not interchangeable). An increased workload for generation and assessment of PSURs and RMPs is expected. 6. Definition of “important risk” as per GVP V rev.2 lacks clarity We also believe that the currently proposed definition of the term “important potential/identified risk” is not clear, and different interpretations between regulators in different member states, industry and other stakeholders will lead to confusion and disharmonisation. Firstly, as outlined above we believe that a definition worded in a nested set/long, complicated sentence, which includes 3 conditional parts (and/or, and, or) is very difficult to read and understand.

Stakeholder number *(To be completed by the Agency)*	General comment
	Secondly, we believe that the definition itself lacks clarity. We have concerns that a common understanding could be established across the EU what "*managed appropriately in daily clinical practice"* would mean. Theoretically, the concept of a standard clinical practice, as decisive factor if risk minimization is still needed, might work. However, in practical terms standard clinical practice differs across all member states with very different health systems in the EU. It remains therefore unclear how "standard clinical practice" should be defined itself, and how a full integration into standard clinical practice across all member states should be determined. From other parts of the RMP it is understood that the concept should be to focus on risks "to be followed-up". However, the last part "*risk minimisation activities beyond routine risk communication*" mostly reflects items in section 4.4 of the SmPC. This would then mean that the definition of an important risk basically covers the "old" definition of GVP V rev.1. The last point of the above cited definition also considers a risk as important if it requires "*risk minimisation activities beyond routine risk communication (V.B.7)"*. It is unclear why items in section 4.3 of the SmPC are not considered "beyond routine communication", whereas warnings in section 4.4 are listed as examples. The examples provided in section V.B.7, which are highly welcomed, cover many items included in section 4.4 of the SmPC (= old definition of important risks as per GVP V rev.1). This would then again not reflect the approach that only risks with additional activities or specific follow-up are considered important. In consequence, we are concerned that it is left to the interpretation of the reader which approach is taken to classify a risk as important. This will then lead to a situation that different MAHs and also different NCAs will propose different safety specifications for the same medicinal products and where incongruent approaches of application of the guidance might emerge upon preparation or assessment by different MAHs and NCAs. We therefore see the need for a more consistent approach and interpretation of the new concepts and guidance. However, in line with above mentioned comments as regards transparency, harmonization and interchangeability of concepts, we strongly favour a full alignment of the RMP safety specification with the PSUR content. 2. *Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as*

Stakeholder number *(To be completed by the Agency)*	General comment
	category 4 studies) be included, for information, in the RMP annex 2? In order to have a full oversight of all ongoing studies, we believe it would be beneficial to have these studies in RMP annex 2. If not included in an annex of the RMP, it might become difficult to gain overview over on-going category 4 studies that might be sources for safety information. We consider it however important to have the possibility for review and overview of on-going activities as part of the obligations of NCAs and Rapporteurs for monitoring, which includes information about ongoing category 4 studies. 3. *Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?* Yes. It allows the Rapporteur and different member states to get an overview of the educational material on the market. In addition, member states might recognize advantages of educational material in other member states (e.g. different colour coding etc.), and implement these into their educational material with the next update. Moreover, it allows the Rapporteur/inspectors to check whether educational material has been implemented in all member states in which the medicinal product is marketed. In addition, for measurement of effectiveness it is essential to know how the risk minimization material looks like in other member states. 4. *Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?* Section V.B.10 should be maintained. As outlined above the focus of the modular format of PSUR and RMP to minimize duplication and enabling interchangeably was a driver when implementing GVP modules. However, this will be reduced with the current draft of GVP V rev.2. In our view, decreased interchangeably increases the workload for MAHs and NCAs.

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')*
170 ff		Comment: The definition of important risk is difficult to read and understand. We therefore consider the following definition more appropriate: *"An important identified or important potential risk is a risk that could have an impact on the product's benefit-risk balance when at least one of the following criteria are fulfilled:* • *It is not managed appropriately in daily clinical practice.* • *It would usually lead to further evaluation as part of the pharmacovigilance plan within the RMP (e.g. to investigate or monitor frequency, severity, seriousness and outcome of this risk under normal conditions of use; which populations are particularly at risk).* • *It requires risk minimisation activities beyond routine risk communication (V.B.7)."*
185-188		Comment: The paragraph states that an adverse reaction associated with long-term use, off-label use, or use in special population not studied should be considered a potential risk. However, there are ongoing discussions whether the risk itself with context (e.g. cancerogenicity in long-term use) or the condition itself should be stated in the RMP (e.g. off-label use). It would be helpful if GVP V rev.2 could provide clarification if off-label use, long-term use etc. can be labelled as a risk itself or whether a different approach should be preferred by e.g. rather naming the potential risk associated with these circumstances. Proposed change (if any): See above
190 ff & 279 ff Draft guidance on		Comment: In the definition of a missing information, we would welcome a strengthening of clinical significance as the decisive factor. We often see that "populations excluded in clinical trials" are directly transferred to "missing

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
format of the risk management plan (RMP) in the EU – in integrated format		information" in the RMP. In the "Draft guidance on format of the risk management plan (RMP) in the EU – in integrated format" additional information could be included that the absence of information itself does not constitute an important risk, and some evidence for clinical significance is needed. E.g. for substances, which have no hepatic metabolism, safety in patients with hepatic impairment is no missing information as it is unlikely that there is any clinical significance. In addition, regarding paediatric use as missing information, the extent to which this product could be used in paediatrics should be taken into account. Median age for certain cancer therapy in > 60 years of age, and these cancer types are super rare in children. In our view, there is no clinical significance for the overall population. Proposed change (if any): Draft guidance: *SIV.1 Exclusion criteria in pivotal clinical studies within the development programme* *Discuss the important exclusion criteria in the pivotal clinical studies across the development programme. Please take into account the concept of clinical significance if something should be considered a missing information or not (e.g. product without hepatic metabolism → safety in patients with hepatic impairment is unlikely to represent missing information).* GVP V rev.2: "*Gaps in knowledge about a medicinal product, related to the anticipated utilisation patterns such as long-term use or use in particular patient populations, which could be clinically significant. The absence of data itself (e.g. exclusion of a population in clinical studies) does not constitute a risk. Instead, additional evidence for a potentially different safety profile in the particular population is needed for the inclusion as missing information. For instance: …*"
232-234		Comment: *"It may be that important potential risks can be removed from the safety specification in the RMP (e.g. … 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')*
		when there is no reasonable expectation that any pharmacovigilance activity can further characterise the risk, thus questioning the importance of the risk). " The concept, that a risk can only be "important" if it can be further investigated, is considered questionable as a risk might merely not be further investigable due to constraints of available data sources and methods while the risk itself might be relevant. The fact of not being able to further investigate a risk does not necessarily result in the risk not being present and clinically relevant. Following this approach, a risk such as teratogenicity or cancerogenicity, that upon confirmation would have impact on B/R, has to be removed from the RMP when at a specific time point regulators see no PhV activity to further characterise it, e.g. if pregnancy registries conducted by the MAH are ended while in principle further information on the risk will be gathered on an on-going basis through public registries or teratology services. Many risks are not further evaluated based on feasibility grounds (e.g. very old drug, many generics, but data on cancerogenicity/teratogenicity from animal studies). However, these risks might become be very relevant for the drug´s B/R upon confirmation or further investigation or characterisation, even if not included in the RMP. We believe it is not communicable to the public that such a risk is not included in the RMP (public summary) because it is not regarded "important" as per GVP V definition (see general comments response to question 1 on which the Agency seeks specific feedback, number 4). Proposed change (if any): Delete the respective example.
236-239		Comment: *"In certain circumstances, important identified risks may need to be removed from the safety specification (e.g. for products marketed for a long time for which risks and the required risk minimisation measures have become fully integrated into standard clinical practice thus reducing the risk to a level when is no longer considered an important risk)."* In other words, a risk is no longer considered "important" in the concept of the RMP (not for the PSUR) if it 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')*
		managed appropriately in clinical practice. This implies that upon effective implementation of risk minimisation measures, a risk might no longer be considered as important risk in the concept of the RMP, while in principle it might only be effectively managed through effective risk minimisation, which would in our view imply inclusion as an important risk. Further on, effectiveness of risk minimisation might not be constant, may vary across member states and might need further review over time, which would again lead to the need to include this risk as important risk. We do not support this view. In any way the conclusion that a safety concern is no longer considered a safety concern in the context of pharmacovigilance planning would need throughout evaluation of the "appropriate management in clinical practice in each Member state" based on transparent criteria as part of the safety specification. Theoretically, the concept of a standard clinical practice, as decisive factor if risk minimization is still needed, might work. However, in practical terms standard clinical practice differs across all member states – with significant differences between countries. It remainsunclear how "standard clinical practice" should be defined itself, and how a full integration into standard clinical practice across all member states should be determined. Proposed change (if any): Delete the respective example.
243-246		Comment: *"… the classification as missing information will not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information. Summary of product characteristics (SmPC) changes should be made accordingly."* The second example is non-compliant with the definition of missing information defined in GVP V rev.2 on p.7, which is largely unchanged compared to GVP V rev.1. *"Gaps in knowledge about a medicinal product, related to the anticipated utilisation patterns such as long-term use or use in particular patient populations, which could be clinically significant."*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 definition does not mention that the possibility to follow-up on a gap in knowledge about a medicinal product defines it as a missing information or not. The definition states clinical significance as the decisive factor. Taking teratogenicity as an example, which is clearly of clinical significance: In >90% of the old drugs, teratogenicity cannot be adequately followed-up. It is a missing information as per current definition of missing information, but not according to the above cited example. Hence, clarification is needed here. In our view the above cited example is not optimal. It postulates that a gap in knowledge is only a gap in knowledge if there are ways to fill the gap in knowledge. In other words, missing data on teratogenicity in humans for a certain drug would not be considered as a gap in knowledge when we are not aware of any feasible method to investigate it. Some risks might at least be further characterized by spontaneous reporting and generated case series which might be seen as routine pharmacovigilance activities, but might however contribute to increasing the knowledge on these risks. It should be kept in mind that unlike the PIL, the RMP public summary currently summarizes in which populations gaps of knowledge exists. This will be lost using this example. If the proposed approach is maintained, it might be helpful to clarify in the template for public summaries that the RMP list of missing information relates to planning purposes and does not specify a full list of gaps in knowledge with regard to safety of the product. Moreover, the current wording might be misinterpreted, e.g. that the SmPC should be updated once no additional data is expected. It might be beneficial to rephrase this section to provide more clarity Proposed change (if any): "... *the classification as missing information will not be appropriate …~~, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information~~. Summary of product characteristics (SmPC) changes should be made accordingly."*

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327		Comment: Indications might differ between member states if an RMP includes multiple medicinal products authorised through decentralised and national procedures. In these cases, the MAH should be asked to insert a footnote indicating that this indications is only granted in country X, Y and Z. This could either be included in GVP V rev. 2 directly or into the Draft guidance document. Proposed change (if any): Indications (specify differences in indications between MS in a footnote);… In case different indications exists this should also be reflected in part VI.
336-339		Comment: *"The purpose of the safety specification is to provide an adequate discussion on the safety profile of the medicinal product(s), with focus on those aspects that need further risk management activities.* *It should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information."* The safety specification includes the summary of the important identified risks of a medicinal product, important potential risks, and missing information, but is not defined by this summary itself. It also includes all identified and potential risks irrespectively of being designated as "important". In conclusion the relevant sentence should be revised as follows (proposed change): Proposed change (if any): "It should ~~be~~ include a summary of the important identified risks of a medicinal product, important potential risks, and missing information."
365-367		Comment: "*RMP summaries for most recently approved centrally authorised medicinal products (CAPs) are published on EMA website. The CMDh has published the summary of safety concerns for selected medicinal products for*

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		which an RMP is in place, on the CMDh website." We endorse that the MAHs are informed on which websites they can find RMP summaries. However, to our knowledge only a very small percentage of approved RMP summaries have already been uploaded to EMA and CMD(h) websites. Potentially, a number of questions/requests will come asking for uploading certain RMP summaries or asking for reasons why respective RMP summaries have not been uploaded. Proposed change (if any): -
387		Comment: "*This RMP module should include incidence, prevalence, outcome of the target disease (i.e. indications)…"* Maybe it should be specified if outcome of the target disease means the outcome without or with state of the art treatment. Proposed change (if any): *"This RMP module should include incidence, prevalence, outcome of the (untreated) target disease (i.e. indications)…"*
410ff		Comment : "*This RMP module should present a high-level summary of the important non-clinical safety findings, …*" Revision 2 of GVP V defines an important risk as a risk that warrants further investigation. It is unclear how this definition should be applied to the non-clinical section. At this stage it is impossible to determine if a certain risk/safety finding requires further investigation. In our view, the word "important" will confuse the reader here. High-level summary of significant findings is

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		sufficient to inform the author of an RMP to stick to the main points. Proposed change (if any): *This RMP module should present a high-level summary of ~~important~~ significant non-clinical safety findings,…*
456-460		Comment: *"When exclusion criteria from the clinical trial development programme are not proposed as contraindications for the medicinal product, then RMP module SIV should also include a discussion on the relevant subpopulations, including whether or not any use in populations excluded from the clinical trials (e.g. women of childbearing potential, older people) might be associated with a different list of safety concerns and should be included as missing information in the RMP."* In our view the wording "*might be associated with a different list of safety concerns"* is difficult to understand. According to the definition in draft GVP V rev.2, a missing information is included into the summary of safety concerns based on clinical significance. If it is the intention to rather draw attention to missing information as gap of knowledge that could and should be further investigated, the above cited explanation means that the MAH should discuss in this part whether he believes a study population excluded in clinical trials should/could be further investigated. The above cited paragraph might therefore benefit from rephrasing as proposed in the following Proposed change (if any): *"When exclusion criteria from the clinical trial development programme are not proposed as contraindications for the medicinal product, then RMP module SIV should also include a discussion on the relevant subpopulations, including whether or not any use in populations excluded from the clinical trials (e.g. women of childbearing potential, older people) might be associated with risks of clinical significance ~~different list of safety concerns~~ and should be included as missing information in the RMP."*

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501ff		Comment: Here, no clear recommendation is included whether medication errors itself, or the adverse events or potential for adverse events as a consequence from medication errors should be included into the RMP. We propose to add a statement analogous to overdose that medication errors could be included as a safety concern on their own. Proposed change (if any): *"Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible remedies given including discussion whether this should be considered as a safety concern. Where applicable… .* *Adverse reactions related to medication errors in the post marketing period should be discussed in the updated RMP. The inclusion of medication errors as a safety concern into the RMP should be discussed and ways of limiting the errors proposed;"*
529-530		Comment: *"The evidence supporting the interaction and possible mechanism should be summarised, the potential health risks discussed for different indications and populations. Important (potential) risks following clinically important interactions should be considered for inclusion as a safety concern;"* We consider the wording confusing. If a risk was already classified as "important", it needs to be included into the summary of safety concerns (and not considered for inclusion). In addition, the concept to include the risk rather than the interaction might be misleading. Interactions might be associated with a bunch of risks especially when catabolism of a drug is affected. Therefore, approaches to minimize the risks of an interaction will always aim on the interaction rather than the specific risk(s) (symptoms) arising from the interaction.

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		In our view, it might therefore be more helpful fill to name the risk, which could be general (e.g. increased toxicity), in conjunction with the drug interaction. Example: Increased overall toxicity when used in combination with strong CYP3A4 inhibitors Moreover, based on the new definition of important risks, the MAH needs to discuss here if/how he plans to further characterize interactions. If further characterization is planned, the interaction should be included into the summary of safety concerns. Proposed change (if any): "The evidence supporting the interaction and possible mechanism should be summarised, ~~and~~ the potential health risks discussed for different indications and populations, and plans to further characterise and minimise the risks described. ~~Important (potential) risks following clinically i~~Important interactions along with their associated risk should be ~~considered for~~ inclu~~sion~~ded as a safety concern;
532		Comment: *"…contraception recommendations can be considered as risk minimisation measures."* According to V.B.7 contraception is a routine risk minimisation activities beyond routine risk communication. It might be helpful to clarify whether it is intended that every time contraception is recommended, an important risk (teratogenicity?) should be included in the RMP. Proposed change (if any): risks in pregnant and lactating women, e.g. teratogenic risk - direct or through exposure to semen: contraception recommendations can be considered as risk minimisation measures. If contraception is considered necessary this risk qualifies for inclusion as safety concern (See V.B.7).

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603-606		Comment: *"This RMP section should contain the initial identification of safety concerns and is expected to be populated for RMPs submitted with the initial marketing authorisation (MA) application, or with a new RMP submitted post-authorisation (at the competent authority's request or without request).* We believe it should be clarified that not the update of existing RMP is meant here, but an RMP which was requested for the first time in the post-authorization phase. Proposed change (if any): "*…with the initial marketing authorisation (MA) application, or with a new RMP ~~submitted~~ newly introduced in the post-authorisation phase (at the competent authority's request or without request).*
617-621		Comment: Heading and text of V.B.4.8.2 are not aligned properly. The heading states "Identification of safety concerns…", whereas the text asks for discussion of new significant emerging data of risks not considered important. Per GVP V module rev.2 a safety concern is defined as "*Any of the important identified risks, important potential risks, or missing information included in the RMP*." Therefore, either the heading is correct and in this section details of safety concerns (=important risks) should be included, or the text is correct, and only data on risks not considered important should be included. We assume that this section should report on the latter. In addition, the term "identification" in V.B.4.8.2 does not fully match to the concept of re-classification as mentioned in V.B.4.8.2b. Proposed change (if any): *"V.B.4.8.2. RMP module SVII section "~~Identification~~New significant data on ~~of~~ ~~safety concerns~~ risks not considered important ~~with a~~ since the last submission of the ~~an updated~~ RMP"*

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623		Comment: *"Data presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1.1.."* There is no section V.B.4.8.1.1. – only V.B.4.8.1.a. It should be specified that data on risks not considered important should be included here. Proposed change (if any): *"Data on risks not considered important presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1.~~1~~a.."*
734-738		Comment: *"RMP annex 3 – part A should contain protocols submitted for assessment, when the protocol submission has been requested by the competent authority; RMP annex 3 – part B should contain protocols that have been agreed with competent authorities and are being submitted with the RMP for amendment, when the protocol submission has been requested by the competent authority;"* This section might benefit from clearer guidance and clarification if and whether 3A should be used for non-approved or assessed protocols and whether 3B should be used to include already agreed protocols when submitting routine RMP updates or whether updates to previously agreed protocols that need approval as major protocol amendment themselves should be submitted as part of part B. If the intention of 3A and B is to clearly separate materials that need further agreement from the ones already agreed, a more concise wording might be helpful. In addition, direct cross reference to V.B.9.3 should be given. Moreover, it is important that assessors are informed early that an RMP is accompanied by a study protocol. The MAH should therefore be asked to clearly state within scope of variation and cover letter that study protocols/protocol updates were submitted and whether these have already been agreed with the responsible

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		authorities. Proposed change (if any): Update of annex 3 to ask the MAH to clearly state in the scope of the variation and/or the cover letter that study protocols/protocol updates are submitted for assessment with the same application. *RMP annex 3 – part A should contain protocols submitted for assessment, when the protocol submission has been requested by the competent authority; RMP annex 3 – part B should contain previously agreed protocols that ~~have been agreed with competent authorities and~~ are being submitted with the RMP for amendment, when the protocol submission has been requested by the competent authority;*
745-752		Comment: In Table V.3, for category 1 and category 2 studies, it could be added that these are found in Annex II D and Annex II E of the SmPC for medicinal products with a central marketing authorisation respectively. Proposed change (if any): See above
845ff		Comment: *"routine risk minimisation activities beyond routine risk communication: usually found in sections 4.2 and 4.4 of the SmPC but can also be found in sections 4.6 and 4.5 and accordingly sections 2 and 3 of the PL; warning and precaution messages and recommendations in the SmPC will include information on minimising the risk of the product by e.g.: – performing a test before the start of treatment;* *– monitoring of laboratory parameters during treatment* *– monitoring for new signs and symptoms* *– adjusting the dose or stopping the treatment when adverse events are observed or laboratory parameters*

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		change *– performing a wash-out procedure after treatment interruption* *– providing contraception recommendations* *– prohibiting the use of other medicines while taking the product* *– treating or preventing the risk factors that may lead to an adverse event of the product* *– providing long-term clinical follow-up to identify in early stages delayed adverse events. "* In our view the cited examples of routine risk minimisation activities beyond routine risk communication mostly reflect common warnings in section 4.4 of the SmPC. Taking into account that the definition of important risks defines a risk as important if routine risk minimisation activities beyond routine risk communication are required, we feel that the specification what constitutes routine risk minimisation activities beyond routine risk communication in V.B.7 leads to a definition of an important risk that is very similar to the old definition in GVP V rev.1. However, reading the preamble and other parts of the revised module, we have doubts that this understanding might be correct. In summary, reading through draft GVP V rev.2, we are not sure if all risks with above cited warnings in section 4.4 should be included into the summary of safety concerns, or if an important risk is characterized by its ability to be further characterised. Proposed change (if any): Clarification throughout the RMP and especially in the terminology and V.B.7 is needed to avoid confusion what an important risk as per GVP V is. A clear definition of an important risk needs to be provided.
918-920		Comment: We endorse that applicants are asked to consult patient and HCPs and discuss risk minimization activities with

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		them. Proposed change (if any): -
926-927		Comment: Information could be added that patient alert cards are attached to the PIL and thereby directly available for patients (as per QRD template). Proposed change (if any): See above
936-959 & 764ff of Draft guidance on format of the risk management plan (RMP) in the EU – in integrated format		Comment: The restriction of the evaluation of risk minimisation measures to additional risk minimisation measures only is not considered helpful and also not considered in line with the legal requirements from IR Art 30(1)(c): *1. The risk management plan established by the marketing authorisation holder shall contain the following elements:* *(c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions;.* In line with this legal requirement and also in line with PSUR section 16.5 (which is itself established by the requirements from IR Art 34(3) *"The periodic safety update report shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment.")* all risk minimisation measures established to minimise safety concerns, irrespectively of being "routine" or "additional" shall be evaluated for their effectiveness. Especially in cases of restricted indications due to safety concerns it is essential to monitor continuously the number of ICSRs reported for the relevant risk and the prescription data stratified for indication to evaluate whether this routine risk minimisation measure is effective in daily clinical practice. Therefore, evaluation of the

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		effectiveness of risk minimisation measures is crucial also for routine risk minimization measures and should not be restricted in part V of the RMP to additional risk minimisation measures only. The evaluation of the effectiveness of routine risk minimization measures is necessary as only with such evaluation any conclusion can be drawn whether an important risk can be considered as being “managed appropriately in daily clinical practice”. Proposed change (if any): In conclusion these sections need revision to re-establish the evaluation of the effectiveness of routine risk minimisation measures. (Please also refer to the comment on interchangeability of sections from PSUR and RMP). *“When the RMP is updated, the risk minimisation plan should include a discussion of the impact of ~~additional~~ risk minimisation activities. Where relevant, such information may be presented by region. A discussion on the results of any formal assessment(s) of ~~additional~~ risk minimisation activities should be included when available.”* *“In the RMP section on the risk minimisation plan, for each safety concern in the safety specification, the following information should be provided:* *• routine risk minimisation activities, including details of whether only inclusion in the SmPC and PL is foreseen or any other routine risk minimisation activities are proposed;* *• additional risk minimisation activities (if any), individual objectives and justification of why needed; ~~for each additional risk minimisation activity, the following information on measuring their effectiveness should be presented:~~* *• for each risk minimisation activity, the following information on measuring their effectiveness should be presented:* *– how the effectiveness of each (or all) of the risk minimisation activities will be evaluated in terms of*

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		attainment of their stated objectives; *– what the target is for the ~~additional~~ risk minimisation measures, i.e. what are the criteria for judging success;* *– milestones for reporting on the effectiveness of the ~~additional~~ risk minimisation measures as well as milestones for evaluating the need to maintain the activities (e.g. at renewal and thereafter with the PSURs).”*
975ff of GVP V rev.2 & 907ff of Draft guidance on format of the risk management plan (RMP) in the EU – in integrated format		Comment: Unlike draft GVP V rev.2 , the “draft guidance on format of the risk management plan (RMP) in the EU – in integrated format” does not contain specific information that a plain-language approach should be used. In contrast, the draft guideline often states that information from other parts of the RMP should be copied (e.g. Use text from RMP Part II SVII.3.1 under ‘Evidence source and strength of evidence’). Information is missing that this text should be “translated” in plain-language. Proposed change (if any): Add throughout the draft guidance that in part VI a plain-language approach should be taken and that the copied parts have to be amended to be understandable for laymen.
1000-1006		Comment: *“The summary of the RMP part VI should be consistent with the information presented in RMP part II modules SVII, SVIII and RMP parts III, IV and V. It should contain the following information:* *• the medicine and what it is used for;* *• summary of safety concerns and missing information;* *• routine and additional risk minimisation measures;*

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		• *additional pharmacovigilance activities. "* There is a lack of detail what should be provided in the four subsections. GVP V rev.1 provided guidance on each individual section. This is also needed here. The draft guidance document outlines that for the public summary of safety concerns information on "evidence for linking the risk to the medicine", "risk factors and risk groups", "risk minimization measures" and "additional PhV activities" should be included. Especially for MAHs of old and generic medicines, it will be very difficult to retrieve the "evidence for linking the risk to the medicine". Guidance is needed here what should be taken into account (e.g. number of cases, increased frequency compared to placebo in clinical trials, causality assessment as per WHO-UMC etc.). In our view, it would also be important to inform patients about completed PhV activities and updates of the significant RMP in general. Therefore, we believe that the section "Summary of changes to the risk management plan over time" from GVP V rev.1 should be kept. Proposed change (if any): Please provide more guidance on what is expected to be included. Keep the Summary of changes to the risk management plan over time" from GVP V rev.1.
1002 of GVP V rev.2 & 864 of the Draft guidance on format…		Comment: The title "the medicine and what it is used for" might be misleading. Drugs are often used off-label. Therefore, the heading should be changed and clearly stated what the respective drug was authorised for. Proposed change (if any): "the medicine and what it is ~~used~~authorised for"
1101-1106 & 764ff of the Draft guidance on		Comment: It is proposed that Part V of RMP section "Evaluation of the effectiveness of risk minimisation activities" and Section 16.5 of PSUR "Effectiveness of risk minimisation (if applicable)" are interchangeable. However for the

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format…		relevant PSUR section it is required that in line with IR Art 34(3) "*The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment".* Therefore, also the effectiveness of routine risk minimisation measures is displayed in section 16.5 of the PSUR. Interchangeability of these relevant sections from PSUR and RMP is therefore only possible if the effectiveness of routine risk minimisation measures as required from IR Art 34(3) are assessed and included also in part V section "Evaluation of the effectiveness of risk minimisation activities" of the RMP. In conclusion based on the current definition these sections are not considered interchangeable. Proposed change (if any): For full interchangeability routine risk minimisations measures needs to be evaluated in the context of part V of the RMP or reference to interchangeability should be deleted.
1192ff		Comment: In GVP V rev.1 a table was included which parts are needed for which type of application (Figure V.3. Requirements for new marketing applications). We believe this table was/will be very helpful. Proposed change (if any): Please include an updated table "requirements for new marketing applications" (analogue of figure V.3 from GVP V rev.1).
1203-1213 of GVP V rev.2 & 907 of the Draft guidance on format…		Comment: New applications under article 10(1) i.e. generic do not require part II SI-SVII in case the originator has an RMP or an RMP is published on CMD(h) website. In addition, part V may also be omitted if the originator has no additional risk minimization activities. However, in part VI new applications under article 10(1) i.e. should provide the same elements as for a full initial MA. Here, the "draft guideline on format…" asks new applications

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		under article 10(1) to provide elements from part II SVII and part V (part VI.II.1.2 und VI.II.1.3 of the table (line 907)). Thereby, generics do not have to provide part II SVII and part V in the RMP body, but have to provide the respective information in part VI. This is inconsistent. Proposed change (if any): It should be specified that new applications under article 10(1) in situation 1 and 2 do not need to provide "SVII data" in part VI. OR More advice in the "draft guidance on format…" is needed how generic applications in situation 1 and 2 (line 1203-1213 of GVP V rev. 2) should populate the table in line 907 of the RMP template.
1212		Comment: "safety profile" should be replaced by "safety concerns" since the safety profile usually includes more risks than the safety concerns which on the other side also includes "missing information" which is not considered to belong to the "safety profile". Proposed change (if any): Originator does not have an RMP but the safety ~~profile~~concerns of the originator product is published on the CMDh website[11].
1214-1218 of GVP V rev.2		Comment: "3. *Originator does not have an RMP and the safety profile of the originator product is not published on the CMDh website: Full modules SVII and SVIII should be included in the RMP. Module SVII should critically analyse available relevant information (e.g. own pre-clinical and clinical data, scientific literature, originator's product information) and propose a list of important identified and potential risks as well as missing*

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		information. " One of the aims of GVP V rev.2 was to decrease complexity of the RMP. Albeit, the idea is acknowledged to include details of risks and scientific evidence into the generic RMPs, we believe that this will increase complexity of generic RMPs and will lead to a strong increase in workload for MAHs and NCAs. The vast majority of the generic MAHs will not have pre-clinical or clinical data, and therefore will not be able to provide details for each risk (all risks, not only important risks, see SVII.1.2) especially regarding the "level of scientific evidence for <risk> to be added in the safety specification as an important potential risk" (line 450 of "draft guidance on format…") when applying for a new generic marketing authorisation. Evidence of generic MAHs is often limited to the SmPC of the originator. However, as SVII and the respective evidence should also become part of the public summary (see draft guidance on format…) detailed discussion on evidence of each risk is needed, which in turn will increase workload for NCAs and MAHs for a relevant number of generic products. Proposed change (if any): Remove the three different situations for new applications under article 10(1). Only part SVIII should be required for all new applications under article 10(1).
1214-1218 of GVP V rev.2 & 360 of the Draft guidance on format…		Comment: "3. *Originator does not have an RMP and the safety profile of the originator product is not published on the CMDh website: Full modules SVII and SVIII should be included in the RMP. Module SVII should critically analyse available relevant information (e.g. own pre-clinical and clinical data, scientific literature, originator's product information) and propose a list of important identified and potential risks as well as missing information.* " Generics should now provide module SVII if no RMP is available as per GVP module V rev.2. However, the draft guidance document states that SVII is not required for generics (line 360). Proposed change (if any):

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		Remove inconsistency.
1304-1306		Comment: "*As stated in V.C.1.2. an RMP update is expected to be submitted at any time when ….*" Here, cross reference to V.C.1.2 is given. However, the respective section V.C.1.2 "Risk management plans first submitted not as part of an initial marketing authorisation application" does not state when an RMP update is expected. Proposed change (if any): Delete the reference to V.C.1.2: *"A~~s stated in V.C.1.2. a~~n RMP update is expected to be…"*
1304-1306 1311-1316		Comment: *"An RMP update is expected to be submitted at any time when there is…"* *"An update of the RMP might be considered when data submitted in the procedure results …"* It might be easier for the reader to identify the difference in the two paragraphs if it starts with the situation when it updates should be submitted. In line 1304 ff, the RMP update should be submitted at any time if…, whereas in line 1311 ff, the RMP should be updated within a procedure. Moreover, we are not in favour of a wording like "might be considered", this leaves too much space to interpret the need for RMP update differently across EU MS states and MAHs. We consider it helpful if GVP V rev. 2 could give advice how minor changes (update of post-marketing exposure, new non-clinical data, closing of trials etc.) should be handled. The accumulation of significant number of minor changes should also trigger an RMP update. Update of the RMP at the next regulatory opportunity could be proposed. Alternatively, GVP V rev.2 could recommend that the MAH should check the RMP yearly/five-yearly for minor changes and submit an update once a significant number of minor changes

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		accumulated. Proposed change (if any): *"An RMP update is expected to be submitted at any time when there is…"* *"Within a procedure, an update of the RMP should ~~might~~be ~~considered~~submitted when ~~data submitted~~ ~~in~~ the procedure ~~-~~results …"* Further proposals see above.

Please add more rows if needed.

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Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Boehringer Ingelheim

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

1. General comments

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

Questions on which the Agency has sought specific feedback by means of the public consultation:
1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?
As the PSUR and the RMP have different purposes and different periodicities, the safety concerns described in the RMP should be limited to those that are classified as important and for which there is focus on risk management.
2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2?
We agree to the proposal in GVP V rev 2 not to include voluntary studies in the RMP in line with EMA's aim to keep the RMP focused.
3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?
We recommend not including these multiple documents as these would increase the volume of an RMP significantly. Instead, the English master version may be appended.
4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?
We recommend maintaining text in V.B.10 and deleting V.B.10.1 as the table incorrectly implies that the sections interchangeable.

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')*
160		Comment: If the definition of risk changes from an 'untoward occurrence' to an 'undesirable outcome', will there be guidance from the Agency on how to update existing RMPs. For example should the risk of medication errors with an insulin product be modified to the risk of Hypoglycaemia/hyperglycaemia, with a root cause/MOA as the medication error? Proposed change (if any): Provide a Qs & As as a separate document providing process instruction to update existing RMPs.
174-177		Comment: Is our understanding correct that according to the newly proposed definition of important risk, in the future, a risk is only considered important if there are additional pharmacovigilance activities and/or additional risk minimisation activities? In other words, risks with only routine measures are not considered important? If this is the case, will the existing important risks with routine pharmacovigilance and risk minimisation measures be re-classified as non-important? Proposed change: Please clarify the terminology.
185-195		Comment: This concept of justified supposition of an ADR related to long-term use and use in populations not studied needs to be clarified against lines 191-197. Classification as a potential risk (line187) is contradictory to lines 196 where it is stated that use in population not studied with an expected different safety profile should be missing information. It is the difference between 'justified supposition' and 'expected' that needs to be clarified, especially when clinical judgment is applied to both scenarios. Proposed change (if any): Please clarify.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
236-239		Comment: More guidance when an important risk can / should be re-analysed and removed from the RMP would be appreciated.
286-289		Comment: The linking of the CTD with the RMP is considered practical for an initial MAA but will add complexity in the post marketing setting considering that not all documents / document versions referenced in the RMP may be available in the eCTD. Proposed Change: Maintain the RMP as stand-alone document containing references instead of hyperlinks. This would still allow keeping the RMP focussed.
295-296		Comment: A clarification whether full text or a list of references should be appended would be appreciated. It is impractible to include literature references as full texts in the RMP annex 7.
483-489		Comment: Module SVI has been substantially revised and now only contains the potential for misuse for illegal purposes. Proposed change: Consider moving this section to another module or part of the RMP to facilitate module administration.
615-616		Comment: This requirement on justification why a risk is not taken forward as a concern may misinterpreted as a lengthy review of all risks contained in the PI (contraindications, warnings and precautions, all individually listed side effects, drug interactions, pregnancy and lactation, drug interactions…) and justifications for each. However, the review of all risks and decisions on which are classified as important are part of the MA procedure and in postmarketing in procedures related to PSUR reviews and RMP updates. In addition, any new risk included in the PI would trigger an RMP update to justify its non-inclusion although there are no changes to the risk management system.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Omit last bullet in module V.B.4.8.1 and delete SVII.1.2 and SVII.2.2 in RMP template
713-714		Comment: Requested observed vs expected analyses are not required according to the PSUR guidance. Proposed change: Delete
921-923		Comment: RMP Annex 6 is incorrectly referenced ("Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III" instead of "Details of proposed additional risk minimisation measures (if applicable)"). Proposed change: Please correct to Annex 3.
950-952		Comment: Clarification is needed with regard to Annex 2 – Summary of on-going and completed pharmaco-epidemiological study programme. This should list all studies included in the pharmacoepidemiological programme. However, according to the proposed template, this should list all studies included in the Pharmacovigilance Plan (current or in previously approved RMP versions). Proposed change: Please revise.
1107		Comment: Table V.4 is inconsistent with regard to the correspondence between RMP Part II, module SV "Post-authorisation experience" and PSUR Section 3 "Actions taken in the reporting interval for safety reasons". In fact, the RMP section "Actions taken for safety reasons" has been removed from the proposed template. Proposed change: Please correct.
1311-1318		Comment: Clarification is needed on the need for RMP updates when the SmPC changes, e.g. "when monitoring of renal function is added as a recommendation in the Special warnings and precautions for use section 4.4 of the SmPC ".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Please provide more guidance on RMP update requirements.
1369		Comment: This paragraph is unclear when compared to the requirement in Module XVI to present country specific differences in the imposed additional risk minimisation activities. XVI.C.1: *In circumstances where some key elements are specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State) or where additional risk minimisation measures are not imposed as a condition for marketing authorisation these shall be included in the RMP.* Proposed change: Please clarify this paragraph and harmonise with module XVI.
Template 58-59		Comment: The following instructions need clarification: "… is advisable to use a major version number (e.g. version 1.0., 2.0, 3.0, etc.)" This advice is unpracticable since the MAH cannot foresee which (minor) version will receive a positive opinion, therefore the last submitted minor version would be the approved one. Proposed change: Please clarify requirements for versioning.
Template 67		Comment: Table Modules 1; inconsistent heading for Annex 3: ANNEX 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan Proposed change: "Completed" should be removed according to heading and instructions provided later on in the template.
Template 855-862		Comment: A definition of important risk is missing; more context and explanations are needed regarding to 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')*
		concept of risk minimisation measures and additional pharmacovigilance activities. Proposed change: Please add definition and further explanations in the annotations.
General remark		Comment: It would be helpful to have a cross-reference to the guidance on RMPs for biological medicinal products (EMA/168402/2014) in module V Section V.C.1.1 (and subsections). Proposed change: Please add cross-reference.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

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

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

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1. General comments

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

In general, the changes of revised GVP module V, which will result in shortening of guideline and template as well, are appreciated. This will be associated with a more focused RMP, with lower number of redundancies. Furthermore, the guidelines gives a good introduction in the need and aim of a RMP, including the legal background. The reduction of table number in the corresponding template will also contribute to a more focused document.

The new opportunity to link the RMP with other documents as the CTD is also an advantage, to avoid redundancies and to create a streamlined document.

Some disadvantages, which were not resolved with the new guideline version, are the low numbers of examples given in the entire document. However, such examples would be very helpful to illustrate the objective of the sections and the information enclosed and thus will be the basis for clear and appropriate created document. This would be a big advantage for authors, assessors, and user of the RMP.

The identification of safety concerns is a central part and forms the basis for creation of adequate and useful RMP. In this context, the definition of the term “important” in connection with identified and potential risk is of crucial importance. Under specific circumstances, it is very difficult to classify a risk as “important” or as “not important”. However, such a decision might have large consequences including studies, which are probably not necessary. Therefore, in the context of definition of an important risk, various examples should be given, which help the authors of a RMP to categorise the risk more appropriately to keep the RMP focused on real important risk and to avoid burden to test person for studies, costs, and time. In this context it should be also noted that status of an initially “not important categorised” risk can change to “important”, for example when more information are available.

General Comments / different parts:

- **Part I:**
    - The QPPV-signature seems only to concern the “currently approved RMP”, but for this already approved RMP a new QPPV signature is not necessary. A QPPV-signature for the new version of the RMP is missing. On the first page the information of the current RMP for assessment should be given, not the information concerning the already approved RMP because the document is newer than the already approved RMP.
    - What should be done instead of the hyperlinks (e.g. for spc and literature) if the product does not have an eCTD at the moment? How could these hyperlinks be managed if there are different products concerned in the RMP but not all products are concerned in the current assessment procedure (e.g. different DCP procedures in different assessment steps)? Furthermore it is sufficient to refer to the relevant document (spc and literature) in the RMP without setting a hyperlink due to the fact that the structure of the CTD is harmonized.

- **Part II SVII:**
  "Risk not considered important for inclusion in the safety concern":
  The RMP as a document for the benefit-risk-management and –planning should only focus on important risks. The benefit-risk-assessment is done in the PSUR where the assessment "Important – not important" should be defined already. The safety concerns of the RMP and PSUR should be in line. Therefore information concerning "not-important safety concerns" are not necessary for the RMP.

- **Part V:**
  Section V.3 is a summary of V.1 and V.2.
  The duplication of information in Part V should be reduced. There should be only one complete table for safety concerns and the necessary risk minimization measures in Part V. Pharmacovigilance activities which were added in the new RMP Template in section V.3 are already described in Part III and this content is not relevant for the section "risk minimization measures". This part of the table should be deleted. More details regarding additional risk minimization measures can be described in section V.2.

- **Part VI:**
  The numbering in section Part VI, "II. Risks associated with the medicine…" seems to be wrong:
  It starts with 1.1 and ends with 1.4.2. In the table in 1.2 and 1.3 there is a crossreference to "section 2.3" which we could not find in the RMP Template.

Responses to general questions:

- **Question 1:**
  The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is subset of the list of the product safety concern as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP List of safety concern or a fully alignment with the PSUR content?

  A focused RMP list is appreciated. This is in line with the aim of RMP, to be a document/tool focused on data collection, which were needed but currently not available to characterise known or potential risk. If such information is gained and the risk is appropriately characterised, then there is no need to further enclose this risk as safety concern in the RMP. In contrast, the PSUR/PBRER is a document to characterise the benefit/risk balance of a substance comprehensively. Such information is and should be essential for the PSUR and has to be discussed and assessed in this document. In consequence, RMP and PSUR are documents with different focus (prospective vs. retrospective/integrative), there should be the possibility to list different safety concerns in both documents.

- **Question 2:**
  Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4

studies) be included, for information, in the RMP annex 2.

All studies with aim to analyse data concerning safety concerns, which are listed in the RMP should be included in the RMP, independently from origin of study. However, if a study does not focus on the safety of the product, inclusion in RMP annex 2 is not recommended.

- **Question 3:**
  Should the risk minimisation materials as they were distributed in the Member states be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?

  The risk minimization materials must be included in English language in RMP Annex 6. This English document is the central document and will only be translated in different national languages without changing the content of the risk minimization material. Therefore the national translations do not result in any additional information concerning the RMP. It is not necessary to add these translations in the RMP, the English version is sufficient.

- **Question 4:**
  Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1)?

  The documents RMP and PSUR are based on the safety concerns of a drug product. The safety concerns of both documents should be in alignment. But the documents are different: PSUR for retrospective, integrated, post-authorisation benefit-risk-assessment; RMP for prospective pre- and post-authorisation benefit-risk management and planning. This should be clearly described in the relevant GVP-Module. Therefore Part V.B.10 of the GVP Module V should be maintained.

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')*
225ff		**Comment**: As this a very important step in the life cycle of an RMP, examples should be given here under which circumstances safety concerns could be removed from the RMP.
285ff		**Comment**: The term 'most important risks' should be defined more clearly and examples should be given. What distinguished it from an important risk?
289		**Comment:** Does that mean that the link to the respective document is sufficient or has the cited document to be listed in annex.
424-430		**Comment:** In this section it should be clearly stated that safety concerns only comprises risks/missing information with a possible/known impact on patient's health. **Proposed change:** It should be clearly stated here again that non-clinical safety findings, which are not considered relevant for human, should not forwarded to section SVIII and thus their discussion should stop at this point.
619		**Comment**: Does that mean that only information on "newly identified" risk should mentioned here and information on potential risk are excluded in this section? **Proposed change:** Give some examples for "newly" identified risk.
619ff		**Comment:** As this a very important step in the life cycle of an RMP, examples should be given here under which circumstances safety concerns could be removed from the RMP.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
984		**Comment:** What should be the language for national authorised products?
995ff		**Comment:** No information about the language were given. Is an English summary sufficient?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
CSL Behring

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Questions on which the Agency seeks specific feedback by means of the public consultation: 1. *The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?* The RMP content in the safety specification should be in full alignment with the content of the PSUR. Changing the definitions in Module V to diverge from the definitions in other GVP modules would in many cases result in different lists of risks in the EU RMP to the PSUR. This is likely to result in confusion for stakeholders, and makes communication between MAH and CA regarding important risks unnecessarily complex. In addition, whilst many countries outside EU follow the EU GVP guidance, there are still many who base their requirements around the original ICH E2E template and definitions. Therefore, these changes would result in differing lists of important risks being included in RMPs in different countries/regions- causing difficulties for both MAH and inter-agency communications. There is an appreciation for the proposed changes in definitions to provide a less complex pharmacovigilance plan and risk minimisation plan, which is targeted to only risks which require further characterisation or additional risk minimisation measures. An alternative to changing the definitions would be to provide a subset of important risks under a new definition of 'Risks requiring additional activities'. This would allow the safety specification to remain in line with the PSUR and other documents, but the pharmacovigilance plan and risk minimisation plan to target those risks which require actions in addition to routine PhV (such as activities to characterise the risk or additional risk minimisation measures). As an example, the content of Module SVIII (summary of safety concerns) could be changed to look like this:

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

Category	Risk	Risk requiring additional activities
Important identified risks	• Anaphylactic reactions • Migraine • Thromboembolic events	No No Yes
Important potential risks	• Anaemia • Stevens Johnson syndrome	Yes Yes
Missing information	• Safety profile in pregnancy and lactation	Yes

Only risks which are indicated with a 'Yes' would be discussed in Part III and Part V. A rationale would need to be provided for risks which are indicated with a 'No' as to why no actions were needed (eg. well characterised risk with no additional actions needed, current clinical practice sufficient to manage this risk).

2. *Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2?*

In line with the current GVP Module V, MAH should have the option to provide category 4 studies in the table for completeness.

3. *Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?*

Given that materials could differ in various member states, depending on the structure of the health system and product distribution in each member state, this appendix could be unnecessarily cumbersome. The proposed key messages in Appendix A should be sufficient.

4. *Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?*

Stakeholder number *(To be completed by the Agency)*	General comment
	Section V.B.10 should be maintained and expanded in line with the current GVP Module V (Section V.B.14 in current module). The reasons for not adopting the new proposed terminology in V.A.1 are provided in the response to question 1.

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')*
156-158		Comment: New definitions not used in the entire context of the pharmacovigilance legislations may lead to confusion and inconsistencies. Proposed change (if any): Do not introduce definitions which are not used consistently throughout all GVP Modules
160, 167		Comment: Proposed is the phrase "*An undesirable outcome….*" Definition of the term "*undesirable outcome*" required Proposed change (if any): Please continue to use "*an adverse reaction….*"
168		Comment: Not clear whether the term signal includes also not yet confirmed signals. Would a confirmed signal be synonymous with potential causal association? Proposed change (if any):
171		Comment: Unclear why among the term "*important identified risk*" and "*important potential risk*" the term "*important risk*" is used in this document. Use of latter mentioned term may lead to confusion and/or misinterpretation and inconsistency. Proposed change (if any): Do not use the term "*important 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')*
182-184		Comment: Sentence " *If confirmation….*" This sentence is somewhat redundant and not logical linked to sentence 2 of this paragraph. Proposed change (if any): Sentence and should be merged with the first sentence of this paragraph or –alternatively- should follow the first sentence. Current second sentence is not logical linked to the first one and should be moved to the end of the paragraph.
201		Comment: Additional value of introduction of the term "safety concern" unclear because just an umbrella term for already defined terms. There is the danger that the term "safety concerns" is used inconsistently. Proposed change (if any): Do not use the term in context of this document
205		Comment: Suggest to strike the term pharmacovigilance and replace by risk minimization activities, because in many instances one need cooperation between functions and other organizations including Heath Authorities Proposed change (if any): Replace term "*pharmacovigilance*" by "*risk minimization*"
214-216		Comment: Highly unclear and confusing to understand why one would have different definitions and different use of these terms in different modules. It is of eminent importance that terms are used in a consistent manner throughout all GVP Mules because of significant interdependencies between Modules. 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')*
		Use defined terms consistently in ALL GVP Modules
234		Comment: Example given in brackets to elevate a “important potential risk” to “important identified risk” does not comply with the definition of “important identified risk” provided earlier in the document Proposed change (if any): Delete above mentioned phrase “*(e.g. if they result in associated additional risk minimisation activities)”*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
[redacted] DADA Consultancy

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Q1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? A1: the priority should be a focused RMP. Whenever both PSUR and RMP would influence one another they can be aligned.
	Q2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? A2: I am questioning the removal from part III. If the aim of such a study would be the same as of a category 1 to 3 study, why not include? I would definitely leave it at least in annex 2.
	Q3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? A3: No. They are approved separately and that documentation I presume can be shared between NCAs if required/requested.
	Q4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? A4: maintained. With this revision I do not see a major change in the purpose and relationship of both documents.

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')*
288-289		Comment: How is this linking to other parts of the dossier envisaged? With actual functioning hyperlinks or sufficient to include some kind of reference? Proposed change (if any):
295-296		Comment: Similar comment as above. This wording implies some technical approach in drafting the RMP that is not totally clear to me. Proposed change (if any):
333-334		Comment: When can a version be considered the final version? If version 0.8 is approved, would the MAH need to resubmit that RMP as version 1.0, with QPPV signature? Proposed change (if any):
617-620		Comment: Wording used: "V.B.4.8.2. RMP module SVII section "Identification of safety concerns with a submission of an updated RMP" For post-authorisation RMP updates, newly identified risks not considered important or missing information" I checked against the definition of safety concern and these concern either important (identified/potential) or missing info. So such newly identified risks would not be safety concerns. I do not understand this text.
623		There is no section V.B.4.8.1.1
708-710		MAHs are "strongly encouraged to share" but can apparently still reject to provide their questionnaire(s). Would it be possible to include these on the EMA website in the document section for the applicable product?
960-969		Glad to see this clarification that the sections on measuring effectiveness only apply to additional RMMs
1296-1297		Is it envisaged that unlike now, Annex 1 may also become applicable to NAPs? I find this wording not very helpful.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2016

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) – Module V – Risk management systems (Rev 2)' – EMA/838713/2011

Comments from:

Name of organisation or individual
EFPIA [redacted]

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: **1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?** **Response:** The priority of the GVP Module V should be an EU focused RMP list of safety concerns highlighting important identified and potential risks, or (important) information which is missing for the product._ It should not include description of other ADRs or risks which do not qualify as "important" by definition. This approach is well highlighted in Lines 24-28 of the Guidance on format of the RMP Integrated Document. **Rationale:** The EU RMP list of safety concerns reflects those agreed with the European regulators which should be a focused list in line with the principles well described in this GVP revision. The PSUR/PBRER, however is a document with international scope as it can be submitted multiple agencies outside the EU/EEA. As a result, it is not unusual for some regulatory authorities (including Japan, Canada and Switzerland) to require additional safety concerns over and above those included in the EU RMP. As such, it would be inappropriate for the PSUR/PBRER submitted in these countries to exclude the safety concerns highlighted locally, even if not in the EU RMP. This situation was clearly addressed in the ICH E2C (R2) Implementation working group Q&A endorsed by all the ICH regions including the EU. This Q&A recommended inclusion of all the safety concerns required/requested by all countries and that additional safety concerns would need to be addressed in the PSUR/PBRER. As such it is inevitable that the EU-RMP and PSUR content will not always be fully aligned although clearly this would be a desirable situation. EFPIA hope that the welcome clarification of what truly constitutes a safety concern in this revision of Module V will help achieve greater harmonisation with non-EU countries that require submission of the EU-RMP and minimise instances where additional safety concerns (not considered so by the company or the Agency) are requested to be added by a non-EU agency. EFPIA consider that this important factor will play a more significant role in any discrepancies than the updated terminology and guidance. This takes into account that conceptually nothing has changed and that the principles of risk and important risk remain the

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	same. Nevertheless, we acknowledge that different explanations and terminology could easily cause confusion to different stakeholders; for example under the current definition of " identified risk " in Annex 1, there is a statement that *"Adverse reactions included in section 4.8 of the summary of product characteristics (SmPC) are also considered identified risks...."* In this respect the terms ADR and risk are being used interchangeably which is incorrect as the risk is the undesirable outcome of the ADR. This may well be another route cause of some of the issues raised previously when requests have been received to classify an ADR as an important identified risk. EFPIA will make recommendations to update the terminology in Annex 1 in the detailed comments below to promote consistency and understanding. **2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2?** **Response:** Category 4 studies should not be included. **Rationale:** Per Directive Article 8(3), the primary aim and focus of the EU-RMP is (and should remain) risk management planning for those required/imposed studies contained in Part III (PV Plan). It is not a repository of every study conducted anywhere in the world with a primary or otherwise safety objective. As such, Annex 2 should contain a summary of the Category 1-3 studies listed in the PV Plan. From a practical perspective, inclusion of the protocols from such studies in Annex 2 (invariably from countries such as Japan and Korea) would require translations from multiple documents, adding an undue burden to the organisation which is not consistent with the principle a risk management system that shall be proportionate to the safety concerns highlighted in the document. Not least, it will add considerable length to the document, as well as frequent updating whenever a new study is set up in an affiliate and it is difficult to determine what purpose it will serve or indeed if such extensive additional documentation that is not actively contributing to the EU risk management system will actually be read and/or acted upon. Whilst EFPIA is completely supportive of transparency, the burden imposed on MAHs in relation to the unclear "benefits" cannot be justified, especially when CHMP and the NCAs are not planning to assess category 4 studies. This position, furthermore, takes into account that, should any new safety findings emerge from these Category 4 studies, then the information would be communicated per standard obligations of MAHs under the PV legislation. In addition, data from these studies are disclosed via other ways such as the PASS register for EU voluntary non-interventional trials, as well as listed in the PSUR standard appendix **3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?** **Response:** No, risk minimisation materials distributed in the Member States should not be included in the annexes of the RMP. Only the Core materials should be included in the proposed Annex of the RMP, with locally modified materials retained locally.

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	Rationale: Sponsors should have a core set of additional risk minimization materials (in translated versions) which are distributed to Member States per GVP Module XVI Addendum 1 (Section 2 Principles for Educational Materials). Member States may have comments and changes which are then reviewed by the Sponsor and may be accepted or negotiated. It should be the Sponsor's responsibility to ensure that the final additional risk minimization materials which are agreed upon by the Member States adhere to the core additional risk minimization program. Addition of these materials to an Annex of the RMP would not add value since there may be differences in the materials for some Member States and this would be based on comments from those Member States. Overall, inclusion of materials for risk minimisation measures in the RMP after Member State approval would not be logistically feasible due varying MS approval times, translation requirements, etc. Thus, national risk minimization material might not be available at the time of the initial RMP and will only become available in variable time frames which would lead to a lot of unnecessary updates if all material would be added to the annex. **4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?** **Response:** Section V.B.10 should be maintained **Rationale:** Per lines 1089- 1100 of the revised guideline, EFPIA acknowledge that the EU-RMP and PSUR/PBRER documents have different objectives and hence, useful to keep wording that outlines the key differences between the objectives of the PSUR and the RMP. Nevertheless there is still an appreciable degree of overlap in a number of the sections and it should be possible to utilise the same sections across multiple documents wherever possible in the interests of efficiency and in order to minimise unnecessary duplicated effort. As such, Section V.B.10 provides additional clarity on the overlap between some sections of information contained in a PSUR and that in an RMP. Retention is also consistent with the modular approach agreed internationally by ICH E2C (R2) and provides direction on what can be done if the two documents are submitted together. It furthermore retains the possibility to future developments in the concept of the modular approach in order to promote further streamlining to future submission of these safety related documents.
	Overall General Comments by EFPIA EFPIA would like to acknowledge the Agency's and all other parties involved in the revision of this Module for the welcome, thoughtful and considerable efforts taken to make the revised document/accompanying template, a more user friendly document which more clearly outlines the EU requirements for the development of a RMP. Overall, EFPIA agrees that the revisions to the GVP Module V provide a more concise and clear description of risk management and

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	how safety risks evolve through a product's lifecycle based on evidence from a variety of sources. We particularly appreciate the attempts to realign with fundamental principles originally set out by ICH E2E which remain relevant now and which facilitate a document that focusses on what really matters in terms of promoting public health and optimising benefit risk. Lines 219-250 nicely describe the principles and thought processes involved in risk management. EFPIA`s outstanding comments largely reflect fine tuning of a document which has undergone considerable revision including removal of several redundancies present in the current version, based on very thorough process by the Agency. Our outstanding concerns generally reflect how reworded sections could be misinterpreted although we understand the intent behind them **Concerns**: • Consequences of refocussing Modules VI and VII • Absolute clarity in the revised terminology • Differentiation between an ADR and identified risk • Inconsistency of terminology across GVP Modules and Annex 1 • Practical Implementation **Consequences of refocussing Modules VI and VII** This is EFPIA's biggest concern with the revised Module V guideline as it appears to have moved a lot of the considerations from the previous Module VI into Module VII, as well as introduce duplication within Module VII As noted elsewhere we are particularly concerned about the apparent need in V.B.4.8.1 to "justify risks not taken forward as safety concerns. This is being widely interpreted that any ADR listed in section 4.8. of the SmPC requires a justification that it is not an important risk; this will certainly be how it is interpreted in the future particularly in the light of existing Annex 1 wording which stated that any ADR in section 4.2 should be considered " an identified risk" which is clearly incorrect. We understand from the Implementing Regulation (Article 30 1a) that the safety specification should identify or characterise the safety profile of the medicinal product. Clearly the focus should be on important risks and missing information but the apparent need to justify why every ADR is not a safety concern seems excessive and unnecessary and we are not sure that this was the intent. We do accept that there are safety topics derived from specific situations/data sources that need to be considered to see if they could be a safety concern but including them for discussion in Module SVII will inevitably be interpreted that they are an important risk or missing information as this section of the RMP has always been focused on characterising important risks (despite the title of the module) It is EFPIA`s considered opinion that this refocussing of Modules VI and VII will lead to a lot of confusion and misinterpretation and recommend that Modules II, IV and VI focus on identification of safety concerns (acknowledging that some safety concerns may arise from other considerations not covered by these modules) and that Module VII should focus on characterising important risks

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	(including why a risk is considered to be important) and life cycle aspects of the safety concerns. As a result, the safety topics currently listed in lines 495 – 537 of Module VII would be moved back into Module VI where the focus would be to assess whether or not each safety topic could be an important risk or missing information Only those assessed as being a safety concerns, namely if the associated risk was deemed to be important, would be carried forward for further characterisation in Module VII. In addition to the concerns raised above with respect to the new proposal that "risks not considered important" should be discussed and justified in Module VII, EFPIA firmly considers that this is not warranted in an RMP, since the RMP should focus on risks which are important enough to be categorized as identified, potential and missing information. Apart from the confusion and likely misinterpretation that will undoubtedly arise, the task of keeping such a section up to date will be daunting e.g. as new ADRs are added to section 4.8 of the SmPC as well as tracking over several sections of new information throughout the product life cycle. During the marketing authorisation application procedure, all accumulated information is provided to the EMA and Assessors/PRAC/CHMP with detailed safety analysis and summaries at a point in time including determination of what is and what is not a safety concern to be included in the RMP. As a result, the information in this proposed new section will potentially constantly change during development creating more work for all stakeholders and effectively duplicating already established MAA processes and procedures for agreeing the content of the RMP and what should be considered to be safety concerns. Similarly, in the post authorisation period, there are established systems in place including signal management and periodic safety update reports, through which newly identified ADR/risks can be evaluated in order to determine whether or not they constitute important risk. To include again in the RMP would constitute unnecessary duplication. EFPIA`s overall assessment of this new section to justify risks not considered important is that it does not add any new scientific understanding to risk management planning or create efficiencies in the RMP system but detracts from understanding of important safety concerns. To avoid duplication of efforts this new section should be deleted Further practical suggestions, including proposals to minimise duplication are also given in the detailed comments below. **Absolute clarity in the revised terminology** Extensive industry experience to date has demonstrated that, whilst guidelines are written by subject matter experts and generally reviewed by stakeholder experts during consultation who understand the intent of the verbiage included in the guideline, the content and wording of the document may be interpreted entirely differently once it is released for implementation e.g. by less experienced personnel or by PV inspectors particularly if there is an ambiguity in the verbiage in the guideline. In this respect, wording that was included in the original GVP Module V and its subsequent revision (R1) were considered to be a reasonable reflection of ICH E2E concepts (on which it was based) and the generally accepted standards upon which the classification of important risks and missing information were based. Subsequent experience proved that literal interpretation by new Assessors and other stakeholders was entirely different, a situation that underpinned the original AESGP/EFPIA Position Paper supported by EGA and which prompted the current R2 revision to Module V.

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	As one example, EFPIA note that the term "risk" is often used in the guideline when it should actually be "important risk". Given the concerns already expressed that the term " risk" will inevitably be interpreted as any ADR, then the term should always be qualified with "important" wherever this is the intent and in order to avoid any possible misinterpretation that would otherwise occur. We will note where this applies in the detailed comments below. EFPIA therefore consider that absolute clarity in terminology and amendment of any potentially ambiguous wording is crucial to ensure consistent understanding and implementation of the revised guideline. Proposed amendments in the specific comments section below have aimed to remove any possible ambiguity and wherever possible we have also included illustrative examples to provide further clarity **Differentiation between and ADR and Risk** EFPIA very much welcomes the revised definitions and improved focus on "undesirable outcomes" in the definitions of risk. We are concerned however that, without further explanation and illustrative examples, the erroneous understanding by stakeholders that all ADRs are identified risks will continue. This situation is further encouraged by the current wording in Annex 1 (alluded to previously) that all ADRs listed in section 4.8 of the SmPC should be considered identified risks which is clearly incorrect. Not least the definition of risk and ADR are different and the content of section 4.8 is adverse reactions (Adverse Effects) Furthermore, this misunderstanding seems to be continuing , even in this revision, notably in section SVII.1.2 which requests that any risk not taken forward as a safety concern should be justified. This will almost certainly be interpreted as justifying why every single ADR listed in section 4.8 is not considered to be an important risk even if it is clearly a non- serious ADR e.g. nausea, flushing, rash. While all identified risks are ADRs , not all ADRs are identified risks, as the risk of some ADRs is purely driven by the outcome so, for example if thrombocytopenia is a listed ADR in 4.8, then the associated risk would be " bleeding"; similarly if elevated hepatic transaminases is an ADR, then the associated risk is hepatoxicity or DILI. Likewise Prolonged QTc interval may be an ADR but the risk per se is Torsade de Pointes. On the other hand, myocardial infarction, ventricular arrhythmia, CVA can be both an ADR and a risk. As a consequence of this misunderstanding, it is not unusual for both the ADR and risk to be listed in the RMP as if they were completely independent important risks Further clarification is therefore considered to be important in order to avoid perpetuating the confusion or we anticipate that there will be no significant impact on the identification and categorisation of risks in RMPs prepared under the revised GVP Module V guideline without this clarity and lack of ambiguity. In addition illustrative examples, including sources of identified risks other than from CTs, would be very helpful in order to promote clarity, consistent understanding, and hopefully avoid further misinterpretation.

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	Inconsistency of terminology between Module V(R2) and Annex1 This inconsistency in terminology between the revised Module V and the current Annex 1 has already been highlighted in relation to impact on the list of safety concerns in the PSUR/PBRER vs the new refocussing in future RMPs. Although conceptually the approach has not changed in that important risks have always been those that could impact benefit risk or public health, the interpretation and guidance surrounding the classification, documentation and management of risks has been refined and misunderstanding and confusion is only likely to continue until the terminology is aligned across this module and Annex 1. EFPIA appreciate that Module VII would also be impacted but there is not the opportunity to make changes that deviate from ICH standards. Having said that the PSUR is less of an issue than differing terminology with Annex 1, so we strongly consider that Annex 1 should be updated to be consistent with Module V(R2) as a matter of high priority. We appreciate that updating any guideline or Annex will take time so would recommend a Q&A in the interim. EFPIA would be happy to work in collaboration with the Agency on this if it would be helpful. **Practical Implementation** It is important that the roll-out of the new template is adequately planned. Some key points are as followed: • It is essential that NCAs are ready to receive the new simplified RMPs (including training of assessors on the new template); • While implementing the new template for new products will be relatively straightforward, the complexity of managing a template change for products that already have an RMP in place should not be underestimated. Clear instructions will be needed to clarify: o whether the new template will need to be implemented proactively for all products, o if yes, whether it will need to be done within a certain timeline, o whether the template change can be introduced with another planned change to the RMP, or via a separate variation, o which type of variation the template change would be (it is assumed that it would be a type IB). o how to handle the template change if there are multiple versions of the RMP under evaluation. Revision 2 of GVP Module V is scheduled to come into effect at some time during Q3 2016. It is not clear to us if this timeframe also applies to adoption of the revised RMP template. In addition, it is not apparent to which RMPs the template requirement will apply or if it will be phased in over time. MAHs face a substantial amount of work under what apparently will be a highly compressed timetable in order to change their internal documents and processes. This burden would be eased considerably through advanced notice from EMA to industry of the agency's implementation plans. We recommend that the agency issues an advanced communication of its anticipated implementation schedule for the revised RMP template, both for products requiring an initial RMP and for those with existing RMPs. Ideally this would occur as soon as logistically feasible prior to the final versions of Module V and the RMP template being released. It is recommended that this is discussed with industry stakeholders once the template is finalised. **Other General Comments and Suggestions for fine tuning:**

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	To ease navigation between the GVP module and the template, EFPIA suggest referring to the section number from the template rather than just the part, module and section title e.g. in line 602 this would read V.B.4.8.1 RMP Module SVII.1 identification of safety concerns....and likewise when providing guidance on subsections such as in line 607, minimise complexity by removing the subheadings number V.B.4.8.1.a and refer to the relevant section number of the template instead i.e. line 607-608 becomes V.B.4.8.1.a RMP Module SVII sections SVII.1.1 and SVII.1.2 for example. The numbering of the GVP module is quite difficult to follow and errors were noted during review. • While EFPIA welcomes the clarification and the effort made in reducing duplication with the document, there is still a fair amount of duplication between the GVP Module and the RMP template and sometimes some inconsistency as noted between the two documents. Consideration for reducing the duplication, e.g. by using cross-reference to the template where possible may help. • GVP P.III is not available yet so EFPIA consider that alignment between the two documents is important with respect to biological medicinal product. We assume that EMA has already reviewed the implications and need for consistency between these two guideline and had adjusted the content of the two documents accordingly RMPs depending on when the updated GVP will be in force vs the new GVP P.III

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')*
116		**Comment:** Although EFPIA fully understands the intent of the phrase "not all actual or potential adverse reactions...", we recommend that standard terminology is used as proposed below in order to avoid any potential for misinterpretation by less experienced stakeholders and for absolute clarity. **Proposed change:** "However, not all ~~actual or potential~~ adverse reactions or identified or potential risks will have been identified....."
119-122		**Comment**: Line 119 appears to mix the separate concepts of a risk management system and a risk management plan. Although this is undoubtedly unintended, it coulc cause confusion so early in the guidance. We propose that it should be more closely aligned to the wording in the legislation. Also the concept of managing known important risks seems to be missing **Proposed change** (if any): The aim of a risk management plan (RMP) is to ~~address uncertainties regarding the safety profile at different points in a medicinal products life cycle and to plan risk management activities accordingly~~ document the risk management system considered necessary to identify, characterise and minimise a medicinal product`s known important risks and to address uncertainties at different points in its lifecycle. These efforts should be focused on optimising a product's benefit-risk balance
123-125		**Comment:** EFPIA acknowledge that the verbiage in these lines exactly reflects that in Article 30 of the Implementing Regulation, however use of the terminology "safety profile" is readily open to misinterpretation that it pertains to **all** ADRs or risks associated with the medicinal product when, in fact the focus of the RMP is on important risks and missing information. We therefore propose the following modification to provide further clarity and avoid any ambiguity. In addition, "which risks need to be further characterised **or managed proactively**" in relation to the safety specification appears to be introducing an element of risk minimisation into the safety specification which is likely to be unintended.

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		Proposed change 1. identification and characterisation of the safety profile of the medicinal product, which focuses on important identified and potential risks and missing information that may need to be further studied and characterised ~~or managed proactively~~ (the 'safety specification')" 3. Proactive planning and implementation.....
Lines 156 – 158 and Lines 214-216		**Comment:** As noted in the general comments above, EFPIA is concerned that as long as the terminology surrounding (important)identified and (important)potential risks remains inconsistent across GVP modules and Annex 1, then this will only continue to cause confusion and perpetuate the confusion and misunderstanding that prompted the much needed revisions to Module V in the first place. In fact there is a high likelihood that Assessors and industry alike may continue to revert back to the Annex 1 definitions as these are more familiar; changing behaviours and understanding in the circumstances therefore will be a huge challenge. It is therefore imperative that Annex 1 is updated to align with the revised terminology in Module V(R2) as a matter of high priority. In an ideal world the revised Annex 1 should be released t the same time as the finalised Module V(R2) but we clearly appreciate that this is logistically impractical. In the meantime, EFPIA recommend that to minimise the confusion and provide more clarity that a Q and A is published to guide Assessors and MAHs on how any discrepancies can be addressed practically. It would also be helpful if the wording in this revision reflects that the content of Annex 1 will be updated to achieve consistency with this revision of Module V **Proposed change:** Without prejudice to the terminology provided in GVP Annex 1 until the Annex is revised to be consistent with this GVP Module, more focused definitions.....
Lines160 - 165		**Comment:** EFPIA very much welcomes the revised definitions and improved focus on "undesirable outcomes" in the definitions of risk. We are concerned however that, without further explanation and illustrative examples, the erroneous understanding by stakeholders that all ADRs are identified risks will continue. This situation is further encouraged by the current wording in Annex 1 (alluded to previously) that all ADRs listed in section 4.8 of the SmPC should be considered identified risks which is clearly incorrect. Not least the definition of risk and ADR are different and the content of section 4.8 is adverse

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		reactions (Adverse Effects) Furthermore, this misunderstanding seems to be continuing , even in this revision, notably in section SVII.1.2 which requests that any risk not taken forward as a safety concern should be justified. This will almost certainly be interpreted as justifying why every single ADR listed in section 4.8 is not considered to be an important risk even if it is clearly a non- serious ADR e.g. nausea, flushing, rash. While all identified risks are ADRs , not all ADRs are identified risks, as the risk of some ADRs is purely driven by the outcome so, for example if thrombocytopenia is a listed ADR in 4.8, then the associated risk would be " bleeding"; similarly if elevated hepatic transaminases is an ADR, then the associated risk is hepatoxicity 0r DILI. Likewise Prolonged QTc interval may be an ADR but the risk per se is Torsade de Pointes. On the other hand, myocardial infarction, ventricular arrhythmia, CVA can be both an ADR and a risk. The consequences of this confusion have been previously highlighted in this commentary. Further clarification is therefore considered to be important in order to avoid perpetuating the confusion or we anticipate that there will be no significant impact on the identification and categorisation of risks in RMPs prepared under the revised GVP Module V guideline. In addition illustrative examples, including sources of identified risks other than from CTs, would be very helpful in order to promote clarity, consistent understanding, and hopefully avoid further misinterpretation. The amendments suggested below are being made on this basis. We also suggest adding "clinical" before undesirable outcome for an identified risk as this is determined by clinical data whereas a potential risk may be derived from both clinical and non-clinical sources. Finally, it appears that the sentence "In a clinical trial, the comparator may be placebo, active substance or non-exposure." is derived from Annex 1 under the after the examples stated of sources of identified risks. In that context it is appropriate to refer to what comparators may be used but as used in Line 162, the wording seems redundant and could be deleted. **Proposed change:** An undesirable clinical outcome for which there is sufficient scientific evidence that it is caused by the medicinal product. Identified risks may be derived from adverse drug reactions or the outcomes of adverse drug reactions from multiple sources such as adverse non- clinical findings confirmed by clinical data, clinical trials and epidemiology studies and spontaneous data sources including published literature. They may also be the result of adverse reactions specifically linked to situations such as off label use, medication errors or drug interactions. ~~In a clinical trial, the comparator may be placebo, active substance or non-exposure.~~ Where an adverse event ~~which~~ is an identified risk for an active comparator and the event occurs at a similar ~~(active comparator)~~ or higher frequency with a new product in a clinical trial, this suggests that the adverse event ~~should~~ could also be an identified risk for the new

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		product, particularly if both investigational products are in the same drug class. The identified risk of some ADRs would be the adverse clinical outcome of the effect. For example, laboratory abnormalities may be listed as ADRs for a medicinal product but the identified risk relates to the adverse clinical sequelae if these have been observed and confirmed to be due to the laboratory abnormality such as the risk of bleeding due to thrombocytopenia, the risk of MACE or adverse CV outcomes due to increased cholesterol/ hyperlipidaemia or the risk of infection due to neutropenia. Other examples include the risk of dehydration which has been confirmed as due to listed ADRs such as nausea, vomiting and /or diarrhoea or cardiac arrhythmia due to an ADR of coronary vasospasm or Torsade de Pointes due to QTc prolongation. In these circumstances, both the ADR and associated risk would be listed in section 4.8 of the SmPC Other ADRs listed in section 4.8 of the SmPC can also be identified risks, particularly if the underlying adverse effect leading to the risk is unknown or the ADR is idiosyncratic e.g. pancreatitis, myocardial infarction, insomnia
Lines 167-169		**Comment:** The current terminology defining a potential risk would be clearer if it was more explicit in stating the need for scientific evidence (vs "a basis"). In addition, it would be helpful to clarify that, contrary to the definition of an identified risk, the basis for a potential risk may be non-clinical adverse findings that have not been confirmed or refuted by clinical data. As noted in the AESGP/EFPIA Position Paper on Risk Management endorsed by EGA (submitted in January 2015), a signal can certainly be a source of information from which a potential risk arises but if a signal is refuted following evaluation, then it cannot be a potential risk. As such, inclusion of "signal" without any qualification as an example of a potential risk could easily be misinterpreted and needs to be modified. The changes suggested below reflect these comments, together with some re-ordering to make the sentence clearer. **Proposed change** (if any): … An undesirable clinical or non-clinical outcome for which there is ~~a~~ scientific evidence ~~basis for supposition of~~ to suspect a causal relationship with the medicinal product ~~(e.g. a signal, a class effect plausible also for the new product, findings from (non-) clinical studies)~~ but where there is insufficient evidence ~~support~~ to conclude that there is a causal association i.e. the basis for supposition is more than just theoretical considerations. Examples of a potential risk would include a signal that has been evaluated and the outcome considered to be indeterminate (can be neither refuted nor confirmed), a class effect plausible also for the new product, findings from ~~(~~non-~~)~~ clinical studies

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<tr><th>Line number(s) of the relevant text
(e.g. Lines 20-23)</th><th>Stakeholder number
(To be completed by the Agency)</th><th>Comment and rationale; proposed changes
(If changes to the wording are suggested, they should be highlighted using 'track changes')</th></tr>
<tr><td></td><td></td><td><u>which have not been observed or resolved in clinical studies or undesirable outcomes observed in clinical trials or epidemiological studies</u></td></tr>
<tr><td>Lines 170 - 189</td><td></td><td>Comment: It would be helpful to provide a table at the end of the section on (important) identified risks to summarise the information provided in the text on what constitutes and ADR, risk or important risk

Proposed Change: Insert this table after line 189

<table>
<tr><th>ADR</th><th>Associated Risk</th><th>Associated Important Risk</th></tr>
<tr><td>QTc prolongation</td><td>Torsade de Pointes (T de P)</td><td>Torsade de Pointes (T de P)</td></tr>
<tr><td>Coronary artery vasospasm</td><td>Cardiac arrhythmia</td><td>Serious cardiac arrhythmia</td></tr>
<tr><td>Increased CPK</td><td>Myopathy</td><td>Rhabdomyolysis</td></tr>
<tr><td>Neutropenia</td><td>Infection</td><td>Serious infection/sepsis</td></tr>
<tr><td>Nausea and vomiting</td><td>Dehydration</td><td>Renal impairment</td></tr>
<tr><td></td><td></td><td></td></tr>
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<tr><td>Lines 170-177</td><td></td><td>Comment: Combining the definitions of important identified risk and important potential risk into one somewhat lengthy sentence, has caused confusion and difficulties in determining what differentiates the two concepts as they are clearly not the same. Furthermore it introduces a significant potential for misinterpretation in the future, particularly by less experienced personnel. Although EFPIA appreciate that the proposed re-wording presented below will make the section more lengthy, we recommend that separate definitions are created and additional explanatory text added as clear, unambiguous terminology is (and will be) crucial for optimal interpretation and consistent adoption of this guideline. In this respect, we consider that it is important to convey the principle that the likelihood of an important identified risk having an impact on benefit risk/public health if not managed appropriately is higher than that of an important potential risk. Currently both appear to have "equal weighting", namely both could have an impact. Overall, it seems that it is necessary to provide text that spells out requirements in words that cannot be misinterpreted and are completely</td></tr>
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		unambiguous. **Proposed change :** An important identified risk ~~or potential risk~~ is a risk that ~~could~~ is likely to have an impact on the benefit-risk balance of the product if it is not managed appropriately in daily clinical practice. An important identified risk ~~and which~~ would therefore usually warrant: • Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of the risk under normal conditions of use or which populations are particularly at risk) and/or • Additional risk minimisation measures beyond routine communication in the SmPC. If additional risk minimisation measures are not deemed to be necessary, it is likely that the SmPC will include instructions that are intended to affect clinical practice (e.g. requiring dose reduction or frequent monitoring in certain populations) Consistent with the principles highlighted above in determining what an identified risk is, not all ADRs will constitute identified risks and those which are considered to be an identified risk would not be classified as important unless they have a likely impact on benefit risk or public health. In this respect, even a serious ADR or risk may not be important if it occurs extremely rarely and when it does not require additional PV or risk minimisation activities, particularly in the context of treatment of a serious medical condition. Similarly an ADR which is clinically concerning would not be an important identified risk if it has not been associated with undesirable outcomes which could have an impact on benefit risk e.g. elevated transaminases or CPK levels can be listed ADRs but the associated important risks such as DILI or rhabdomyolysis would remain as important potential risks if these outcomes had not been observed or confirmed. (Please refer to Important Potential Risks). As a result of these factors not all ADRs listed in section 4.8 of the SmPC need to be considered for classification as an important risk, especially if they are non-serious. Further evaluation of important identified risks through additional pharmacovigilance activities would be expected to be included in the initial MAAs for new active substances but may not be necessary to address well characterised safety concerns in the initial MAAs of more mature active substances e.g. generic applications. **Important potential risk** is a potential risk that, when confirmed and further characterised , could fulfil the criteria of an important identified risk and hence have a potential impact on benefit risk for the medicinal product, Important potential risks may be the undesirable outcomes of listed ADRs in section 4.8 of the SmPC if possible outcomes have not

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		been either observed or established e.g. if QTc prolongation is a listed ADR in section 4.8 of the SmPC but there is no compelling evidence that this ECG finding is causally associated with Torsade's de Pointes, then T de P remains as an important potential risk. Similarly if neutropenia is an listed ADR, then serious infections would be classified as an important potential risk in the absence of any clinical evidence of serious infections that could impact benefit risk associated with neutropenia caused by the medicinal product or if the serious outcomes were so infrequent that they did not fulfil the criterion for important. An important potential risk should require further evaluation as part of the pharmacovigilance plan as for an important identified risk and would include assessment of whether or not a likely causal association can be established. Important potential risks are unlikely to require additional risk minimisation measures but may require routine risk minimisation activities via communication in the SmPC if the information provided could impact patient management by the prescriber. Typically, a potential risk.....
Lines 182-184		**Comment:** It would be less confusing if the proposed modification is made to the example given as it is no longer a potential but identified risk. In addition, additional monitoring may be established medical practice e.g. INR monitoring for a new anticoagulant medicinal product **Proposed change**: If confirmation of the potential risk as an identified risk would not result in any changes ~~of~~ to the usual monitoring requirements, then such a ~~potential~~ risk would not usually be considered 'important'."
Lines 185 – 188 And Lines 198 - 200		**Comment:** The additional clarification provided in lines 185 – 188, namely that situations such as off label use or use in populations not studied need to be associated with likely adverse reaction to be considered a potential risk, is much needed clarification. Per line 198, EFPIA also agree that if off label use is considered to be likely, then it would constitute "missing information". The subsequent example given , however , (if a markedly different safety profile than that in the target population is suspected, the specific safety concern that might be associated with off label use should be specified rather than the global term off label use) though absolutely correct is actually indicative of a potential risk than off label use as missing information. We therefore recommend that this wording is moved to the end of line 188. We would also suggest that for off label use to be considered missing information, then off label use would be predicted in unstudied sub populations or indications but there is no evidence to anticipate that the off label use would be associated with a different

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		safety profile or specific adverse effect or that any association with a different safety profile is unknown. This situation would also apply to the other examples cited under " missing information" (See comments under Lines 191 – 200 below) **Proposed change:** .....and if deemed important, should be included as an important potential risk. In these circumstances, the specific safety concern that might be associated with the off label use or long term use or use in populations not studied, as well as other situations (please also see the specific safety topics derived from specific situations/data sources included in Module SV1, which is currently SCII) should be specified rather than the global term ("off label use";" long term use"; "medication error" etc.
Lines 191 - 200		**Comment:** Consistent with the comment for " off label use " above, the definition (including use of the terminology " *Gaps in knowledge.....which could be clinically significant")* seems closer to that of a potential risk and the two need to be clearly differentiated. Based on current experience, EFPIA note there is existing confusion on this point. Expressed very simply, a potential risk would be one where there is evidence to suspect an adverse outcome but as yet unconfirmed; missing information would be situations , circumstances or subpopulations which are likely to arise or occur post authorisation e.g. use in children or pregnant women, off label use, etc. but where the associated risk is unknown or unsure. Use of "could be clinically significant" could well be interpreted that there is some basis to suspect that use in these circumstances would be associated with adverse outcomes when in fact, they represent situations /subpopulations that are likely to occur/be used post authorisation and they simply have not been studied or there is insufficient knowledge to know whether or not there could be adverse outcomes. The slightly revised wording proposed below aims to take these points into account and ensure that the terms potential risk and missing information are clearly differentiated. So, for example, use in pregnancy would be "missing information", if there was no evidence of adverse impact on the foetus to date based on non-clinical and very limited clinical evidence but the medicinal product is likely to be used in women of child bearing potential and was not studied in development. " Adverse effects on the foetus (following use in pregnancy)" or Congenital malformations (following use in pregnancy)" would be an important potential risk if skeletal malformations ad been observed in one or more non-clinical species and these had neither been confirmed nor refuted in very limited clinical experience during development. **Proposed Change:** Gaps in knowledge about a medicinal product.....for which there is no or insufficient experience to date to determine whether or not they could be clinically significant. For instance: • Safety profile with long-term use when ~~there are suspected potential risks~~ most of the current clinical

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		experience is in short term use for a product intended for use in a chronic medical condition so likely to be used for several years. In these circumstances, the data are insufficient to determine whether or not ~~related to~~ cumulative or other adverse effects could occur following long term exposure; • Use is anticipated in subpopulations not studied or only studied to a limited extent (e.g.....) and there is no or insufficient clinical experience to determine whether or not the safety profile will ~~is expected to~~ be different in these sub-populations; • Off label use is anticipated to be likely (e.g. in subpopulations or indications that have not been studied or for which clinical experience is very limited); in the absence of any evidence or information to determine whether or not off label use could be associated with adverse outcomes for patients, then " Off label use" would be classified as missing information. This is in contrast to the situation when there is some evidence to suspect that off label use could be associated with ~~.~~if a markedly different safety profile than that in the target population. ~~is suspected,~~ In the latter circumstances, if considered to be important, the specific safety concern that might be associated with off label use should be specified as important missing information rather than the global term "off label use" (see previous section on important potential risk in the RMP
214-216		**Comment:** The same comment applies here as already made for lines 156-158. In addition, it is unclear in ".....the definitions in GVP Annex 1 apply without the respective above **for the EU GVP"** which EU GVP is being referred to (presumably the revised Module V). If this is the case "for the EU GVP" is redundant and can be deleted. **Proposed change:** .....without the respective focus described above ~~for the EU GVP.~~ This situation will only apply until Annex 1 is revised to be consistent with the terminology in this GVP Module.
236-238		**Comment:** There may be other more common circumstances when it is medically and scientifically justifiable for an MAH to propose that an "important identified risk" can be removed from the RMP. Typically such circumstances would include when " important identified risks" were assigned based on assumptions taken some years ago that have been rectified in this revision e.g. non – serious events such as flushing, injection site reactions and nausea/vomiting classified as important identified risks or where adverse effects such as elevated liver enzymes seen in clinical development were interpreted as an important identified risk of hepatotoxicity but several years and extensive exposure demonstrated that there was no evidence that DILI is occurring or is occurring so rarely in the context of extensive exposure that, whilst

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		clearly a serious ADR, it is no longer considered to be important, especially if no additional risk minimisation activities are considered to be necessary and no additional monitoring is required above usual clinical practice. **Proposed change** (if any): Add as a third bullet point: • There may be other circumstances where existing RMPs list as " important identified risks", adverse effects or outcomes that would not meet the criteria for " important " or an "identified risk" as defined in this Module. Such situations could include the listing of common adverse effects that are generally mild or non - serious such as nausea, injection site reactions or serious ADRs that extensive clinical experience has shown to be so rare that they no longer are considered to be important from the point of view of minimal impact on benefit risk, especially if no additional PV or risk minimisation activities are needed. Similarly, an important identified risk could be considered for removal if it had been added to the RMP as a conservative measure at the time of authorisation or early in the post authorisation period based on limited data but then subsequent extensive exposure demonstrated that it was occurring very rarely and/ or was generally presenting in a non- serious or mild form. Other situations could also include ADRS of laboratory abnormalities such as neutropenia, thrombocytopenia or increased CPK, when the adverse outcome or important risk is Serious infections, Serious bleeding/Haemorrhage, or rhabdomyolysis respectively. Removal of the laboratory abnormalities could be considered if the associated risk was already included as an important risk and/or if the subsequent clinical experience had failed to demonstrate any adverse outcomes of the laboratory abnormalities included as ADRs.
234-235		Comment: The rationale for elevating an important potential risk to an important identified risk should be the strength of the association between the risk and the product, not whether additional risk minimization activities are proposed. 1. Proposed change (if any): (e.g. ~~if they result in associated additional risk minimisation activities~~ if scientific and clinical data strengthen the association between the risk and the product whether or not additional risk minimisation activities are considered necessary.)
Line 238		**Comment:** The phrase" "*the required risk minimisation measures have become fully integrated into standard clinical*

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		practice", may be open to interpretation so EFPIA propose a slight modification that adds an example of what we think is intended **Proposed Change:** .....the required risk minimisation measures have become fully integrated into standard clinical practice such as inclusion into treatment protocols or NICE/equivalent guidelines",
Lines 249-250		**Comment:** The sentence about change to additional risk minimisation activities should also include that the results of effectiveness evaluation could lead to the need for change. Per the comment to line 238, EFPIA suggest adding examples. societies. **Proposed change** (if any): "The need to continue additional risk minimisation activities may change as they become part of the routine practice such as inclusion into standard treatment protocols in the EU , or in response to the findings of effectiveness evaluations."
Lines 261-269		**Comment**: Highlighting the need to continuously review the safety profile and list list of safety concerns is appreciated. The advice provided here would also benefit being reflected in section V.C.1 to provide further clarity in the later section **Proposed change**: Similar wording to be reflected in section V.C.2.1 describing the maintenance of the RMP over time.
Lines 264-269		**Comment**: EFPIA appreciate the practical advice given with respect to suggesting specific "milestones" when it is recommended that MAHs should reflect on the need to review the list of safety concerns. The way in which it was worded has led to some confusion, particularly reference to 8-9 years, therefore we propose some small amendments to enhance clarity and reduce the potential for any ambiguity or misinterpretation. We have assumed that the milestone around the time of generic applications is on the basis of a likely stable and well characterised safety profile at that time as well as facilitating consistency with the generic RMPs which may need to be brought in line with a revised list of safety concerns of the innovator.

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		Proposed change: In addition, there are two specific ~~moments~~ milestones when the MAHs are advised to reflect on the need to review.....and risk minimisation activities: with the 5-year renewal and in the time period when ~~around the submission of~~ the first PSUR following that 5-year (~~first~~) renewal ~~is~~ due for submission~~.~~ It is anticipated that this PSUR submission would ~~(~~usually occur approximately 8-9 years following the granting of the marketing authorisation and at a time when the assessment of the generic products for the active substance commences~~)~~ As such, the safety profile of the medicinal product is likely to be sufficiently stable and well characterised to allow an update list of safety concerns in the innovator RMP. In addition, this would facilitate efforts to maintain consistency between the revised innovator RMP and that/those of subsequent generic RMP(s)
Line 276		**Comment**: It appears that reference to V.C.2.1 is an incorrect cross-reference **Proposed change**: Replace V.C.2.1 with V.C.1.1.
Lines 283-284		**Comment**: The sentence "The safety specifications in the RMP should not be a duplication of data submitted elsewhere" has caused some confusion with respect to what is intended by " data submitted elsewhere". EFPIA assume that the intent is to not duplicate data already submitted in the CTD/eCTD or where sections of other documents such as the PSUR/PBRER are intended to be common modules. We have therefore modified the wording on this assumption **Proposed change:** The safety specifications in the RMP should not be a duplication of data submitted elsewhere in the CTD/eCTD or unless the sections are intended to be common modules with other documents such as the PSUR.
Line 287		**Comment**: Although this line refers to data presented in other modules of the eCTD, not all (nationally approved) product dossiers have been transferred into an eCTD format. As all dossiers irrespective of regulatory procedure use the CTD format, EFPIA recommend that whenever there is reference to eCTD, the CTD is given as an alternative. **Proposed change**: .....presented in other modules of the eCTD or CTD.
Line 326		**Comment:** An eCTD link to the currently approved PI is suggested as part of the administration information for the RMP

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		but there are situations where eCTD submissions are not available such as for a nationally submitted MAA dossier. EFPIA therefore propose that reference to eCTD is only "where available" and have proposed an alternative solution when there is no eCTD. This takes into account situations where submissions are still paper based in some Member States for NAPs. **Proposed change :** eCTD link to the currently approved PI, where this is available or reference to the respective CTD knot (either as hyperlink or in written form e.g. embedded pdf file)
328-329		**Comment**: It is unclear what is meant by "only related to main population". **Proposed change:** (summary information – only related to the recommended dosage that will be used by the majority of the target ~~main~~ population; not a duplication of all dosages/dosage adjustments for the sub-populations listed in Section 4.2 of the SmPC.
333-334		**Comment:** EFPIA full agree that QPPV oversight of the EU-RMP is imperative, however question the continued need for a "wet signature" in an age when documents are managed electronically and where all MAH approvals are documented and auditable. As long as an MAH is able to demonstrate QPPV oversight of the RMP and can produce evidence of approval on request that should be sufficient. Where the internal procedures of an MAH do require a QPPV signature for the RMP, then this can be easily handled separately to the European template document. Reference to GVP Module 1 is probably not needed as the QPPV role is well established now. The current wording also implies that the finalised approved version of the RMP is in the closing sequence of the eCTD which may not be the case e.g. for national authorisation submissions they may be no eCTD. The revised wording for the eCTD has been aligned with that in the template. **Proposed change:** The QPPV`s actual ~~(see GVP Module 1)~~ signature is not required for the RMP but evidence that there has been QPPV oversight of the document is still considered to be important. This evidence can be achieved by a statement on the front page that the RMP has been approved by the MAH`s QPPV and that the electronic signature is on file. This statement is not needed for versions submitted for assessment~~; this~~ but can be included ~~in the closing sequence~~ in the finalised approved version of the RMP. For eCTD submissions, this would be with the RMP submitted in the last eCTD sequence of the procedure.

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336		**Comment:** As noted earlier, EFPIA appreciates that reference to the safety specification as the section of the RMP which identifies or characterises the safety profile of the medicinal product, we are nevertheless concerned that this implies that every single ADR listed in section 4.8 of the SmPC be evaluated in this section along with other conditions of use that may also be a concern. The focus of the safety specification is clearly on specific aspects of the safety profile which could become a safety concern, namely, important identified and potential risks and missing information and in the presentation of scientific evidence as to which adverse outcomes fulfil the criteria for a safety concern. The terminology "adequate discussion on the safety profile", can be interpreted that the safety specification has to discuss every single aspect of the ADR profile along with other situations but rather than its intended purpose which is a more focussed approach. **Proposed change:** The purpose of the safety specification is to ~~provide an adequate discussion on~~ identify and characterise key aspects of the safety profile of the medicinal product(s), with a focus on those aspects that need further risk management activities. As such, it ~~It~~ should be a summary of the appropriate scientific evidence that supports what constitutes the important identified ~~risks of a medicinal product~~ and potential risks and missing information of a medicinal product ~~and~~ It should also address....
409-430		**Comment:** Although other sections of the guideline contain advice that the content can change with the experience from the post-authorisation phase, the non-clinical section does not. Of all the sections in the RMP, however, the non-clinical data relevant at the initial authorisation of a product is the most likely to become obsolete or even prove to be an inaccurate predictor of human experience for products with several years of extensive clinical exposure. EFPIA therefore propose to include guidance that the content should be maintained and assessed for relevance over time. **Proposed change:** Add at the end of the section in Line 430 "The content of this section should be assessed for relevance over time. Post-authorisation, this section would only be expected to be updated when new nonclinical data impact the safety specification and/or benefit: risk of the product. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed even after several years of post-marketing experience can be removed."

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424		**Comment:** Significant non-clinical findings in the absence of confirmation in human experience are invariably important potential risks. Clarification is therefore needed that this type of safety concern is considered to be a *potential* risk. **Proposed change:** "...safety finding could constitute an important potential risk to the target population..."
Line 426		**Comment:** It would be helpful to clarify that if the non-clinical safety finding is not considered relevant for humans and a rationale is provided, then it is not carried forward to SVIII. **Proposed change** (if any): "...for human beings, provision of a brief explanation is required, **and then the risk is not carried forward to SVII and SVIII."**
Lines 432-453		**Comment:** Similar to the comment made above with respect to the non-clinical data section, it would be helpful to clarify when there is a need to update the section on clinical trial exposure. It would also be useful to indicate that this section too should be reviewed for relevance over time, taking into account that clinical trial exposure becomes increasingly irrelevant (in the absence of major updates due to clinical data for new indications etc.) the longer a medicinal product is on the market when post authorisation exposure greatly exceeds that in a CT setting. **Proposed change:** In this RMP module, in order to assess the limitations of the human safety database, summary information on the patients studied in clinical trials should be provided in an appropriate format (e.g. tables/graphs) at time of submission of the initial RMP or when there is a major update such as an updated RMP with exposure data from clinical studies in a new indication. The content of this section should be assessed for relevance over time and, in the absence of clinical trial exposure data in new ind cations /populations or formulations etc. the CT exposure does not need to be updated when post authorisation exposure significantly exceeds that in a clinical trial setting.
Lines 456 - 460		**Comment:** The EU-RMP template includes important wording and instruction that would be useful to include in the guideline document as well for clarification purposes and to minimise the potential for misinterpretation. The EU RMP template refers to "important exclusion criteria" so it would be helpful to provide guidance on which exclusion criteria are considered 'important' (e.g. those in the protocol for the well-being of subjects vs those in the protocol to define an 'efficacy' population). As noted before , use in a subpopulation or circumstances not studied where there is evidence to

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		suspect an adverse outcome, then the adverse outcome should be specified as an important potential risk if it is expected to fulfil the criteria of a safety concern. **Proposed change:** Exclusion criteria from the clinical trial development programme should only be included as missing information when they are not proposed as contraindications for the medicinal product e.g. a contraindication may not be relevant to the target population or, for reasons that should be explained, the exclusion criteria are reflected in Section 4.4 of the SmPC (Warnings and Precautions) or the exclusion criteria pertain to efficacy considerations.. When exclusion criteria ~~from the clinical development programme not proposed as contraindications for the medicinal product, then RMP Module SIV should~~ are listed as missing information, then module SIV should also include a discussion on the relevant subpopulations, including whether or not any use in populations excluded from the clinical trials (e.g. women of childbearing potential, older people) might be associated with a different list of safety concerns. If use in populations not studied and /or available information is insufficient to determine whether or not use in these circumstances could constitute a safety concern, then ~~and~~ this should be included as missing information in the RMP. If there is evidence that use in excluded populations could be associated with important adverse outcome(s), then the important adverse outcome(s) should be included as an important potential risk
Lines 467 - 468		**Comment:** The suggestion currently is that the degree of renal, hepatic or cardiac impairment **"should"** be specified as well as the type of genetic polymorphism. This would not give enough flexibility as for all products the type of genetic polymorphism may not be available. **Proposed Change:** It would be helpful to include at the end of the sentence "where available/appropriate".
470-482		**Comment:** EFPIA note that there is now a discrepancy between the advice given in the Module V RMP template, which requires only **exposure** data to be presented, and the proposed GVP Module text which requests a discussion of patterns of use arising from that exposure. Given that patterns of use in practice, including off label use and use in special populations in specifically addressed in the PSUR and /or other sections of the RMP, then further inclusion in Module SV could be considered duplicative which seems contrary to advice provided in Line 474 (not intended to duplicate information from PSURs).

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		We acknowledge that the proposed revision in the guideline considerably reduces the extent of discussion stipulated in previous versions of Module V but this may be an opportunity to focus even further on post authorisation patient exposure only (as the accompanying template suggests) and to move any discussion on the implications of post authorisation drug utilisation to the other section(s) that address off label use, use in pregnancy, use in other subpopulations such as children. The current guideline indicates that this discussion would be in Module SVII but for reasons already highlighted as a concern in the general comments we recommend that this is included as an EU specific requirement in Module VI. **Proposed change: (EFPIA Preference)** Delete lines 477 – 482 and consider whether or not they would be more appropriately placed in the section(s) of the RMP that address whether or not these situation/ use in sub-populations constitute a safety concern. If post marketing exposure data are available.....It is not intended to duplicate information from the PSUR. High-level information on the number and characteristics of patients such as age and gender should be included, when available. Or **Alternative proposed change:** Amend the EU RMP template to create a sub section in Module V that addresses the utilisation discussion currently stipulated in lines 477 - 482 which would then be retained.
Lines 483 - 489		**Comment:** As noted in the General Comments section above, EFPIA are concerned that the scope of Module SVI has changed significantly and that situations/sub-populations previously evaluated in this section appear to have been effectively moved to Module VII. Furthermore, the rationale for moving the majority of safety topics previously included Module SVI to Module VII and not the potential for misuse for illegal purposes is far from clear. In effect all are specific EU requirements for the safety specification that were not covered in ICH E2E so nothing has changed in this respect. This is a significant concern as, inadvertently, it will create much confusion and a perception that the safety topics listed will automatically be considered to be safety concerns as they are being discussed in the Module that was intended to focus on the characterisation of important risks. EFPIA`s considered opinion is that sections prior to Module VII should focus on the **identification** of safety concerns and that Module VII should focus on the **characterisation and life cycle aspects** of the safety concerns. This can be easily rectified by clarifying that Module VI is intended to address safety topics derived from specific situations/data sources that are of particular interest in the EU and with a view to determining whether or not they constitute a safety concern to be characterised in Module SVII. Taking into account comments made above for Module SV, the scope for patterns of use

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		such as off label use and use in sub-populations could be expanded to post authorisation experience where this is available and relevant to the assessment of whether or not such topics warrant classification s a safety concern to be characterised in Module SVII, **Proposed change:** Some safety topics were not included in the ICH E2E format.....or prior experience of a safety issue. The purpose of this section is to concisely discuss the topics listed to determine whether or not they could constitute a safety concern, namely that there is some evidence to suspect they could be associated with undesirable outcomes sufficient to impact benefit risk or public health. The discussion for all topics should take into account available experience which may include how the product is being used in practice such as labelled and off label use and use in special populations when relevant to the assessment of whether or not the topic constitutes a safety concern. If off label use is considered to be a safety concern in the EU, data on unauthorised use in markets outside the EU should also be summarised and the implications for the, authorisation in the EU discussed, but only where appropriate and relevant. ~~This~~ The particular safety topics of interest in the EU include: • Potential for harm from overdose Then move lines 495 t0 537 to follow the content of this bullet point **NB: 1.comments on the content of the individual bullets points moved from Module VII will be included in the comments below and pertaining to the lines in which they are currently placed.** **2. We note that risks associated with the disposal of the used product, risks related to the administrative procedure and specific paediatric safety information per section 5 of Annex 1 of the PIP opinion are included in the accompanying RMP template but not included in the Module V guideline. Presumably these need to be added and , again recommend that this is in Module VI** **3. Similarly, we note that risks in pregnancy /lactation and effects on fertility are included in Module V but not in the template.**
Line 491		**Comment:** The fact that this section of the RMP is titled " Identified and Potential Risks" despite the focus being on **Important** Identified and **Important** Potential Risks is an ongoing and perpetual cause of confusion and a justification for including ADRs/Risks that are clearly not " important" being included for characterisation. This point is alluded to in

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		many sections of this commentary and a source of concern. The current instruction given seems clear but , nevertheless is still being misinterpreted so EFPIA advise that it is spelled out in completely unambiguous terms. Per comments documented before too , EFPIA strongly consider that the purpose of Module SVII is the characterisation and lifecycle management of safety concerns and not the module in which safety concerns are identified. Identification should occur in earlier sections of the RMP, notably sections II, IV and VI: **Proposed Change:** Despite the title of this section being "Identified and Potential Risks, the focus and content of this RMP Module is to ~~should~~ provide a focussed discussion on the ~~identification~~ characterisation of **important** identified and important potential risks and missing information (i.e. safety concerns)
Lines 495 -537		**Comment:** As highlighted previously , discussion on all the safety topics currently listed in Module VII, are better placed in Module VI. In addition, in order to avoid further **Proposed Change:** Move lines 495 to 537 to immediately follow line 489 in Module VI.
Lines 507 - 509		**Comment:** As currently written it appears as if the sentence in Line 507 should finish after reference to the Good Practice guide on recording, coding, reporting and assessment of medication errors. The wording that follows seems to be redundant and makes little sense. **Proposed change:** Delete "including in Annex 2 – Design features which could be considered to reduce the risks of medication error an extensive list of potential medication errors and their consequences to the patients.
Lines 520 - 521		**Comment:** EFPIA welcome the clarification that off label use needs to be linked to an undesirable outcome or a different safety profile in order to be considered a possible important risk. Per previous comments, we recommend that the assessment of whether or not the outcomes of the off label use constitute a safety concern should be in Module VI and not Module VII and that inclusion in Module VII should only be on the basis that the potential or important risk associated with the off label use are important and warrant characterisation. The current wording could be interpreted that any outcome could be considered important which is probably not what was intended.

		Proposed change: In such cases, If the potential or identified risks arising from the off label use of the product are considered to be important, following evaluation in Module VI then they should be ~~considered for inclusion~~ included as a safety concern for characterisation in Module VII
522 to 524		**Comment:** As noted previously, it is important to qualify "risk" with "important" when this is appropriate or it could easily be misinterpreted that that every single ADR included in 4.8 or Warning and Precaution included in section 4.4 of other members of the pharmacological class should be discussed. This is an important point to clarify as EFPIA has experienced already such requests from some national Competent Authorities. Overall, establishing what constitutes an important risk for the class of NAPs is a challenge in the absence of an existing RMP. **Proposed change:** if an important risk common to other members of.....
Lines 615 – 616 Lines 619-621		**Comment:** EFPIA fully supports the concept of providing the scientific evidence supporting why an ADR or risk is being considered to be an important identified or potential risk. As such we welcome its addition to this Module of the RMP as it forces a critical and objective assessment of the data and why a risk could truly impact benefit risk and or public health. As noted in the general comments however, we remain extremely concerned with the proposed new sub- section (Risks not considered important for inclusion in the safety specification) which is and will continue to be interpreted as effectively needing to justify why every single ADR included in section 4.8 of the SmPC or even in section 4.4 is not an important risk. In addition to the reasons already discussed in the general comments section, this proposal would also be highly duplicative of the eCTD/CTD Summary of Safety which is considered to be the more appropriate place for a detailed description. In particular, lines 615-616 would necessitate a document as long as the SCS, and thus make the RMP an extremely lengthy document with no added value. It could also be argued that this sub-section could duplicate sections of the PSUR/PBRER where signals evaluated during the period have been closed and refuted or where new information on a known risk does not warrant an "upgrade" to an important risk It is our firm scientific opinion that the safety information in the RMP should be focused on the safety concerns that meet the definition of a "important risk" and which require risk minimisation to prevent harm to patients.. It is not necessary for the RMP to mirror all of the ADRs included in section 4.8 of the SmPC, that are documented in the Summary of Safety for the initial RMP or the PBRER for updates. This seems to go against the intention of streamlining the RMP and focusing on valuable and relevant information. MAHs should document their internal discussions and evaluations as appropriate, but we propose that this justification not be included in the RMP; the RMP should focus on what is included and why. For the same reasons EFPIA also consider that " newly identified risks not considered to be important or missing information" have no place in a section that should focus on what is a safety concern Not least, the way in which it is worded is very confusing, ambiguous and open to variable interpretation. As such there is considerable uncertainty regarding scope. Is the expectation to discuss newly identified risk not considered important or missing information or previously identified risk not considered important or missing information for which new emerging data is available since the last submission of the RMP or both? This section too could become very large, include non-value added information to the RMP and be duplicative of the PSUR and other documents.

		Proposed change; 1.Delete lines 615-616 ~~For risks not taken forward as safety concerns the justification for not including them as a safety concern~~ 2.Delete Lines 619-621 ~~For post authorisation RMP updates, newly identif ed risks not considered important or missing information, for which significant emerging data is available since the last submission of the RMP, should be discussed in this RMP section.~~ **Note: these proposed changes above do not take into account separate comments below relating to simplification of the different sections.**
602-623		**Comment:** Although EFPIA fully appreciate the intent of the information in this section of the RMP, we are concerned that it has become unnecessarily complicated and fragmented as well as highly duplicative. Not least, it seems to have lost focus and stands in danger of becoming overly long and bureaucratic. As highlighted before, EFPIA strongly consider that this section of the RMP should focus on the characterisation of important risks which would include the scientific basis for inclusion as a safety concern, as well as when important risks and missing information can be either reclassified or removed. Overall what is being proposed does not appear to be in line with the principle of refocus and streamlining of the RMP and we consider that there are simple ways of achieving the same end so that the current complexity of V.B.4.8 can be largely eliminated without loss of important information. In particular, it will help reduce the significant concern and confusion that it is currently causing. In particular: • The rationale for presenting the safety concerns in the initial RMP separately to those subsequently determined is unclear and over complicates this important section. EFPIA consider that it is preferable to have the RMP always reflect the current situation is not clear, especially given the earlier guidance about linking to other sections of the eCTD. It will also lead to potentially duplicative tables with over-lapping information. It should be very easy to identify which important risks are newly identified by a simple addition to the subsection in which important risks are characterisec (V.B.4.8.3) • Clear duplication of information is apparent between V.B.4.8.1 and V.B.4.8.3 The information requested in Lines 612-614 for each risk 1.e., on scientific evidence for the risk, seriousness, frequency and clinical and benefit-risk impact is repeated again SVII.3. Such duplication is completely unnecessary and can be readily managed, again, by inclusion of an additional subheading in V.B.4.8.3 that relates to "Rationale for classifying the risk as important. Accompanying instructions in the template can provide guidance on which considerations are considered necessary to make the determination. If the rationale includes evidence source and strength of the evidence (scientific basis for suspecting the association, seriousness, frequency, clinical and benefit risk impact), then it is not necessary to repeat later on in that sub- section as all the relevant information is contained in a single subsection. • EFPIA completely support the proposal to include a justification for reclassifying or removing safety concerns which is entirely in line with appropriate life cycle management of an RMP, taking into account the principles discussed earlier in the guideline. As it is unlikely that an MAH could unilaterally take action before the

justification has been agreed with the agency (ies), then it makes more sense to place V.B.4.8.2 (b) after V.B.4.8.3 on the assumption that the content V.B.4.8.3 would remain unchanged until the justification had been considered and agreed. Furthermore instructions to that effect would be helpful as it is currently unclear if a justification is made whether or not it is possible for the MAH to act upon it for that version of the RMP. It would be inefficient to go ahead and remove or reclassify only to have to change if agreement is not reached.

Proposed Changes:

V.B.4.8.1 RMP Module SVII section " ~~Identification~~ Characterisation of ~~safety concerns~~ Important Identified Risks and Important Potential Risks ~~in the initial RMP submission~~

This RMP section should ~~contain the initial identification of safety concerns~~ provide more information on the medicinal product`s important identified and important potential risks, including the scientific rationale for classifying the different risks as important. Where appropriate, this section can also include a justification for one or more important risks or missing information to be re-classified or removed. The information provided should be made in order to appropriately characterise each important risk. ~~and is expected to be populated for RMPs submitted with the initial marketing authorisation(MA) application or with a new RMP submitted post authorisation (at the competent authority`s request or without request)~~
For RMPs covering multiple products where there are significant differences in the important identified and potential risks and missing information for different products(e.g. fixed dose combination products), it is appropriate to make it clear which safety concerns relate to which product.
This RMP section applies to all stages of the product`s life cycle.

Lines 607 – 623 should be deleted.
Lines 624-627 should be moved to after the current section V.B.4.8.3 and will become V.B.4.8.2
Modify the title slightly: **V.B.4.8.2~~b~~ Justification on the reclassification of safety concerns ~~re-classification~~ (deletion, ~~addition,~~ downgrade and/or upgrade)**
lines 630 – 633 moved to the introductory paragraph above (new section V.B.4.8.1)

~~Presentation~~ Characterisation of important identified and important potential risks ~~data~~

- Name of the important risk (using MedDRA terms where appropriate)
- Newly Identified Important risk (Yes/No)
- Rationale for classification as an important risk
  - Evidence source(s) and strength of evidence (i.e. the scientific basis for suspecting the association)
  - Seriousness
  - Frequency (incidence rates with confidence intervals)
  - clinical and benefit risk impact
- ~~frequency (interval rates and confidence intervals~~

		• potential mechanism • ~~Evidence source(s) and strength of evidence (i.e. the scientific basis for suspecting the association)~~ • Impact on the individual patient(~~e.g.~~ i.e. absolute risk.....as well as quality of life • Risk factors and risk groups (including.....or synergistic factors, such as interaction with other medicinal products) • Preventability (i.e. predictability of a risk.....could mitigate seriousness) • ~~Impact on the benefit risk balance of the product~~ • Public health impact (absolute risk.....at population level)
647		**Comment:** In terms of "impact on the benefit-risk balance", further guidance would be useful to advise MAHs what kind of information the Agency anticipates would be included for impact on benefit risk. EFPIA appreciate that there is further wording provided in the template but even this is not very helpful. Important risks, by their very nature, are usually relevant to the benefit-risk assessment. **Proposed change:** Add wording from lines 577-579 of the template and, if possible, add some illustrative examples that would meet expectations
Lines 650 - 656		**Comment:** This section is new to the RMP and, as noted before in relation to comments for Lines 191-200 (terminology on missing information), use of terminology "such as description of the risk" is confusing and more descriptive of a potential risk than missing information. Missing information is a critical gap in knowledge in relation to anticipated utilisation patterns, generally in patients not studied/or studied to only a limited extent or following long term or off label use. If there was reason to suppose that use situations were associated or with a risk, then this would constitute a potential risk and, if important listed as such as a safety concern. Missing information implies that whether or not there is an associated risk is unknown or uncertain. In these circumstances, EFPIA assume that the purpose of this section is to give an update on information received this indicated that such situations or subpopulations may be associated with an adverse outcome of different safety profile. As such the purpose of this section is unclear and would merit some explanation to avoid further confusion and misinterpretation. " description of a population in need of further characterisation" is, by implication the " missing information" so this can be deleted. **Proposed change:** **Update on the status of Missing Information Data** The purpose of this section is to provide an update, where applicable, on the status of new information received e.g. from PASS or other data sources to address missing information listed as a safety concern in the safety specification of the RMP. It is possible that new data may provide reassurance that use in the situations/subpopulations does not appear

		to have an associated risk of provide an indication or confirmation that there is an associated risk or different profile. If the risk is shown to be important then the important risk due to use e.g. in children or in off label indications should be included as an important identified or potential risk (depending on the strength of the association) and " off label use" or "use in children" (per the examples) could be removed as missing information. If there is no new information or no change in the status of the missing information, this section does not need to be completed. Where new information has been received, the following information should be included: • Name of the missing information • Description of any potential or identified ~~the~~ risk(s) demonstrated from the new information e.g.in the population not previously studied ~~or the description of a population in need of further characterisation;~~ • Evidence that the safety profile either is or is expected to be different.....target population, if applicable • The changes in the benefit –risk.....(i.e. worst case scenario) • Whether or not findings warrant classification as an important identified or important potential risk with or without additional risk minisationa activities.
Line 665		**Comment:** As noted before, wherever the term risk is used and important risk intended, then this should be clarified in order to avoid misinterpretation. **Proposed change**: to further characterise the important risks identified in...or characterise the safety concerns identified in...
667		"...the investigation of whether a potential risk is real or not" **Comment:** "Investigation of whether a potential risk is real or not" could be more clearly expressed to avoid misinterpretation **Proposed change**: "...the investigation of whether a potential risk ~~is real or not~~ confirmed as an identified risk or refuted.
Lines 701-704 and Lines 1060-1064		**Comment:** The continued requirement to include copies of targeted follow up forms linked to the safety concerns listed in the RMP is a large administrative burden, especially as these may well be amended over time. The objective of including them in Annex 4 is unclear to EFPIA and we would question the extent to which they are actually reviewed during assessment of the RMP, what value they add and, whether or not they exist and /or are appropriate is better placed under the purview of the PV inspectors than in a scientific document. We would therefore ask for consideration as to whether this Annex is still needed at all, especially if, in practice the forms are not or only rarely reviewed. **Proposed change:** 1.....~~and copies of these forms should be provided in Annex 4~~ -or if inclusion of the forms is considered to be essential for evaluation of the RMP in order to assess whether or not the

		applicant or MAH has appropriate follow up in place 2.....and copies of these forms should be provided in Annex 4 unless applicants or MAHs have made these forms available on a website for access by either competent authorities or other applicants /MAHs in the interests of consistency and public health. If this is the case, then the availability and website should be noted in this section and in Annex 4 without the additional need to include copies of the forms.
711-714		**Comment:** Although this is likely to be inadvertent, lines 712 to 714 (Other forms of routine pharmacovigilance activities, appear to be introducing additional requirements for the PSUR/PBRER which are over and above those recognised as " routine PV activities" such as observed vs expected analyses in the PSUR, and cumulative reviews of events of interest. This position fully takes into account activities already under discussion for the " PSUR roadmap" **Proposed change:** EFPIAs preference would be to delete lines 711 – 714 Alternatively the following amendments should be made: Other forms of routine pharmacovigilance activities to be described in this section include e.g. enhanced passive surveillance, ~~requested~~ observed versus expected analyses ~~in the PSUR~~, ~~requested~~ re-evaluation of risks ~~in the PSURs~~, ~~cumulative reviews of adverse events of interest.~~
715-742		**Comment:** This section would benefit from a description, in simple terms, of the different categories of PASS, namely 1, 2 and 3. Module VIII (Rev 2) has been updated to include a list of reasons why a PASS may be required and refers to Module V. Although Table V.3 in the PV Plan section of Module 3 summaries the different categories, there is no adequate descriptions to distinguish the categories. Since the categorisation is important, and a source of confusion and misinterpretation, clear and simple explanations or at least a cross reference to Table V.3 would be helpful. In addition, it would be useful to include reference to the point that the PV Plan would only include Category 1-3 studies. **Proposed change:** Either cross reference to Table V.3 and/or include the following in section V.B.5.2. **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation. **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances. **Category 3** - Required additional pharmacovigilance activities
Lines 733-740		**Comment**: The different subsections proposed for Annex 3 appear to be somewhat complex although understandable from a competent authority perspective. In the circumstances, clarity as to whether an updated RMP, incorporating the draft protocols for part A and B is expected to be submitted when the protocol is submitted for review (which is not the current understanding) or whether MAH`s should continue to follow the same process that consists of a submission of the cover letter/protocol with the protocol to be added to the RMP at the earliest opportunity after it is finalised. In addition, for those protocols submitted for information only (Part C) – confirmation that such submission of initial protocol and protocol amendments can be undertaken at the earliest opportunity and not necessarily prior to study

		start/implementation would be welcome. **Proposed change:** RMP annex 3 – Part A should contain protocols ~~submitted for assessment~~ **that had been agreed**, when the protocol submission has been requested by the competent authorities; RMP annex 3- Part B should contain protocol **amendments** that have been agreed with competent authorities ~~and are being submitted when the RMP for amendment~~, when the protocol submission has been requested by the CA **(i.e. previously in Part A);** RMP annex 3 – part C should contain ~~protocols already approved and~~ other category 3 studies protocol, submitted for information only **when available** (see V.B.10).
Line 741 - 742		**Comment:** It would be useful to a) clarify that the final report submission milestone is mandated for all studies, while other are to be agreed on a study by study basis and b) specifically mention how to handle protocols in RMP annex 3 – Part 1-3 when the final study report has been submitted. **Proposed change**: ~~Milestones, including~~ **T**he time point for the final study report submission to the CA should be included for each study. Additional milestones if requested may need to be added. *Relevant sections of the RMP should be updated to include data from completed studies and protocols of completed studies should be removed from RMP annex 3 once the final study reports are submitted to the competent authority for assessment*
757-759		**Comment:** The second part of the first sentence"...unless they are also imposed (...) or required by a national competent authority" is causing confusion as it si being interpreted that it contradicts the second sentence "Studies not required by the EU or national competent authority should not be included in the pharmacovigilance plan in the RMP". There is lack of clarity as to whether or not if a study is required, but only by an outside-EU competent authority should it be included or not? **Proposed change**: Studies that are being conducted for safety reasons in jurisdictions outside the EU at the request of non –EU regulatory agencies should not be included in the EU RMP unless they are imposed as a condition of the MA.....obligation, or required (as a Category 3 study) by the Agency or an EU national competent authority. This is without prejudice to safety concerns.....
Lines 786 - 808		**Comment:** The reference to a baseline discussion on benefit seems to have been removed. EFPIA recommend that this section be reinstated to include a high level summary of the product's efficacy. This summary would provide a description of the product's efficacy (to inform benefit-risk) and when PAES are listed in Section IV, provide context for these imposed / obligatory studies. **Proposed change (if any):** Please reinstate the summary benefit information (even if it is extremely short.) It can be linked from module 2.5.6

Lines 812-816		**Comment:** The proposed changes are included below to encompass other key strategic important elements, including the concept of burden of any proposed additional risk minimization activities. **Proposed change**: "Consideration must be given to the risk proportionality of the risk minimisation activity proposed, the feasibility of implementing any additional risk minimisation activity in all Member States, whether the proposed measures are necessary for the safe and effective use- or whether they are likely impact the product's benefit- risk balance in the proposed indication (e.g. by limiting exposure to those populations for whom a greater benefit has been demonstrated ~~in the all patients~~, and the possibility to adapt distribution modalities for such risk minimisation activities ~~so as~~ to best ~~to~~ suit different healthcare settings. The burden of any proposed additional risk minimization activity on the stakeholders (ie. to the patients, healthcare practitioners, and healthcare system) should also be considered."
Lines 823-824		**Comment:** Consider inclusion of the statement below to provide clarity and avoid ambiguity. **Proposed change**: Add "If the additional risk minimization measure becomes standard medical practice, the risk minimization measure should be discontinued after consultation with the Agency."
846		**Comment:** SmPC Sections 4.2, 4.4, 4.5 and 4.6 are discussed, but the status of warnings in Sections 4.3, 4.7 and 4.9 is not included . EFPIA consider that these sections be included for the sake of completeness and to avoid ambiguity **Proposed change**: Add sections 4.3, 4.7 and 4.9. to the list in line 846
908		**Comment:** EFPIA consider that it is important to clarify that a Direct Healthcare Professional Communication (DHPC) is included in additional risk minimisation activities **Proposed Change:** (Line 909) Additional risk minimisation activities which may include a Direct Healthcare Professional Communication, should only be suggested.....
Lines 922-923		**Comment:** These lines refer to protocols for category 1-3 PASS studies (i.e. additional PV activities) in a section that relates to **risk minimisation activities**. As this GVP module seems to refer to the current RMP annex 6, this discrepancy should be corrected. **Proposed change**: delete lines 922-923 as not referring to the correct Annex and does not involve risk minimisation activities. .
Line 931		**Comment:** In the current version of Module V which is in effect, section V.B.11.2 RMP Part V section – "additional risk minimisation activities" includes a paragraph about the PRAC's oversight of additional activities. Importantly this paragraph clarifies that only activities which are recommended by the PRAC and subsequently agreed by the CHMP are

		allowed in the risk minimisation plan and become, once agreed by the European Commission, conditions of the marketing authorisation (Line 1369 of draft Guidance). This information is now moved to the very end of the document, under section V.C.3. This is rather confusing to the reader. **Proposed change**: Consider referring to Section V.C.3 at the end of Line 931 or add text: "The Pharmacovigilance Risk Assessment Committee (PRAC) is the body mandated to review RMPs and make recommendations on their content and on the suitability of proposed pharmacovigilance activities and risk minimisation measures. For centrally authorised products, only additional risk minimization measures which are recommended by the PRAC and subsequently agreed by the CHMP will be allowed in the risk minimisation plan." along with a reference to Section V.C.3, so the reader has access to this information in V.B.7.
940 - 943		There is no need for another impact assessment by region, since GVP Module XVI already mandated assessment of the effectiveness of risk minimization measure. Evaluation of effectiveness of the risk minimization activities should be based on formal assessment criteria already established in GVP Module XVI. In addition, as this guideline relates to the EU RMP " such information may be presented by region" could be interpreted as the effectiveness of risk minimisation measure across regions outside the EU which was probably not the intent **Proposed change** (if any): "When the RMP is updated, the risk minimisation plan should include ~~a discussion of the impact of additional risk minimisation activities~~ interpretation of evaluation of the effectiveness of additional risk minimization measure, if available. Such summary should include information on attainment of risk minimization objectives, important challenges on implementation or recommended changes based on results of the evaluation. Where relevant, such information may be presented by Member State e.g. if the results differ significantly ~~region~~."
Line 1011		**Comment:** the phrase "educational material in annex 6 might only be applicable to the RMP" is unclear; this may be a typographical error. **Proposed change**: (e.g. a follow up form in Annex4or educational material in Annex 6 might only be applicable to the products containing the active substance that is causally linked to the event; ~~educational material in annex 6 might only be applicable to the RMP~~)
1017		**Comment:** The title word "pharmacoepidemiological" should be replaced with "pharmacovigilance" as studies in the PV Plan may also include clinical trials or even non-clinical studies **Proposed change: Tabulated Summary of ongoing and completed ~~pharmacoepidemiological~~ pharmacovigilance study programme**
1025-1026		**Comment:** As noted in response to EMA`s specific question, EFPIA do not consider that Category 4 studies should be

		included as these do not add any value to the RMP. Stating that they are not required ensures clarity and a consistent approach by MAHs **Proposed change**: Studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as Category 4 studies) ~~can also be included for information in annex 2~~ are not required to be included in annex 2
Line 1032-1035		**Comment;** In line with previous comments (Lines 733 – 740), EFPIA recommend that it should not be necessary to update the RMP at the time of submission of the draft protocol(s)/protocol and/or subsequent amendments as this may require several updates during a procedure to align with the latest drafts and add unnecessary burden to companies, the Agency as well non-EU agencies that require all RMP versions to be submitted. EFPIA consider that the protocol submission should be handled as a standalone PAM (cover letter + protocol) and only when the protocol/protocol amendment is considered final, the RMP should be updated. Titles of the sub- sections headings are overly long and complicated. **Proposed change: Approved Protocols of ~~Proposed~~ Studies that have been ~~submitted~~ requested for regulatory review ~~with this updated version of the RMP~~** This part of RMP Annex 3 should include the protocols that ~~are proposed for assessment~~ have been agreed within the same procedure that the RMP has been submitted in and when the protocol submission has been requested by the competent authorities;
Lines 1040 - 1043		**Comment:** Same comment as for 1032 – 1035 **Proposed Change: Agreed Updates of previously approved protocols ~~of Proposed~~ that have been requested for regulatory review ~~with this updated version of the RMP~~** ~~This~~ Part B of RMP Annex 3 should be completed only when the study protocol update has been requested to be submitted within the RMP review by the competent authority. It should contain protocol amendments that have been agreed with competent authorities ~~and are being submitted when the RMP for amendment~~, when the protocol submission has been requested by the CA submitted for information only when available (see V.B.10). Delete line 1046
Lines 1048 - 1058		**Comment:** based on the previous feedback that Part A and B should contain final agreed protocols **Proposed change:** ~~Previously agreed protocols for on-going studies and~~ This part of Annex 3 should include the protocols of other category 3 studies not reviewed by the competent authority and are submitted by the MAH for information only. ~~in this part of RMP Anne 3, as follows~~ Delete lines 1050 1056

		Move lines 1057 – 1058 to follow after line 1031
Line 1060-1061		**Comment:** As noted before on relation to comments to lines 701 – 710, the continued requirement to include copies of targeted follow up forms linked to the safety concerns listed in the RMP is a large administrative burden, especially as these may well be amended over time. The objective of including them in Annex 4 is unclear to EFPIA and we would question the extent to which they are actually reviewed during assessment of the RMP, what value they add and, whether or not they exist and /or are appropriate is better placed under the purview of the PV inspectors than in a scientific document. We would therefore ask for consideration as to whether this Annex is still needed at all, especially if, in practice the forms are not or only rarely reviewed. **Proposed change:** 1.....delete Anne 4) lines 1059 – 1064 -or if inclusion of the forms is considered to be essential for evaluation of the RMP in order to assess whether or not the applicant or MAH has appropriate follow up in place 2. This annex should include copies of all follow – up forms used by the MAH to collect additional data on ~~specific~~ the important risks and missing information. If applicants or MAHs have made these forms available on a website for access by Competent Authorities or other applicants /MAHs in the interests of consistency and public health, it is not necessary to include the follow up forms in Annex 4; only reference to the availability and website reference/link should be noted in Annex 4 in these circumstances.
Line 1075-1082		**Comment:** For all the reason highlighted in response to the direct question on this point by EMA (including sheer volume of material and need for continual updates as materials are approved at different times and in different languages by the various Member States) EFPIA strongly considers that the additional risk minimisation materials as they were distributed in the Member States does not warrant inclusion in RMP Annex 6 (part B) of the RMP. Reference to the key messages or core materials distributed (which would be included in Annex 6 Part A would suffice. **Proposed Change:** delete lines 1075 – 1082
Lines 1311-1316		**Comment**: Based on previous experience, EFPIA consider that the wording as written is open to interpretation that an update to the RMP will be needed for any new routine PV measures or any updates to the SmPC for safety reasons. We appreciate that this is unlikely to be the intent. Cross reference to V.B.5.1 would therefore be helpful with respect to clarifying routine PV activities. Reference to monitoring renal function, however is probably not a good example of a routine risk minimisation activity as if this has been added into the SmPC, it will invariably be in relation to a new safety concern that would trigger an RMP update anyway. As such that example is best deleted. **Proposed change:** An update....beyond routine communication, (Please refer to V.B.5.1) For example~~.....when monitoring of renal function is added as a recommendation in the Specific Warnings and Precautions for use section 4.4~~

		~~of the SmPC (routine risk minimisation activity).~~
Lines1319 to 1321		**Comment:** The requirements for how emerging safety issues should be handled in the context of an RMP update are unclear. In addition it is not clear to EFPIA if the term "emerging safety issue" is being use as a "generic term" or as defined in GVP Module VI. If the latter reference to a confirmed safety signal is confusing as a confirmed safety signal may only represent a non-serious ADR and hence not an emerging safety issue in the sense intended by GVP Module VI. **Proposed Change:** When an emerging safety issue is still under assessment (reference GVP Module VI), in particular in the context of a signal or potential risk that could be an important risk, an RMP update may be required ~~upon confirmation that this impacts the safety specification~~ if the emerging safety issue is confirmed as an important risk requiring addition to the list of safety concerns in the RMP.
Lines 1358-1360		**Comment**: PRAC only review by default RMP for centralised products so this section appears to contain conflicting information. As stated in lines 1357-1358 PRAC is not involved in the RMP assessment for nationally products. **Proposed changes**: Clarify situations where the RMS would be involved or delete this part of the sentence "or with the RMS as appropriate". For the RMP assessment, the PRAC appoints a PRAC rapporteur who works closely with the (Co) Rapporteur(s) appointed by the CHMP ~~or with the Reference Member State as appropriate.~~"
Lines 1376-1378		**Comment:** NCAs should also ensure that MAH of the originator (reference) product is informed when a generic or biosimilar product has changes to its RMP/risk minimisation activities. **Proposed change:** When necessary, the competent authorities should ensure that all marketing authorisation holders of generic and/or similar biological medicinal products are informed and make similar changes to their risk minimisation measures when changes are made to those of the reference medicinal product. In some circumstances, it may be necessary to inform the innovator of changes to the RMP of generic or biosimilar products
		Minor Typographical and Editorial Comments
Line 126 - 127		**Comment:** A typographical error was noted. Sentence should read: **Proposed Change:** Planning of PV activities to characterise & quantify serious or clinically relevant risks or adverse reactions, and to identify new adverse reactions."
Line 169		**Comment:** This part of the sentence would be clearer if the word "support" was replaced with "evidence".

		Proposed change (if any):...clinical studies) but where there is insufficient ~~support~~ evidence to conclude that there is a causal association.
Line 211		**Comment:** Delete "s" **Proposed change (if any):** Any intervention intended to prevent or reduce the occurrence of an adverse reactions associated with.....
Lines 261 - 262		**Comment:** Insert "the" between "of" and "safety". **Proposed change:** The critical review of the safety profile of the product is a continuous activity and is reflected in data submitted.....
Line 296		**Comment:** Consider reference to the exact section of relevance. **Proposed change:** see V.B.9.**7.**
Line 504		**Comment:** This sentence would be more clear if "remedies" was replaced with "risk minimisation measures". **Proposed change:** "Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible ~~remedies~~ risk minimisation measures used. ~~Given.~~
Line 607		**Comment:** remove subheading that makes it complicated and refer to the section number of the relevant sections form RMP when appropriate for ease of navigation between both documents. **Proposed change:** ~~V.B.4.8.1.a~~ RMP Module SVII sections **SVII.1.1** and **SVII.1.2**
Line 658		**Comment:** reference to Part of the RMP for clarity. **Proposed change**: V.B.4.9 Part II RMP Module SVIII "Summary of the safety concerns"
Line 673		Proposed change: summarised in RMP **Part II** Module SVIII of.....
Line 679		**Proposed change:** V.B.5.1 RMP Part III section **III.I** "routine.
Line 715		**Proposed change**: V.B.5.2 RMP Part III section **III.2** "Additional...
Line 843		**Proposed change:** Recommend that the term 'adverse effects' or 'undesirable effects' replace 'side effects'
Line 926		**Comment:** Whilst the acronym "QRD" is well known to regulatory personnel, it has been the source of questions from PV colleagues who will be the broader audience for this module **Proposed change:** Clarify that QRD refers to template instructions for the SmPC and provide a reference.

Line 1291	**Comment:** the wording infers the RMP should be submitted as multiple pdf files. Clarify of change to singular.

31 May 2016

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)' (EMA/838713/2011 Rev 2.)

Comments from:

Name of organisation or individual
European CRO Federation (EUCROF)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	Questions on which the Agency seeks specific feedback by means of the public consultation: 1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Response: The identification of 'non-important' safety concerns in the RMP appears duplicative of the PSUR. The recommendation would be that this list is NOT included. If it is decided that they should remain, it is recommended that it is aligned with the PSUR to reduce the resource burden to create this section. 2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Response: As any new information from all studies is presented and analysed in PSURs, it is recommended that it is omitted from the RMP, unless there are new safety issues, impacting the product B/R balance with impact on the public health. 3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Response: As the RMP is only required to be updated in specific situations, it is likely that copies of distributed documentation will become outdated over time due to administrative and/or logistical considerations associated with the underlying documentation. It is recommended that they are NOT included in the RMP annexes. 4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? Response: It is recommended that V.B.10 is retained as an understanding of the differences between the PSUR and RMP is key and not explained by the definitions provided in V.A.1. Regarding the terminology described in section V.A.1, it should be omitted and the module should refer to GVP module Annex I. definitions, that needs to be updated.

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

31.5.2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
[redacted] German Society of Pathology

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The following general and specific comments refer to the missing requirements for applicants to supply quality criteria for the implementation of stratifying predictive biomarkers in the context of approval of biomarker-drug combinations by EMA. This poses a considerable risk for the patient since low-quality patient stratification – amongst many other problems - leads to improper prescription of drugs to wrongly stratified patients producing considerable unwanted side effects in patient populations not benefitting from treatment. It is felt that GVP has to address this issue. Today, specifically in the field of oncology a tissue (or blood) based biomarker relevant for patient selection is usually proposed (and approved) along with the drug, the respective biomarker-drug combination then becomes mandatory by publishing the EPAR. A companion diagnostic system (FDA type) is not implemented in Europe, which is without doubt positive, since it gives flexibility and allows for the possibility of evolution of biomarker tests. However, two major issues remain severely problematic in this context in the EU: A) Measures of quality assurance for biomarker tests used for prediction in Europe are usually not defined, not paid for and not enforced B) Pharmaceutical companies are not obliged to care for (and pay for) quality controlled test implementation and maintainance in the context of approved biomarker-drug combinations in Europe at all. This leads to the peculiar and unsatisfying situation that in the context of tissue based predictive testing, the whole responsibility (and all costs) for quality assured test implementation and long term use and therefore – ultimately - risk management lies in the hands of the academic institutions such as the German Society of Pathology. However, the rapidly increasing number of new tests and the increasing test complexity will make it impossible for us to assure quality controlled test implementation in the future without further support, a problem which we certainly share with many other European countries. To overcome this in our view it is necessary to A) Implement a European biomarker advisory board discussing this topic for novel drugs with EMA prior to approval.

Stakeholder number *(To be completed by the Agency)*	General comment
	B) A priori make pharmaceutical companies responsible to interact with relevant national stakeholders (and ultimately supply sufficient funds) to ensure quality controlled biomarker test implementation and maintenance in Europe for approved biomarker-drug combinations.

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')*
186		Comment: Here "improper biomarker-based patient stratification" might be added as a source for a "potential risk".
196		Comment: Again, improper biomarker-based patient stratification might be added since low-quality biomarker evaluation produces "patient populations not studied", e.g. if the biomarker was used as an upfront stratificator in the pivotal clinical study.
389		In biomarker selected populations the respective epidemiology must also be given. In this regard it is often problematic that data on biomarker prevalence is missing for differing target populations (e.g. Europe vs. US vs. Asia). Pharmaceutical companies should provide/generate such data prior to approval.
431-468		Again, no reference to biomarker selection strategies is made (includes both "information on clinical trial exposure" and "populations not studied in clinical trials").
522		Potential risk for biomarker misclassification should be added and discussed.
670		Here – in our view – an additional topic on what measures have been taken and how the applicant plans to avoid initial misstratification of patients when biomarker entry criteria are part of the approval is essential.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
716-742		This chapter should also contain continuing measures to guarantee European wide high quality biomarker detection in the context of specific biomarker-drug combinations.
811-826		Also applies for the issue of risk minimisation with respect to imprecise biomarker selection strategies.
1176 following		Submitted risk management plans should contain measurements taken by the applicant for biomarker validity/quality assurance .

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27th May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd.

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This updated Module V text creates a question over PASS definition and the forthcoming Module VIII update, including the requirement to register studies in the PAS register: Module VIII reads, as if studies routinely required post-authorisation in non-EEA countries may have to be registered in the EU PAS register. However, the text here in Module V specifically states that they should not be included in the EU RMP. What is the intention – to capture all relevant studies in the EU RMP and match these with the PAS register or is it acknowledged that the PAS register may contain more studies for a product than are listed in its corresponding EU RMP?
	Response to Agency Question 1 (line 19): The RMP should focus on the important risks for the product (see comment on Lines 615-616 and 619-621 below)
	Response to Agency Question 2 (line 19): See comment on lines 743-761 and 1025-1026 below
	Response to Agency Question 3 (line 19): Given the long time it can take to get materials approved by national authorities and the frequency of RMP updates, it does not seem appropriate to include national authority approved materials in the RMP. Per the updated module and template it appears that draft text for educational material no longer needs to be included in the RMP. Is this the intention?
	Response to Agency Question 4 (line 19): recommend deleting

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')*
211		Comment: Slight grammatical correction needed to clarify singular vs plural of 'adverse reactions'. Proposed change (if any): Remove the word 'an' in the sentence
216		Comment: 'for the EU GVP' – Should this more specifically refer to Module V, as otherwise there is a potential for conflict with Annex I definitions? Proposed change (if any):
236-239		Comment: Lines 172-177 refer to an important risk usually needing further evaluation or risk minimisation activities beyond routine. Therefore once additional PV activities have been completed for an important identified risk for which there are no additional risk minimisation activities, should the risk no longer be considered important? If this is the case, suggest it is reflected in Lines 236-239. Proposed change (if any):
288-289		Comment: Does the request for links to eCTD documents in the RMP core mean that the RMP is no longer a stand-alone document? How will these links work, when the RMP is updated separately from CTD required submissions and how will the links be maintained over a sequence of submissions or should they be removed? How will the data remain source-referenced over several versions of the RMP? Proposed change (if any): Propose to remove this text
294		Comment: Table V2: The cross-reference proposals suggest an entirely hyperlinked RMP across the eCTD –

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		How will this work when only parts of the RMP Modules are updated over successive submissions? Or if the RMP contains more than one product? Proposed change (if any):
295-296		Comment: Suggests the RMP is no longer a standalone document. Proposed change (if any):
393-394		Comment: Does relevant AEs refer to those that are due to the underlying indication? Proposed change (if any):
464-466		Comment: Are the populations in parentheses intended to be examples? They may not always be appropriate. Proposed change (if any): The exposure or the lack of, in special populations (e.g. pregnant women…..
470-471		Comment: Does this include combination products where one component is the same active substance? Proposed change (if any):
483-489, 493-494, 495-500, 501-511, 512-515, 516-521		Comment: SVI now only mentions misuse for illegal purposes, despite the word 'includes' in line 486. Should this topic be the only one for the module? The move of overdose, transmission of infectious agents, medication errors, off-label use and paediatrics to Module SVII is creating the question whether these topics should only be discussed in case they constitute an important identified/potential risk or missing information. Proposed change (if any): Retain the discussion of overdose, transmission of infectious agents, medication

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	
		errors, off-label use and paediatrics in this module SVI and include only relevant text for risks on these topics in module SVII, if they merit inclusion as specific risks/missing information for module SVIII and Part V.	
522-524, 525-530, 531-534, 535-537		Comment: Class effects, drug-drug-interactions, pregnancy & lactation, fertility – it is not clear whether these topics require a general and separate presentation in SVII or whether they should only be mentioned if there are specific concerns to be treated as important identified/potential risk or missing information. Proposed change (if any): These discussions could all be moved to Module SVI, so that SVII can focus on those items that are the key important identified/potential risks or missing information requiring list in SVIII and Part V.	
525-527		Comment: Does information on non-clinically important interactions need to be included? Proposed change (if any):	
538-601		Comment: Special considerations for ATMPs – should these form a separate module for RMPs of such products? Proposed change (if any):	
610-614		Comment: This information seems repetitive to section V.B.4.8.3. Proposed change (if any): Remove	
615-616		Comment: 'the justification for not including them as a safety concern' – would this be whether or not they are considered important? It is confusing to use different terminology here. What are the expectations for discussion here? It can hardly be the intention to discuss every reported ADR from all clinical trials or every signal ever investigated for a marketed product here. What is the threshold 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')*	
		including such a discussion in the RMP and is it the expectation that the RMP be updated every time a risk is being evaluated by the MAH and rejected as not important? Would this mean that every PSUR requires an RMP update concomitantly to keep track of these rejected signals? It appears logistically challenging and somewhat redundant with the PSUR and other submissions on such matters, particularly considering the apparent intention to link the RMP across the eCTD and therefore recognising it as not being a standalone document. Proposed change (if any): Remove the sections to justify risks that are not taken forward as safety concerns.	
619-621		Comment: As above, it appears that the introduction of a request to include discussions on newly identified risks not considered important would go beyond the reasonable scope of a focused RMP and create duplication with PSURs and other reports dealing with such matters. It would also create a need for constant update without necessarily any important new data contributing to the demonstration of a changing risk profile. Proposed change (if any): Remove	
679-699		Comment: Description of routine PV activities would appear important to be presented for the Module SVIII risks in a structured form, rather than by routine PV activity. The text is not clear that the description is to be structured by each of the SVIII items. Proposed change (if any): Clarify that the required outlines should be for each of the module SVIII identified items where applicable.	
700-704		Comment: As above – the text should clarify that the use of specific adverse event questionnaires is relevant to a specific risk from Module SVIII. 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')*	
711-714		Comment: Requested analyses and reviews are likely to change over time. Given that the RMP is not routinely submitted with the PSUR suggest removing this section. Proposed change (if any): Remove section.	
729-730		Comment: The sentence is rather truncated and is not entirely clear therefore. Is the meaning: …according to the respective legislation in place 'and' recommendations in the GVP Module VIII? Or 'as per' recommendations in the GVP Module VIII? Proposed change (if any):	
715-742		Comment: The text makes no reference to the categorisation of studies (Category I, II, III). It would be helpful to mention that the activities should be presented by Category in this section already and not retain this solely for the summary section. Proposed change (if any):	
743-761 and 1025-1026		Comment: It appears that the Category IV has been omitted from the update, both in this module text as well as the new RMP template – is this intentional and does this mean that the Category IV studies are no longer to be listed in the RMP? This is seemingly in contrast to the text for RMP Annex 2, where such studies may still be listed. Is it useful to have different study lists in the Annex from the Body of the RMP? The question also arises about definition of PASS under such circumstances – is it possible that the MAH conducts voluntary PASS, but these are not required for inclusion in the RMP, as they are not falling under the categories I, II or III? 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')*	
803-805		Comment: Does the text intend to state that agreed studies as part of a PIP to add a paediatric indication have to be listed as PAES in the EU-RMP? The text is not clear in that regard. Proposed change (if any): Clarify. If the intention is not to add the PIP studies in the PAES part of the RMP, then perhaps the details of the regulation provided here should be removed.	
940-941, 1162		Comment: The text suggests that every RMP update needs to include a discussion of the impact of additional risk minimisation activities. Is this the intention? There are many possible reasons for RMP updates and not all of them may affect the risk minimisation plan. It would be better to specify a timetable for impact assessment and reporting and update the relevant RMP section at such a milestone. Proposed change (if any): Clarify when an update of the impact of additional risk minimisation activities is needed.	
973-974		Comment: Given the section is on risk minimization, it does not seem appropriate to include PV activities in Part V Section 3 unless it is limited to those addressing the effectiveness of a risk minimisation activity. Proposed change (if any): Remove PV activities from Part V section 3.	
1030/1031, 1067/1068		Comment: Similar comment as before – in a multiple update situation for an RMP, would the expectation be that the eCTD links are provided only for the most recent updates and the protocols for previously included studies be then added in full? Proposed change (if any):	
1095-1100		Comment: This speaks to the comments made above, the example provided here is that a RMP will reflect a new risk that is discussed in the PSUR – as these two documents are complementary, the addition of 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')*	
		regarding those risks that are not taken up in the RMP as important safety concerns can be limited to the PSUR and should not be repeated in the RMP. Proposed change (if any):	
1317/1318		Comment: Lines 960-969 imply that the effectiveness only needs to be assessed for additional risk minimization activities. Proposed change (if any): Remove sentence	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1st May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Guild of Healthcare Pharmacists

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1. General comments

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

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

1. *The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?*

   We feel that it should be a focused Risk Management Plan (RMP) list of safety concerns. This would highlight the potential risks with medicines and fill knowledge gaps before approval of the product by regulators. Also, as pointed out in the module, the primary post-authorisation pharmacovigilance documents for safety surveillance are the RMP and the periodic safety update report (PSUR) and although there is some overlap between the documents, the main objectives of the two are different and the situations when they are required are not always the same. The main purpose of the PSUR is retrospective, integrated, post-authorisation benefit-risk assessment whilst that of the RMP is prospective pre-and post-authorisation benefit-risk management and planning. As such, the two documents are complementary. When a PSUR and an RMP are submitted together, the RMP should reflect the conclusions of the accompanying PSUR.

2. *Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2?*

   It may be useful if such studies could be made available for anyone seeking clarity on particular issues but we do not see that they need to be included in annex 2. Instead, we suggest that hyperlinks are provided in the document to enable commands to a web browser to load a target web page that list these studies.

3. *Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?*

   As above, we do not see that these need to be included, and instead the provision of hyperlinks in the document would be preferable.

4. *Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?*

Section V.B.10 should be maintained as section V.A.1 does not make any reference to PSURs. Furthermore, lines 738 to 740 in the module make reference to section V.B.10 regarding RMP annex 3 – part C needing to contain protocols already approved and other category 3 studies protocols.

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

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Healthcare Improvement Scotland

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Healthcare Improvement Scotland is the national healthcare improvement organisation for Scotland and part of NHSScotland. We work with staff who provide care in hospitals, GP practices, clinics, NHS boards and with patients, carers, communities and the public. **Our work drives improvements in the quality of healthcare people receive by:** • **supporting and empowering people** to have an informed voice in managing their own care and shaping how services are designed and delivered • **delivering scrutiny activity** which is fair but challenging and leads to improvements for patients • **providing quality improvement support** to healthcare providers, and • **providing clinical standards, guidelines and advice** based upon the best available evidence. Through its Quality Strategy, the Scottish Government has a commitment to improving quality and has, for the last 10 years, committed to improving safe use of medicines across NHSScotland. Healthcare Improvement Scotland has a key role to play in supporting delivery of this agenda through strengthening collaborative working between Area Drug and Therapeutic Committees (ADTCs). These are Committees responsible for providing advice to the regional NHS boards on the use of medicines to meet the needs of the patients in that health board area. There are 14 regional health boards in Scotland. Healthcare Improvement Scotland welcome any proposal to make the risk management plans developed by product manufacturers more widely available to allow the risks of medicine use in clinical practice to be more effectively managed. We look forward to developing mechanisms in future to allow us to drive improvement in the safe use of medicines.

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

21 May 2016

Submission of comments on (GVP) 3 - Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev. 2)

Comments from:

Name of organisation or individual

International Plasma Fractionation Associatio (IPFA)
Our ref. IP-16-114

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Answers to Questions
	1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Answer: The full alignment with the PSUR content is highly preferred. See comments below.
	2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Answer: This proposal is acceptable but only in annex 2. Section V.B.5.2 should clarify that these studies are not part of the pharmacovigilance plan. See comments below.
	3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Answer: No. See comments below.
	4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? Answer: This should be maintained as in revision 1 of the guideline.
	General Comments
	Comment 1: This revision 2 is the 2d major revision of Module V within 2 years (revision 1 came into effect in April 2014) and will come into effect Q3 2016. In case of update of an existing RMP (i.e. addition indication or others), will it be mandatory to update the document in order to be

Stakeholder number *(To be completed by the Agency)*	General comment
	compliant with revision 2 of the guideline? If yes, this could have an important impact on business workload for MAH. It is important to take that into account with an adequate transitory period.
	Comment 2: This revision 2 is the 2d major revision of Module V within 2 years (revision 1 came into effect in April 2014) and will come into effect Q3 2016. Several eCTD links to other documents of the MA dossier are required in the draft guidance. This approach is opposite to the one presented in revision 1 of the guideline which mentions “Information should be provided in enough detail to enable an assessor to understand the issues being presented. Unless specifically mentioned in this guidance, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document”. eCTD format is mandatory for MA dossiers of CAP but not for NAP. How can MAH be compliant with this guidance for MA dossiers in NeeS or paper format? Addition of links to other documents of the MA dossier will lead to changes in MAH SOPs and processes and technical difficulties will have to be resolved. It is important to take that into account with an adequate transitory period if these changes are confirmed. »
	Comment 3: The different levels of definitions of risks (potential or identified, important or not) from Module V and from other GVP documents (Annex I) are not easy to interpret and to implement for MAH. “Table V.4. Common sections between RMP and PSUR was modified in revision 2 of the guideline (ref: “Table V.3: Common sections between RMP and PSUR” from revision 1), so “SVIII Summary of the safety concerns” and “SVII Identified and potential risks” of a RMP seems to be no more common with respectively sections 16.1 “Summary of safety concerns” and 16.4 “Characterisation of risks” of a

Stakeholder number *(To be completed by the Agency)*	General comment
	PSUR. How should MAH interpret the table of revision 2 in order to define the safety concerns of the PSUR and how can safety concerns of a PSUR be different from those of a RMP?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
156-158		Comment: See general comment 3 on definitions. Proposed change: To use the same level of definitions in Module V and other GVP documents (Annex I).
160 - 165		Comment: The focus definition of an identified risk refers to data from clinical trials, which is coherent in case a new MAA/initial RMP; but any update of a RMP also includes data from post-marketing. Line 163, the term “identified risk” should not appear as it is the term being defined. Proposed change: Use the definition of Revision 1 of the guideline.
167-169		Comment: The definition of a potential risk is less complete than the one provided in revision 1 of the guideline. Proposed change: Use the definition of Revision 1 of the guideline (with examples).
172-177		Proposed change: Give one definition for important potential risk and one definition for important identified risk.
174		Comment: “further evaluation as part of the pharmacovigilance plan” should be clarified. Is it only additional pharmacovigilance activities or also routine pharmacovigilance activities beyond ADR reporting and signal detection? Proposed change: /
176-177		Comment: From our understanding, “or will require risk minimisation activities beyond routine risk communication”

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		should be reworded. Proposed change: "and/or will require routine risk minimisation activities beyond routine risk communication (usually found in sections 4.2 and 4.4 of the SmPC but can also be found in sections 4.6 and 4.5 and accordingly sections 2 and 3 of the PL) and/or additional minimisation risk activities".
178-184		Comment: Do you mean that to know if a potential risk is important or not, MAH should anticipate the actions the MAH would have to put in place in case the risk would be confirmed to identified risk? Proposed change: Clarify this part of the definition (important potential risk).
185-187		Comment: These are details on definition of potential risk. Proposed change: The text should be moved under definition of potential risk.
191-200		Comment: The definition of missing information is clearer than the one from Annex I. Proposed change: Please harmonize the definition in Annex I of the GVP with this one.
214-216		Comment: See general comment 3 on definitions. Proposed change: /
234-235		Comment: From our understanding, the upgrade of an important potential risk to an important identified risk is not linked to associated additional risk minimisation activities but to sufficient scientific evidence that it is caused by the medicinal product.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Please delete "(e.g. if they result in associated additional risk minimisation activities and/or routine activities beyond routine communication)".
236-239		Comment: How can we define that risk minimisation measures have become fully integrated into standard clinical practice ? From our understanding, an important risk that requires routine risk minimisation activities beyond routine risk communication usually found in sections 4.2 and 4.4 of the SmPC or also in sections 4.6 and 4.5 of the SPC and/or additional risk minimisation activities cannot be changed into "not important". As a matter of fact, even if this is fully integrated to standard clinical practice (difficult to define), the corresponding warnings or precautions for use will not be removed from the SPC. Proposed change: Please change the example or to delete the text.
264-269		Comment: this statement does not apply to the products covered by the EURD list and to the products with a PSUR periodicity different from 3 years. Proposed change: "In addition, the MAHs are advised to reflect on the need to review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimisation activities with the 5-year renewal".
282-289		Comment: See the general comment 2. Proposed change: /
295-296		Comment: See general comment 2. Changes will have an important impact in MAH SOPs and processes that should be taken into account with an adequate transitory period. 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')*
326		Comment: See general comment 2. How can MAH be compliant with this guidance for MA dossiers in NeeS or paper format? Proposed change: Please add “If possible/applicable”.
393-398		Comment: It is mentioned that “This section should also describe the relevant adverse events to be anticipated in the target population”. Are adverse events different from co-morbidities mentioned in line 397? Proposed change: Please use the same terminology if applicable.
455-460		Comment: Pediatric population and elderly are no more mentioned. Is it intentional? Proposed change: Please add these populations if applicable.
607		Comment: There is “V.B.4.8.1.a.” without any “V.B.4.8.1.b”. Proposed change: Please modify the numbering of the titles.
617-627		Comment: Lines 619 to 621 should be moved in sub-section “Newly identified risks of the product”. Proposed change: The titles and the subdivisions of the titles should be changed for clarification, as follows: **Title level 1 (for V.B.4.8.1.): “Identification of safety concerns in the initial RMP submission”** **Title level 1 (for V.B.4.8.2.): “Identification of safety concerns with a submission of an updated RMP”**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Title level 2: New safety concerns Title level 3: "New identified risks of the product" (with the text initially mentioned in lines 619-621) Title level 3: "New potential risks of the product" Title level 3: "New missing information of the product" Title level 2: Downgraded and/or upgraded safety concerns Title level 3: "Downgraded and/or upgraded identified risks of the product" Title level 3: "Downgraded and/or upgraded potential risks of the product" Title level 2: Deleted safety concerns Title level 3: "Deleted identified risks of the product" Title level 3: "Deleted potential risks of the product" Title level 3: "Deleted missing information of the product" **Title level 1 (for V.B.4.8.3.): "Details safety concerns in this version of the RMP"**
665		Comment: The term "risk identified" is confusing when compared to "identified risk". Proposed change: "risk listed".
679		Comment: The title need to be clarified. Proposed change: "V.B.5.1. Routine pharmacovigilance activities routine pharmacovigilance activities beyond adverse reaction reporting and signal detection".
715 to 742		Comment: This section should be consistent with section V.B.5.3 Summary table of additional pharmacovigilance activities". Proposed change: Lines 757 to 761 should be included in section V.B.5.2 Additional pharmacovigilance activities

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		and the text “When any doubt exists about the need for additional pharmacovigilance activities, consultation with a competent authority should be considered” should be removed.
827; 835; 859; 868; 908		Comment: The titles and the subdivisions of the titles should be changed for clarification. Proposed change: **Title level 1: Routine risk minimisation activities** Title level 2: Summary of product characteristics (SmPC) and package leaflet (PL) Title level 2: Pack size Title level 2: Legal status **Title level 1: Additional risk minimisation activities** **Title level 1: Evaluation of the effectiveness of risk minimisation activities**
1030-1031 ; 1052-1053 ; 1067-1068 ; 1085-1086		Comment: See general comment 1 on eCTD links. How can MAH be compliant with this guidance for MA dossiers in NeeS or paper format Proposed change: Please add “If possible/applicable”.
1075-1082		Comment: This would a two enormous workload for information only purposes. Proposed change: To be withdrawn.
1106		Comment: See general comment 3. How should the MAH interpret the difference between “Table V.4. Common sections between RMP and PSUR” from revision 2 of the guideline and “Table V.3: Common sections between RMP and PSUR” from revision 1, especially for the content of sections 16.1 “Summary of safety concerns” and 16.4 “Characterisation of risks” of a PSUR ?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: /
1303-1353		Comment: The term “procedure” should be clarified. Proposed change: Replace each “procedure” by “regulatory procedure”.
1319-1321		Comment: It should be explained who should confirm and require the update “RMP update may be required upon confirmation”. Proposed change: /
1325-1328		Comment: To our knowledge, closing sequence refers to the dossier and not to the procedure. Proposed change: “Closing sequence of the dossier related to the procedure”.
1341-1346		Comment: / Proposed change: Add a subtitle “PSUR not PSUSA”.
1343		Comment: The submission of updated RMP at the same time of the PSUR is not always feasible due to expected input on PSUR from the NCA and in addition from business workload point of view. Proposed change: “an updated RMP should be submitted at the same time or subsequently”
1347-1351		Comment: / Proposed change: Add a subtitle “PSUR not PSUSA”.

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

medac GmbH

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

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

Stakeholder number *(To be completed by the Agency)*	General comment
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: Answer to Question 1: The list of safety concerns defined in the RMP should be focused, as per updated risk definitions of Module V Rev 2. However, there should only be one valid definition of safety concerns to achieve a full alignment of the contents of the RMP and the PSUR.
	Answer to Question 2: For information, studies previously classified as category 4 studies should be included in RMP annex 2.
	Answer to Question 3: The additional risk minimisation materials, as distributed in the Member States, should not be included in RMP annex 6 – part B. Key messages of the additional risk minimisation measures, as included in RMP annex 6 – part B, are sufficient.
	Answer to Question 4: Section V.B.10 should be maintained. However, the safety concerns should then follow the same definition in the RMP and the PSUR.
	Further comments on the guideline: Comment 1: As regards updated risk definitions, the guideline should include more examples for risks considered to be important or to be not important.
	Comment 2: Module V Rev 1 V.C.3.1 contains Figure V.3. This figure illustrates which Parts of the RMP are required for new marketing applications depending on the type of new application (e.g. new active substance, generic medicine). This overview figure is very useful. It should therefore be adapted to the new requirements and be included in Module V Rev 2.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 926		Comment: If educational materials such as educational leaflets for patients were also part of the QRD, this would simplify harmonisation within the EU. 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

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Medicines for Europe
[redacted]

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Medicines for Europe (formerly EGA) welcomes this opportunity to comment on this GVP Module and the template, for which the comments are provided in a separate document, as requested. We believe the revision of this documents was very much needed to ensure the balance between the efforts needed to provide all requested information and the final outcome to ensure safe medicines are available for patients is the right one. After more than 3 years of experience the Agency should reconsider if RMPs for generics that do not have imposed additional pharmacovigilance or risk minimization measures are really needed and are of any added value. Below you can find the general comments on overall risk management plan approach (concept and administrative part), followed by more detailed comments on the text itself.
	Please note Medicines for Europe is the official representative body of **European generic, biosimilar and value-added medicines industries**, hence, the comments provided are made with the reference to all mentioned sector groups. Therefore, the term 'generic' in all comments below applies to all three sectors, i.e. generic medicines, biosimilars and value-added medicines.
	There are a number of areas where a stronger alignment between the RMP template and the guidance document could be achieved for completeness and to help facilitate navigation between documents.
	More detailed guidance and alignment between different GVP Modules is needed. For example, no specific requirements for biologicals is provided based on the current GVP P.II draft, i.e. manufacturing changes for biological product – how and where to address them in RMP template (already for initial RMP and update later or addressed only at RMP updates). At least reference to the module P.II should be provided, to avoid confusion what is the scope of this module and where to look for additional, more specific guidance for biological medicinal products. Module P.II should be harmonised with this module to avoid confusion.
	For generics where routine PSURs are not required, clarification is needed on when and where the results of additional risk minimisation measures effectiveness should be discussed.
	Moreover, **the Healthcare Authorities (HAs) acting as a facilitator** between generic and originator Marketing Authorisation

Stakeholder number *(To be completed by the Agency)*	General comment
	Holders (MAHs) would be appreciated. We believe HAs should assure that appropriate information is provided to the generic MAH about list of safety concerns and additional actions, including mock-ups of educational material and questionnaires to fulfil GVP requirement and provide same information to the healthcare professionals and patients. For example, in the complete absence of the list of safety concerns for the reference medicinal product, a generic RMP should base its safety concerns on sections 4.3 and 4.4 of the proposed SmPC. Medicines for Europe member companies have observed different expectations of how these sections are translated into safety concerns by different National Competent Authorities (NCAs). In addition, safety concerns have been requested which are not included in the SmPC, the source of which is not disclosed.
	For improving the objectiveness of the definition of safety concerns, the GVP should add some examples or connections between the reference safety information and the different risks' group (important identified risk, important potential risk and missing information). From our experience, the same Authority, when evaluating a RMP in a National Procedure and in a MRP/DCP, for the same medicinal product, requested different and contradictory updates on safety concerns. Therefore, consistency and uniformity on the evaluation should be considered by the different Authorities irrespective of the type of procedure.
	It should be noted that the guidelines are written mostly from Centrally Authorised Products (CAPs) perspective. When MAH has more national registrations (MRP/DCP/national) the situation is much more complex and this is not properly addressed in the current document. For example, according to guidelines and template, it should be stated that whether the RMP is evaluated in another »procedure«. Does this apply also to different national procedures or just different procedures with the same registration (renewal, variation, PSUR assessment...)? Assessors from different national agencies interpret these guidelines differently. Additionally, in case of parallel procedures (DCPs) of the same active substance (same form, same strength, same indications, etc.) the same RMP is submitted but each RMS and CMS make different comments and we end up with 3 different RMPs for the same product. It is worth mentioning that the differences of these RMP are important, e.g. additional RMMs, additional PV activities... the whole procedure does not make any sense, since for the same active substance different risk management procedures are proposed even to the same MAH.
	Furthermore, **the revised GVP Module misses the opportunity to provide guidance to NCAs, including recommendation to consider work-sharing/mutual recognition of RMP assessment.** In general, there's very little on how to manage all the different procedures on-going in parallel at different NCAs. Communication flow between different MSs is limited, or, in some cases also not welcome, e.g. national assessors not keen on accepting evaluations of the same RMP done by another NCA. This leads to a duplication of work at industry and regulators'

Stakeholder number *(To be completed by the Agency)*	General comment
	side, with no relevant impact on the safety of drug. Medicines for Europe would welcome and be willing to engage in establishment of an assessment process that would facilitate work sharing/mutual recognition of RMP assessment.
	We welcome the new definition of an important risk, nevertheless there are still challenges which need to be properly addressed. I.e. while in practice this can be applied to the new risks, for new generic RMPs the definition cannot be followed when selecting the risks because of the condition to harmonise with the Innovator/other approved generics.
	Including hyperlinks to sections of the eCTD could be challenging. Preparation of the RMP and the eCTD dossier are two separate tasks usually conducted by two separate departments at different time points. The complexity would be even greater in case of RMPs covering multiple products (different registration procedures). An RMP is a standalone document and therefore there is no need to create hyperlinks to other documents within the eCTD. Hyperlinks to other parts of the eCTD should be avoided or at least limit number of hyperlinks Medicines for Europe would not be supportive of this proposal.
	A generic RMP should be a dynamic document and should be revised in line with updates to an innovator's RMP. At present, **there are no apparent mechanisms for generic MAHs to be notified of revisions to the innovator's RMP** (including educational material), other than changes requested as part of a referral, and the revised module fails to address this lack of communication flow. A robust system supporting generic companies in following this requirement needs to be established.
	Using various RMP modules interchangeable, as suggested, with other reports (e.g. PSUR/DSUR) may be not applicable in some cases as the information may become outdated.
	There is no apparent reference to having a single RMP for two or more procedures for the same active substance, with the exception of informed consent procedures. This should be included as this should help to limit the risk of different RMPs being required because of differences in assessment by different competent authorities.
Questions on which the Agency seeks specific feedback by means of the public consultation:	
	1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined

	in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Proposal: Priority should be a focused list of safety concerns in the RMP, but PSUR content should be similarly focused. Safety concerns should always be only important identified/potential risks and missing information, and ideally consistent across both documents. However it is acknowledged that the PSUR/PBRER may be a global document and may be submitted in multiple geographies, where additional safety concerns over and above those agreed in the EEA have been requested.
	2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Proposal: This should not be mandatory as this would not fit with the legislation. The requirements for the RMP are already extensive and the need to provide all such protocols each time they are updated would be an unnecessary administrative burden. Any information from such studies will nevertheless be reported within the DSUR/PSUR/RMP as appropriate. If non-imposed/required studies are to be included in annex 2, clear and explicit guidance should be included on what studies could be included in this section. This to include whether non-EEA studies could be included
	3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Proposal: No, because they are not part of the RMP assessment, per V.B.9.6.2., and this presents significant practical challenges. The processes for the review of these materials at the national level is not subject to consistent processes and timelines. Including such information would also lead to an unnecessary and significant administrative burden to provide it for information only.
	4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? Proposal: Useful to keep, but Table V.4 should include *all* areas of commonality between RMP and PSUR (only two are listed currently). Additional sections in the proposed RMP that appear to remain common with the PSUR include: • Part II SV.1 • Part II SVII • Part II SVIII

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')*
139		Comment: The page on the Agency's website does not include clear guidance on when and how to submit updates. Proposal: Clear and explicit guidance to be included in Module V on when and how, including variation category, revisions to RMPs should be submitted. Specific guidance to be included for RMPs for generic authorisations as changes to these RMPs will mainly be reflecting changes made to the originator's RMP
140-141		Comment: please add the reference to the addendum of Module XVI as this is a separate document Proposed change (if any): This Module includes the principles of risk minimisation and should be read in conjunction with GVP Module XVI, **including addendum 1 on educational material.**
162-165		Comment: The proposed definition of important identified risk in clinical trial sounds rather arbitrary and does not include clinical plausibility dimension. Additionally, it may not be applicable for add-on treatment to standard of care Proposed change (if any): Change "...that the adverse event should also be..." to "...that the adverse event could also be..."
168		Comment: It would be beneficial to further clarify the example of a signal as a potential risk. It should probably be only ongoing/open signals, because a confirmed signal would be an identified risk. Proposed change (if any): Change "...(e.g. a signal,..." to "...(e.g. an unconfirmed or open signal,..."
171		Comment: Including the reference "...or occasionally "important risk"" is confusing and ambiguous. Proposed change (if any): Delete ', or occasionally 'important 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')*
180		Comment: The text "...even if a strong causal relationship were found." is contradictory to the definition of the potential risk which states that for potential risks "...there is insufficient support to conclude that there is a causal association..." Proposed change (if any): Delete: text "...even if a strong causal relationship were found."
198-200		Comment: If a certain ADR is suspected to occur with off label use, should this be a potential risk? – This appears to contradict 185-188 Proposed change (if any): Rephrase 185-188 or 198-200 to remove any apparent contradiction
214-216		Comment: This paragraph is confusing as it implies that definitions are different depending on whether you are referring to the RMP or not. This should be clarified in the text. Also it seems out of place here since it is not terminology as such and so maybe would be better as a footnote to this section. Proposed change (if any): The terms "(important) identified risk", "(important) potential risk", "missing information" and safety concern" must be consistent across all GVP modules and their related appendicies
236		Comment: Proposed change (if any): Change: "...may need to be removed..." to "...may be removed..."
264-269		Comment: This section appears to assume that PSURs will be submitted for all generic MAs. However, if excluded in the EURD list, PSURs and ACOs may never be prepared for a generic MA. Proposed change (if any): Change: "...of the generic products for the active..." to "of the generic products (if not excluded in the EURD 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')*
271-273		Comment: The modules do not seem to be very conducive to reusing in other documents. According to section V.B.10.1 there are only 2 common sections so it does not seem very practical to use interchangeably. Proposed change (if any): In V.B.10.1, list all sections which may be re-used between the RMP and PSURs
287		Comment: Reference to the eCTD assumes that the RMP is submitted as part of an initial submission or a significant variation. For a generic RMP, the submission of a revised RMP may be as a standalone document Proposed change (if any): Change: "...in other modules of the eCTD." to "...in other modules of the eCTD (if applicable)."
287-289		Comment: Requirement for linking to relevant sections of the dossier is a significant administrative burden, especially as the RMP should be a standalone document. These may not always be available as consolidated up to date versions (e.g. following MAA review). Proposed change (if any): Change: "Links to relevant sections..." to "Links to (if applicable for the current eCTD submission) or reference to relevant sections..."
295-296		Comment: The RMP should still be a standalone document. Suggesting cross-reference to existing eCTD sequence may render the RMP difficult to read as a standalone document. In addition, it will make maintenance of the RMP administratively difficult. Proposed change (if any): Change: "This should be in the format of links if already included elsewhere in eCTD..." to "This should be in the format of reference to other modules in the current or previous eCTD."
290-291		Comment: Intent of this sentence is unclear. Clarification would be helpful.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
294		Comment: in Part I, Module 2.2 Introduction and 2.5 should also be added. Proposed change (if any):
302		Comment: Some of the information covered in this section is actually in the cover page of the template (e.g. active substance/ATC code etc) and is not in the template under product overview so this is a bit misleading. Would be better to separate into cover page and product overview. Additionally, a RMP overview table should be added in part I as suggested by many Rapporteurs. Proposed change (if any):
303		Comment: it is stated that information should be current and accurate in relation to the ongoing procedures. This is sometimes difficult for generic applications as changes may have been made to the originator's RMP and which is not available to the generic applicant. Proposed change (if any):
315		Comment: At the time of RMP drafting the exact submission date is often not known and is therefore not possible to populate upfront. Proposed change (if any): As now proposal to use sign-off date.
308-319		Comment: The request is not aligned with proposed RMP template. The information in these lines is not in Part I of the proposed RMP but the cover and table overview pages. Also stating last procedure number where module is approved as proposed in the template is not practical for parallel submissions. Proposed change (if any): Harmonise with the proposed RMP template

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
326		Comment: The RMP should be a standalone document. Linking to other sections of an eCTD should be avoided. In addition, it may not be applicable if the RMP is being submitted as an update and if the sections to be linked to have not been revised and therefore not in the eCTD for the submission. If the RMP is for a new submission, there will not be currently approved PI Proposed change (if any): Change: "eCTD link to the currently approved PI" to "eCTD link to proposed and/or currently approved PI if included in the submission"
327		Comment: The template splits indications out into current and proposed so it would be helpful to add further explanation here about what is meant by this i.e. is it proposed if the RMP is submitted with a variation for a new indication for example? Proposed change (if any):
328-329		Comment: The template splits dosage out into current and proposed so it would be helpful to add further explanation here about what is meant by this i.e. is it proposed if the RMP is submitted with a variation for example? Proposed change (if any):
333-334		Comment: MAH doesn't always submit a closing sequence for example if RMP is approved with no comments. Even if there are comments a revised RMP would be submitted with a response eCTD sequence and we would not routinely submit a closing sequence for every variation. It would be over burdensome to routinely submit a closing sequence for every RMP variation just to add the QPPV signature. Clarification is required. Proposed change (if any):
364		Comment: "then the applicant is expected to propose and justify"- sometimes discrepancies occur at the competent authority level due to inter- and intra-agency assessment differences. In addition, more guidance on type of justification needed would be welcome.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Change: "...then the applicant is expected to propose and justify..." to "...then the applicant and the competent authority(ies) are expected to propose and justify ..."
374-358		Comment: There is nothing currently in the template annotations in relation to ATMPs. May be useful to include this for completeness. In addition, biosimilars are not specifically mentioned (referred to as similar biologicals in the current module). Suggest that a definition be added to V.A.1 for ATMP to include biosimilar/similar biological as a synonym Proposed change (if any):
385		Comment: For this and subsequent section headers for additional clarity proposal that all headers give the full section reference i.e. Part II: Module SI, Part II: Module SII etc Proposed change (if any):
394-395		Comment: A description of "the relevant adverse events to be anticipated in the target population, their frequency and characteristics" does not seem to be within the scope of this section. This is also contradictory to the RMP template text "This section should only contain data relevant for the identification of the safety concerns (see module SVII)" template rows 187-188. Furthermore, the template headings under SI do not seem to fit such information. Proposed change (if any):
399-408		Comment: Suggest adding the 2 examples to the RMP template in green instead of having them only in the GVP. Regarding the first example, it is suggested to give information if the comorbid condition has a higher incidence in the treated population than in the general population. This would require a review of the epidemiologic studies and reporting on this. However the RMP template (row 216) says "a simple list is sufficient" Proposed change (if any): Change: Harmonise the guidance in the GVP module and in the template
425-426		Comment: What is the criteria for "...is not considered relevant..."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
456		Comment: In the corresponding part of the template it might be better to have a table for the criterion/reason for exclusion rather than listed as it is now? Proposed change (if any):
473-476		Comment: When information about patients is not available (no studies were performed) usually the only data MAH has is sales data and that is the same as for PSUR. This section may therefore be a duplication of what is in a PSUR (if required for a generic MA). Characterisation of patients is not routinely possible. Proposed change (if any): Change: "...and characteristics..." to "...and characteristics (if available)..."
477-482		Comment: Suggestion – a separate subheading to be added to the RMP template (e.g. SV. 2) to include such discussions regarding use in practice, off-label use. Proposed change (if any):
531-537		Comment: The 2 bullets on pregnancy and fertility are not covered in the template and so should be added. Similarly paediatric safety information and risk with disposal are covered in the template but not in this guidance so bullets should be added here. Proposed change (if any): Fully align guidance and template to ensure all points are covered in both documents.
607-615		Comment: "For each risk" more explanation is needed on which risks should be included, especially for those not taken forward as safety concern. Sometimes generic MAHs do not know why the originator chose to include one risk over another. 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')*
609, 623, 626-627		Comment: In the template this information is given in a list format - might be better to tabulate. Proposed change (if any):
619-621		Comment: This is not clear. Should it include safety concerns not yet confirmed or only those that have resulted in a labelling change? Proposed change (if any):
623		Comment: This is not clear. Does it refer to important new risks? Proposed change (if any):
679-699		Comment: This section is not clear. Text states that only the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection should be described. Proposed change (if any): Explicitly refer to routine activities beyond ADR reporting and signal detection, e.g. targeted questionnaires etc, in the introductory text for this section of the RMP
694		Comment: This sentence may suggest that only the pharmacovigilance activities requested by PRAC/CMDh/CHMP should be presented. They should be described irrespective of the source (e.g. proposed by MAH) as long as they are part of the pharmacovigilance plan. Proposed change (if any):
708-710		Comment: It is difficult for a company to identify the right contact point for asking for such information from another company. In addition, there is no obligation for companies to share their questionnaires. Being in the public health's interest, competent authorities should make the questionnaires available if they are requested by a generic company.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Add after 710: "Competent authorities must make the questionnaires available to other marketing authorisation holders upon request."
707		Comment: "deliver a consistent message" - it is not the purpose of these tools to communicate information. Suggestion to delete this text Proposed change (if any): Delete: "...in order to deliver a consistent message..."
733-740		Comment: This would be easier to read if the requirements for the different Parts A to C of the RMP annex 3 were in a bulleted list. Proposed change (if any): Format as a bulleted list
739		Comment: This is the first time category 3 studies have been mentioned and although a description of the different categories of studies is provided in the next section in this guideline it might be better to add a brief description of each category in this section to better align with the template and make it easier to follow. Proposed change (if any):
741-742		Comment: To make it easier to manage different regulatory documents it might be helpful if the dates are restricted to only those studies in the RMP that are not covered in other documents (e.g. PIP and Annex II of the MAA). Instead a cross reference could be made to these documents since otherwise it is difficult to manage multiple document updates by different procedures to ensure that all of them have current information e.g. PIP modification, variation for Annex II and variation to RMP. Proposed change (if any):
757-761		Comment: This paragraph is not clear as it seems to contradict itself. If the studies are required, they are usually imposed. Thus, it seems that anyway they should be included in the RMP. Also, these studies should be limited to

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		safety studies only to be consistent with the whole objectives of the RMP. Proposed change (if any): Safety studies imposed as a condition to the MA or as a specific obligation in jurisdictions outside the EU should be included in the EU RMP if required by the EMA or EU national competent authority.
776		Comment: May be appropriate to add a cross reference to the Clinical Trial Regulation in addition. Proposed change (if any):
783-785		Comment: It would be useful to add clarification around how a joint PASS could be facilitated e.g. by the Agency. Also, reference to the PASS module should be included. Proposed change (if any): Add: "see VIII.C.2.d."
809-954		Comment: As a general comment this section could be better aligned with the template e.g. routine risk minimisation activities could be aligned to V.1 Routine Risk Minimisation Measures and titles harmonised across the 2 documents for ease of navigation. A lot of the information in the general section is more specific to the section entitled Risk Minimisation Plan i.e. routine risk minimisation measures, additional risk minimisation measures, evaluation of effectiveness Proposed change (if any):
838-839		Comment: the GVP guideline should not provide recommendation on product information organisation as this is covered by many different guidelines. It is also inconsistent if the main intent is to cross refer to the eCTD link Proposed change (if any):
842-844		Comment: New term is used routine risk communication message Proposed change (if any): Include definition for this term in V.A.1

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845-858		Comment: New term is used routine risk minimisation activities beyond routine risk communication Proposed change (if any): Include definition for this term in V.A.1
868		Comment: The concept of controlled distribution is missing in this section. Proposed change (if any):
872-880		Comment: The legal status may differ from a country to another for the same product. It may not be appropriate in some cases to describe this in the RMP as a core RMM Proposed change (if any):
910		Comment: For completeness it would be useful to describe briefly some examples of what these measures may be as outlined in detail in the template e.g. training materials etc The guideline should provide more details regarding measures considered promotional communication versus RMM communication. The two are not necessarily mutually exclusive. Recommendation on the use of samples and their use in the risk management plan should also be commented upon. Proposed change (if any):
913-914		Comment: Guidance on when aRMM can be stopped is not clear. Examples are required. For example, it could be stopped once a safety concern is added to the SmPC. Proposed change (if any):
915-920		Comment: It should be clear to MAH and assessor that according to GVP, generic medicines should have the same measures as the originator, and the generic MAH does not need to consult the same groups again. Proposed change (if any):

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		Add after 920: For generic RMPs where the additional risk minimisation measures are following those of the originator, such consultation would not normally be expected.
921-923		Comment: Error. This should be referenced to additional risk minimization section in RMP template not additional PhV sections/Annexes. Proposed change (if any): Reference to Annex 6 - Details of proposed additional risk minimisation measures (if applicable) and Part V.
928-931		Comment: An addition describing the possibility of disseminating one set of materials for multiple MAHs when feasible and timelines allow would be welcomed. Also a clarification that the NCA should make the educational materials for the reference product /other approved generic products available upon request is suggested to be added. Proposed change (if any): Add: "For materials for a common active or class of actives with a common aRMM, MAHs and NCAs are encouraged to participate in the preparation and dissemination of one set of common materials." Add: "NCAs must ensure aRMM are readily accessible, usually by posting on their website."
933-934		Comment: This phrase seems to no longer encourage harmonisation between member states with regards to educational materials, not even within the same procedure (DCP, MRP). While certain differences may be totally justified in some situations, the GVP should recommend harmonisation if educational materials are considered needed, unless otherwise is justified by country specific differences in the product use of healthcare system. Proposed change (if any): Add guidance that differences must be limited to specific situations, such as significant country specific differences in clinical practice or healthcare delivery
970		Comment: Align title with template, or vice versa i.e. equivalent to V3 Summary table of pharmacovigilance and risk minimisation activities by safety concern- Proposed change (if any):

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1012-1015		Comment: Align title with the template for consistency (i.e. EudraVigilance Interface) or vice versa Proposed change (if any):
1012 and 1294-1297		Comment: Is this applicable also for not-centrally registered products? On the internet site for Eudravigilance http://eudravigilance.ema.europa.eu/human/EURiskManagementPlans.asp it is stated that it facilitates the monitoring of identified and potential risks and missing information in relation to suspected adverse reactions reported to EudraVigilance for centrally authorised medicinal products in line with Regulation No. 726/2004. Proposed change (if any):
1025-1026		Comment: "Studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) can also be included for information in annex 2." This sentence should be consistent with the sentences in lines 757-760. Anyway, it suggested to limit it to only safety studies to be consistent with the whole objectives of the RMP. Also purpose of the reference to previous category 4 studies, which is not part of revised GVP, is not clear. We would recommend that studies not requested by authorities are not included in the annex nor presented in the RMP body unless they bring new relevant information for the safety concerns in the RMP. Proposed change (if any): Safety studies conducted by the MAH...
1029-1030		Comment: This could be written a bit more clearly first to say for which studies full protocols for category 1, 2 & 3 should be included and then to say that full copies of protocols for non-imposed studies do not need to be included i.e. align with the template which is much clearer: Annex 3 should include protocols of imposed studies (categories 1 and 2) and protocols for those required studies (category 3). Protocols of studies not imposed or not required should not be included. Proposed change (if any): A Table, similar to PIP legally binding elements should be proposed in this annex to avoid the RMP to be updated every time there is a change to the CTA.

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1034-1039		Comments: Consideration should be given to simplify the review of PASS protocols, which can take up to several months and delay the original measure itself. Consideration should be given to a legally binding element tables which would avoid the submission of the entire protocol Proposed change (if any):
1059-1064		Comment: Is term/expression specific adverse event follow-up forms replacing targeted follow up? Proposed change (if any):
1076-1082		Comment: We do not support the additional RMM as they were distributed in the Member States to be added. This would lead to unnecessary delays in the registration process, lots of administrative work with no obvious benefit. It is critical that a certain level of assessment from PRAC is provided at least to core elements/sections. This will avoid delaying access in countries due to national implementation. Proposed change (if any): Delete this section
1095-1100		Comment: Coordination of PSUSA procedure along with RMP submission has proven to be very difficult. Proposed change (if any): Recommendation for PSUR assessment to be made first along with proposed recommendation for RMP updates (if any), rather than submitting the two at the same time – logistic standpoint.
1101-1106		Comment: Since RMP module SV and PSUR – Actions taken for safety reasons are considered common, this contradicts the GVP text that says SV should not be a duplicate of the information in the PSUR. Additional sections in the proposed RMP that appear to remain common with the PSUR include: • Part II SV.1 • Part II SVII • Part II SVIII It is noted that the post-authorisation exposure information in the RMP should not be as detailed as may be given in the PSUR. However, for the majority of cases, only summary information, based on estimates of patient

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		exposure are available. This could be clarified in this section Proposed change (if any):
1121		Comment: There were cases when MAHs submitted generic RMP which were aligned with originator's RMP, but the NCA claimed that it is not. More communication among the NCAs is also needed, so that they would know which is the latest approved originator's RMP. Proposed change (if any):
1164		Comment: What is the criteria of not appropriate summary of RMP. Proposed change (if any):
1199-1271		Comment: The proposed abridged content is welcomed. Proposed change (if any):
1214-1218		Comment: Generic and well established use products where there is no originator RMP are likely to have a well characterised safety profile, as defined in sections 4.3 to 4.9 of the originator product's SmPC. Preparation of full modules SVII and SVIII is therefore excessive and unnecessary. Proposed change (if any):
1221-1227		Comment: SVII should be based on a critical review of the preclinical and clinical data, published literature and originator's product labelling to propose the safety concerns. This is vague and goes significantly beyond what is in the current guideline, e.g. based on sections 4.3 and 4.4 of the originator's product labelling Proposed change (if any):
1233-1239		Comment: If the originator's product does not require aRMM, then a statement that the generic product information is aligned with the originators is sufficient. If, however, the originator requires aRMM, then a full Part V is required.

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		Proposed change (if any): If the originator's product requires aRMM, then Part V information should be provided for the generic product for only those safety concerns that require the aRMM
1233-1237		Comment: How generics will know about additional pharmacovigilance activities of originator product unless these are in the public domain? Proposed change (if any):
1264		Comment: it is not clear does this refer to point 1 or 2. Proposed change (if any): Proposal should refer to point 1.
1268-1270		Comment: It is considered that safety concerns for well-established medicinal use are usually well characterised. Proposed change (if any): Part SVII should be populated only for new safety concerns previously unknown to any MAH. Otherwise, generic approach should be followed.
1276- 1277		Comment: Should every concern be evaluated in Module VII? Probably only the ones which triggered the request for RMP? Proposed change (if any):
1283-1284		Comment: Clearer guidance should be given on what is expected from NCAs. Proposed change (if any):
1294		Resubmission of Annex 1 of the RMP following the EC decision is not needed, if there were no changes to the initially submitted RMP Proposed change (if any):

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1315-1316		Comment: So also in a case where renal failure or something like that is already included in RMP as a risk, the inclusion of additional recommendation about monitoring of renal function would lead to RMP update? Proposed change (if any):
1322		Comment: a track changes may be hard to follow in case there are significant changes, especially due to template changes. Proposed change (if any): Short description of changes or comparison document should be also added as possibility.
1324		Comment: What is meant by "current" approved? Does this refer only to the one registration or the core RMP, which may have been approved in the meantime in another national procedure? Proposed change (if any):
1325-1327		Comment: It is not envisaged that a closing sequences to be submitted with all procedures where an RMP is submitted. It should be clarified if this specifically relates to an initial MAA or if the expectation is that all procedures involving an RMP will necessitate submission of a closing sequence which would be an additional administrative burden on companies. Proposed change (if any):
1331-1332		Comment: Clarification is requested on what is meant by "...another regulatory procedure...". This to include examples. Proposed change (if any):
1336-1340		Comment: The reference to RMP management with parallel procedures is not sufficiently robust to influence how two or more assessors at the same or different agencies pragmatically manage such situations. 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')*
1342-1351		Comment: Even in the context of PSUR impacting safety specification, assessment should be given first by PRAC before recommending changes to RMP. It has been seen where PRAC recommended further amendment to the suggested modifications. Proposed change (if any):
1347-1351		Comment: RMP update cannot be submitted in a context of a PSUR EU single assessment. In what upcoming other procedure to update RMP this can be done? Usually this is connected with additional costs. Proposed change (if any):
1376-1378		Comment: More guidance for NCAs is required on when and how this should be communicated with MAHs. Also, is the "when necessary" clause sufficient to have the competent authority to make an assessment whether the risk identified for the Reference Product is relevant for the generic of biosimilar? There might be situation that are related to the particulars of the Reference Product only and do not apply for the generic/biosimilar, like if risks are related to indications, dosage forms, strengths, devices etc. in which the Reference Product differs from the generic/biosimilar. Proposed change (if any): "When necessary and can be scientifically justified ..."
1407-1408		Comment: The intent of this sentence is not very clear and could be better expressed- is it saying that in addition to the summary of the RMP, certain tables from the RMP are additionally included in the EPAR. In addition, agencies should be required to make aRMM publically available. The relevance of mentioning the product information and conditions is also not obvious and should be put into context. Proposed change (if any):

27th May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
NDA Group

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

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

Stakeholder number *(To be completed by the Agency)*	General comment
	NDA Group welcomes the opportunity to provide comments on GVP Module V rev. 2 and the revised RMP template. In recent years the RMP has evolved from what was envisioned when the pharmacovigilance (PV) legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was being drafted and it is commendable that steps are being taken to make the RMP more risk-proportionate with the ultimate aim of benefitting patients and their healthcare professionals and carers. In this regard the work of PRAC is credited for considering their experience and the lessons learned since implementation of the new PV legislation. Detailed comments are provided separately on both GVP Module V rev. 2 and the revised RMP template with some overlap to be expected. In particular NDA Group welcomes the clear definitions of 'important risks' and 'missing information' which will hopefully streamline the extensive list of risks to focus on what really is important rather than merely adverse reactions being interpreted as 'important risks'. As a living document the opportunity to reclassify and remove important risks and areas of missing information is also fully endorsed. Some constructive criticisms include a proposal to clearly define how to use the terms an adverse reaction vs. an adverse event in the context of a RMP and to provide guidance on the process by which validated and confirmed signals become important risks and how they relate to each other (a diagram would be helpful). We have concerns that some of the requested data are disproportionate to the added value that these data will provide in terms of characterising the safety profile and ultimately benefitting patients. In particular one of our main concerns is the inclusion of section SVII.1.2 "Risk not considered important for inclusion in the safety specification" and section SVII.2.1.2 "Newly identified risks not considered as safety concerns". We recommend the removal of these sections as they have the danger of leading to the open-ended assessment of every ADR and/or AE. The focus should be on the important risks and areas of missing information and not the assessment of risks that are not important, or indeed, that may have been excluded as risks.

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 155		Comment: V.A.1 Terminology It would be helpful to provide a definition in GVP Module V to relate signals to potential risks (i.e. is a validated signal aligned to an important potential risk or a confirmed signal aligned to an important potential risk?). How does risk relate to hazard to make it clearer exactly what the MAA/MAH is meant to minimise? Proposed change (if any): Add clear guidance (e.g. a diagram) on when a validated / confirmed signal becomes a risk or conversely that a validated / confirmed signal does not necessarily become an important potential risk.
Lines 162-165		Comment: In our experience adverse events and adverse drug reactions are often confused and this leads to issues when the SmPC (e.g. section 4.8) is quoted. It would be helpful to provide a definition of what is expected i.e. adverse reaction or related adverse event. Accordingly it would helpful to specify 'related adverse events' in this definition. Proposed change (if any): In a clinical trial, the comparator may be placebo, active substance or non-exposure. Where ~~an~~ a related adverse event which is an identified risk for a comparator occurs at a similar (active comparator) or higher frequency with a new product, this suggests that the related adverse event should also be an identified risk for the new product.
Line 273		Comment: In our experience the RMP and the PSUR have not been procedurally aligned as expected. It is difficult to foresee that this will be taken forward in the future. Proposed change (if any):
Line 288		Comment: NDA Group welcomes the cross linking of the RMP to other modules in the dossier for a MAA. Much discussion in a RMP should already have occurred in documents such as the clinical overview and clinical summaries with the aim of making the RMP solely 'a plan'.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
Line 328		Comment: Define the 'main population' in the context of multiple indications/patient populations. Proposed change (if any):
Lines 333-334		Comment: The QPPV signature at the time of submission is useful for ensuring that the QPPV is fully aware of what is being proposed for the RMP. For larger pharmaceutical companies it is understandable while this could be seen as a unnecessary hindrance but for SME that often outsource their RMPs the signature of the QPPV ensures oversight by the QPPV. It would be preferable to keep the signature as in the current RMP template or to remove it in its entirety but to specify that the QPPV is expected to have oversight of the RMP. Proposed change (if any):
Lines 359-360		Comment: In the RMP template there is reference to generics and fixed dose combination products (lines 147-173) while here there is no mention of the latter. It would be helpful to be consistent. Furthermore it would be helpful to expand this section of the GVP Module V to include wording and a table which outlines which modules can be omitted for the different types of products. [See comment on Line 1192 below] Proposed change (if any):
Lines 393-396		Comment: "This section should also describe the relevant adverse events to be anticipated in the target population, their frequency and characteristics. The text should help anticipate and interpret any potential signals and help identify opportunities for risk minimisation. The text should be kept concise and not be promotional." The term 'adverse events' in the context of medicines implies that the content of this section might refer to responses to other treatments that may be used to treat the indication that may or may not be related to that treatment. Yet, the preceding sentence states that the content of this section "applies strictly to the natural history of the indication" – so presumably nothing to do with the treatment of the indication. This is ambiguous. It is unclear what the intention is – we suspect that the EMA may be referring to complications 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')*
		the indications (e.g. ischaemic heart disease may be a complication of hyperlipidaemia; appendix abscess may be a complication of appendicitis), but that is merely speculation on our part. This section needs to be written more clearly so that it is not left open to interpretation. One should also bear in mind that many applicants will have difficulty distinguishing between what is a complication of the indication, and what is a co-morbidity. Proposed change (if any): Delete or clearly and unambiguously state what you expect to see in this section.
Line 447		Comment: Clearer guidance on preferred pooling should be given i.e. all clinical trials, Phase 2/3 studies only etc. Proposed change (if any):
Lines 516-521		Comment: The wording in the revised RMP template (line 408) “The risks when used off-label” implies that all off-label use is a risk when this is not the case. This should be clarified further in the RMP template and in GVP Module V. Proposed change (if any):
Lines 607-616		Comment: V.B.4.8.1.a. RMP module SVII sections “Risk considered important for inclusion in the safety specification” and “Risk not considered important for inclusion in the safety specification” There is a danger that all ADRs listed in section 4.8 of the SmPC will be assessed in section SVII.1.2 of the RMP which is unlikely to be the intention. It should be fair to assume that if there is no evidence, and no facts or arguments, to suggest that a risk amounts to a safety concern for inclusion in the RMP that it should not be necessary to provide a justification for every risk excluded from the RMP. The value added by section SVII.1.2 is extremely dubious. Furthermore, has the EMA considered the impact that this section will have on products with currently approved and satisfactory RMPs? This section amounts to a huge additional burden placed on regulators,

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		applicants and MAHs with very little to be gained. We recommend that Section SVII.1.2 (and therefore the guidance in V.B.4.8.1.a) should be deleted. If the EMA cannot be persuaded to remove section SVII.1.2 there should be very clear guidance on what amounts to a "risk" in this context to limit the potential scope of this section. For example the guidance should specify that the focus should be on those ADRs that warrant a SmPC warning or justify additional wording in section 4.8 of the SmPC other than inclusion in the Tabulated list of adverse reactions. Otherwise the scope is potentially endless unless the parameters are defined clearly, and this section could easily become the longest in the whole RMP without adding benefit. (the same applies to section V.B.4.8.1.1 Line 623) Proposed change (if any): Delete all subheadings and simply list the risks and areas of missing information to be considered.
Line 614		Comment: "Clinical and benefit-risk impact:" Proposed change (if any): This should be amended to "Benefit-risk impact:" as the clinical impact will be considered as part of the benefit/risk impact.
Lines 634-656		Comment: There appears to be more guidance provided in the template (Section SVII.3) than here. Proposed change (if any): Provide more guidance in GVP Module V and less in the template
Lines 655-656		Comment: Presentation of missing information data "the changes in the benefit-risk balance that are anticipated if a causal relation between a further characterised risk and the product is confirmed to be strong (i.e. worst case scenario)." The proposed wording appears to relate to an important risk rather than missing information – an area where there is limited / lack information e.g. use in a specific population. If a specific concern is anticipated this would make it an important potential 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')*
		Missing information does not actually refer to risks as such – it refers to missing information. So use in pregnancy or off-label use, or use in patients with hepatic impairment would be missing information. It does not make any sense to assume a worst case scenario based on a confirmation of a causal association under these circumstances. There will never be a confirmed causal association for example between use in pregnancy and exposure to a medicine that would allow us to infer an impact on B/R balance. You would have to see adverse outcomes in pregnancy for the B/R balance to be impacted. Likewise you would have to see adverse outcomes as a result of off-label use to infer an impact on B/R, and not just confirmation that off-label use takes place. Proposed change (if any): Remove the subsection “the changes in the benefit-risk balance that are anticipated if a causal relation between a further characterised risk and the product is confirmed to be strong (i.e. worst case scenario).” or reword bearing in mind the definition of missing information.
Lines 757-761		Comment: In the current RMP studies requested by other non-EU Competent Authorities are classified as Category 4 studies. It would be helpful to highlight that these are now listed in annex 2. Proposed change (if any):
Lines 995-999		Comment: What is the intended broad audience and how does this permit use of technical terms if it includes the public? We agree that the public summary should be drafted in plain language but as outlined in our comments on the RMP template (Line 560, Line 567, Lines 691-694, Line 907, Lines 918-919 and 926-927) the technical language used in some sections of the RMP should be retained and then modified for the public summary. Proposed change (if any):
Line 1012		Comment: If Annex 1 is always empty, is there any point in having it in the RMP?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Remove Annex 1 from the template
Lines 1075-1082		Comment: Examples of the additional risk minimisation measures from individual Member States would not be particularly helpful. They should be available on request to Competent Authorities or via a link to a website. If required they could become a post-authorisation commitment to provide updates on an individual case by case basis. Proposed change (if any):
Line 1118		Comment: Part II Module SVI of the RMP template covers the potential for misuse for illegal purposes. Proposed change (if any): Are there specific risks in addition to those not addressed in the RMP~~, i.e. misuse and abuse~~?
Line 1192		Comment: It would be helpful to have a summary table which outlines which modules can be omitted for the different types of products in this section or in section V.B.4.1. [See comment on Lines 359-360 above] Proposed change (if any):
Practical guidance from PRAC/EMA		Comment: When the revised RMP template and GVP Module V are released it would be very helpful for PRAC/EMA to provide some practical advice to help with the transition to the new template. For example guidance on whether a biosimilar applicant should include all the safety concerns of the reference medicinal product or whether there is an opportunity to remove some of the risks that may not meet the definition of important. Once agreed by the PRAC/EMA would the reference medicinal product need to amend their RMP to be in line with the newly approved biosimilar? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Otsuka Europe Development and Commericalisation Ltd

Gallions, Wexham Springs

Framewood Road

Wexham, Bucks

SL3 6PJ

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
Question 1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?	**Response to Question 1.** We propose that a subset of 'important' safety concerns be used in the RMP rather than a longer list of safety risks which aligns with the PBRER. This means that only those safety concerns which lead to additional PV or additional risk minimisation measures will be listed in the RMP concerns. This would add substantial clarity to the RMP by reducing unnecessary descriptions of safety observations which resulted in only routine pharmacovigilance and routine risk minimisation, and would facilitate the evaluation of risk management system for the product.
Question 2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP Annex 2?	**Response to Question 2.** The range of possible post authorisation studies is very wide and could include investigator studies, interventional trials, non-interventional studies, market access programmes, patient support programmes and compassionate use programmes. This would risk making the RMP unclear to read, and impair ready understanding of the presented risks, and their management. We propose that only those studies which add significantly to the safety database for the medicinal product, and which target a particular aspect of safety of the product, would be relevant for consideration as strategies for managing risk in the RMP
Question 3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)	**Response to Question 3.** We propose that it is not necessary to include additional Member State-specific RM materials to the RMP Annexes, since the additional risk minimisation measures themselves will be presented in the RMP Annex. Although individual member states may impose changes in the implementation of additional risk minimisation measures, these member state specific differences would not be relevant to the consideration of the measures as a whole, or change the overall assessment of benefit –risk. Furthermore, since agreement with individual member states on how to implement risk minimisation measures can vary considerably between countries, a requirement to include such materials in the RMP might severely delay the preparation and approval of a given EU RMP.

Stakeholder number *(To be completed by the Agency)*	General comment
Question 4. Should section V.B. 10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1)?	**Response to Question 4.** We propose that this section be maintained. Although there have been further clarifications around RMP terminology, in section V.A.1., the current text in V.B.10. covers different aspects of RMP preparation and remains helpful in helping prepare the PSUR versus the RMP.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
No specific comments on text		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

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Paul-Ehrlich-Institut

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1. General comments

Stakeholder number (To be completed by the Agency)	General comment
[redacted]	[redacted]

Problem statement:

1. Personalized medicine is considered a new era of medicinal product development. Whereas a few products have already entered the market quite a number of investigational products are in the pipeline.
2. Implementation and maintenance of Personalized Medicines (precision medicines), e.g. **patient selection based on predictive biomarker based testing**, into clinical routine has an inherent risk that patients may be excluded from an efficient therapy or that patients may receive an ineffective and potentially harmful therapy when incorrectly classified by the diagnostic. This problem is vastly exaggerated if the respective diagnostic testing is insufficiently quality assured.
3. Currently a specific predictive biomarker based test for patient selection (i.e. the test used in the pivotal phase) **will not be approved** together with the drug (contrary to the FDA pathway for "companion diagnostics" where drug and test are approved at the time).
4. The implementation and maintenance of biomarker based testing for patient selection in clinical routine is within the responsibility of the national bodies. As a consequence the clinical pathologists or laboratory physicians must implement either (a) an **in-house** or (b) a **commercial CE marked tests** according to the requirements fixed in the SmPC for the stratified drug.
5. The information in the SmPC and EPAR on the test requirements comes usually too late in the regulatory process and is normally not sufficient to ensure high quality assured testing in clinical routine at the time of drug approval.
6. The ongoing development of innovative predictive biomarker based test methods exhibiting high complexity, e.g. Next Generation Sequencing (NGS), may lead to an additional high challenge for consistent, standardized and high quality assured clinical routine testing.

Conclusion:

We do think that quality assurance processes for biomarkers used in drug therapy are vital and part of effective risk minimization of certain medicinal products.

It should be discussed, whether MAHs should support national quality assurance programs for biomarker testing with the purpose of ensuring quality assured diagnostic testing and the efforts and outcomes should be reported to the Agency. Similar to submitting a proposal for educational materials on drug use for physicians, there is a need for adequate information on assay specifications and high quality assurance for pathologists, laboratory physicians, virologists etc. to

minimize the risk of inadequate treatment of patients (need of presentation of a "diagnostic testing pharmacovigilance plan" and a "diagnostic testing risk minimization plan" / "diagnostic testing risk minimization measures" by the MAH).

The PEI is of the opinion that this topic needs to be addressed in more detail in GVP module V.

Recommendations for GVP Module V Risk management systems (Rev 2)

Recommendations should best be formulated in sections:

V.B.5. RMP part III "Pharmacovigilance plan" and

V.B.7.1. RMP part V section "Risk minimization plan"

Risk minimization activities (proposed by the MAH) may include:

- Involvement and support of institutions of medical self-organizations which normally establish quality assured testing, e.g. by preforming round robin tests
- Establishment and providing of centralized testing in specialized laboratories, i.e. by performing the test that was used in the pivotal phase (leading to consistency of testing from pivotal phase to clinical routine)

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

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG – the Association of the Austrian pharmaceutical industry welcomes the opportunity to comment on the draft GVP Module V – Risk management systems (Rev 2). Please find our comments below.
	In general we appreciate the improved content and concise information, especially the examples, provided with revision 2 of the guideline.
	1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? We prefer a focused RMP list. 2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? No. 3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Yes 4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?

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

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')*
157 to 158		Comment: Line 156 to 158 clarifies that the definitions of GVP annex 1 to apply in the EU for the purpose of the risk management system. However, in the following below it is mentioned RMP which is the detailed description of a risk management system. For consistency, the wording should be adapted. Proposed change (if any): ..,to apply in the EU for the purpose of the detailed description of the risk management system (RMP) as follows:
185 to 188		Comment: In this section the term “adverse reactions” is used which implies a causality and may lead to confusion. Therefore, the text should be slightly modified for better understanding. Proposed change (if any): Where there is a justified supposition that an adverse event ~~reaction~~ might be associated with the long-term use, off-label use, or use in populations not studied (e.g. because similar effects have been seen with other products of the same class), the adverse event ~~reaction~~ should be considered a potential risk, and if deemed important, should be included in the RMP as an important potential risk
617 to 618		Comment: The header should be consistent with the clarifying text provided. Proposed change (if any): V.B.4.8.2. RMP module SVII section “Identification of new safety concerns with a submission of an updated RMP”
623		Comment: The current wording would result in duplication as this information will be provided in the V.B.4.8.3 update. 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')*
		simple list of safety concerns added should be sufficient. Proposed change (if any): ~~Data presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1.1.~~ Newly identified safety concerns should be simply listed and reference to V.B.4.8.3 done.
636		Comment: Due to the duplication in V.B.4.8.1.a and the proposed deletion, the seriousness bullet point should be added herein. Proposed change (if any): • name of the risk (using MedDRA terms when appropriate) • seriousness • frequency...
667		Comment: For consistency reason the word “important” should be added as only important risk are discussed and taken forward in the safety specifications. Proposed change (if any): • the investigation of whether an important potential risk is real or not
757 to 761		Comment: Including studies required by jurisdictions outside the EU like Japanese PM studies or Chinese requirements does not seem to be necessary and should not fall under category 1 to 3 becoming in such a situation legally enforceable in EU. A inclusion may be justified if the study(ies) addresses a specific safety concern outlined in the EU-RMP as these studies are mostly related to different ethnic groups and transfer of efficacy and safety to this different population.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Studies required in jurisdictions outside the EU should not be included in the RMP unless they further characterize the risk outlined in the safety specification ~~also imposed as a condition to the MA or as a specific obligation, or required by the Agency or a national competent authority. Studies not required by the EU or national competent authority should not be included in the pharmacovigilance plan in the RMP~~. This is without prejudice to safety concerns arising from any such studies, which should be reported as per the applicable legislation.
1025 to 1026		Comment: Voluntary information should only be optional. Proposed change (if any): ~~Studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) can also be included for information in annex 2.~~
1075 to 1082		Comment: As they are not part of the RMP assessment this should not be required also considering the administrative efforts needed. Proposed change (if any): ~~V.B.9.6.2. RMP annex 6 – part B~~ ~~Should include, for information only, the additional risk minimisation materials as they were distributed in the Member States. Materials included in this annex are not assessed and are not considered endorsed as part of the RMP assessment. The content and distribution plan of the additional risk minimisation activities included in the RMP will only be assessed and agreed at national level (e.g. educational materials messages, brevity, target audience; paper brochure, electronic document; distribution: by MAH representatives, on national competent authority website, with each pack of the product).~~

Please add more rows if needed.

<13 May 2016>

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Pierre Fabre

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
39		Comment: On the EU RMP template page 3, on the line “Names of medicinal products to which this RMP refers”: Is it the INN or the brand name that we have to refer as both are already mentioned on this page? Proposed change (if any):
50		Comment: on version of 25 july 2013 of RMP template, in annex 2, SmPC should be annexed, however in the revision version of template there is no reference to annex the SmPC, what is the reference document to use and if SmPC do we have to annex the current version? Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2016

Submission of comments on module V of the good pharmacovigilance practices (GVP) on risk management systems (EMA/838713/2011 Rev. 2)

Comments from:

Name of organisation or individual
Prescrire is a non-profit continuing education organisation that works to improve the quality of patient care. Prescrire publishes evidence-based information about treatments and treatment strategies, in total independence, as a basis for truly informed decision-making. Prescrire is funded exclusively by its subscribers. It receives no other financial support whatsoever and carries no advertising. It has no shareholders or sponsors. More info: english.prescrire.org; [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	To improve patient safety: the priority should be the patients, not the companies In late February 2016 the European Medicines Agency released for public consultation a revised module on good pharmacovigilance practices on risk management systems. Over the years Prescrire has advocated for strong and independent pharmacovigilance systems in the European Union and for the European Medicines Agency to play a proactive role in defending patient safety and protecting the population from avoidable drug-induced harm. Citizens should not be exposed to the adverse effects of drugs that have been released onto the market prematurely. The very high human and financial costs of adverse drug reactions end up being borne by the patients who experience them and by society at large. Yet, instead of strengthening pharmacovigilance in Europe, the EMA proposal falls short in three fundamental aspects: 1. It sustains weak marketing authorisation practices; 2. It tightens marketing authorisation holders' stranglehold on pharmacovigilance; 3. It maintains a lack of transparency. **1. The proposal sustains weak marketing authorisation practices.** Under the misleading reassurance of post-authorisation safety studies and risk management programmes, inadequately evaluated medicines are allowed to reach the market and to be prescribed, dispensed and administered to some patients.

Stakeholder number (To be completed by the Agency)	General comment (if any)
	Risk management systems (RMPs) should be used to complement pharmacovigilance as an add-on to standard pharmacovigilance practices and not to substitute a thorough pre-marketing evaluation of potential harms. They are to be applied to any medicine where doubts about adverse effects exist or emerge, even for those medicines which have been in use for a longer time or even are available as generics. Risk management systems must be designed by and conducted under the close supervision of health authorities (national and regional pharmacovigilance systems in particular), with complete independence. The RMP objectives must be to identify all the adverse reactions of the drug in question, to clarify their frequency and seriousness, both short-term and long-term, and above all, to prevent their recurrence by helping the regulatory authorities to reach a timely decision. Clear timelines for completion of the RMP by the marketing authorisation holder need to be established and, when necessary, coercive measures and/or sanctions for non-compliance must be applied. It is also essential to define the milestones at which the agency will be evaluating the RMP. **2. The proposal tightens marketing authorisation holders' stranglehold on pharmacovigilance** By delegating the collection, analysis and interpretation of data in RMPs to the pharmaceutical industry, the EMA is outsourcing key functions in pharmacovigilance to the party which has a vested interest in delaying pharmacovigilance decisions. Such an arrangement provides an opportunity for pharmaceutical companies to withhold and manipulate

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

the data. Many examples serve as reminders that the pharmaceutical companies' sense of responsibility is often overcome by the enticement to withhold data or delay its disclosure, so as to delay decisions that would adversely affect sales. A recent example is Roche's mismanagement of pharmacovigilance data whereby the company had a cache of approximately 80,000 potential adverse event reports which had not been submitted to the EMA.

Decisions about the measures to be taken are reached slowly and after much avoidance, mostly due to the fact that the preparatory phase of the decision-making process, i.e. data interpretation, is entrusted to the pharmaceutical companies. Indeed, it is up to the pharmaceutical companies – who play the roles of judge and party - to produce the "scientific evaluation of the risk-benefit balance" of their drug within the framework of the periodic benefit-risk evaluation reports (former periodic safety update reports (PSURs)). Evidence has shown that the burden of proof required by agencies to withdraw a drug is much higher than that which is demanded when authorising it on to the market: clearly, this is not placing the patients' interest above those of pharmaceutical companies.

3. The proposal maintains a lack of transparency.

Data about the adverse effects experienced by patients are not commercial data to be collected by pharmaceutical companies as part of their marketing services. These are public scientific data. They are to be analysed and interpreted to prevent recurrence and to help independent decision-making. Similarly, results of RMPs should be publicly accessible, based on EC regulation No 1049/2001. However, in the EMA proposed module there is no clarification about how these studies and their results are to be made available.

We encourage the EMA in its policy to support public health by:

- proactively providing public access to useful qualitative data such as anonymised summaries of cases;

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	• ensure that information to patients about the harmful effects of approved medicines is up-to-date and made promptly available; • granting public access to consumption data of drugs in the EU. This information is available from the periodic safety update reports and is necessary to estimate the incidence of a given adverse drug reaction associated with a drug; • providing access to all drug regulatory authorities' assessment reports of MAH's periodic benefit-risk evaluation reports (former PSURs); • providing access to the protocol and results of post-marketing authorisation studies and risk management programmes, particularly those which are required within the framework on conditional marketing authorisations, or that stem during a review due to safety concerns.

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

<31/05/2016>

. Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) □Module V – Risk management systems (Rev 2)'

. (EMA/838713/2011 Rev 2*)

Comments from:

Name of organisation or individual
[redacted]

Please find below the answer to the 'Guideline on good pharmacovigilance practices (GVP) □Module V – Risk management systems (Rev 2)' by the REGenableMED consortium.

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

All work packages of the project consider what we call the 'institutional readiness', i. e. the capacity and willingness of key pre-existing organisations and inter-organisational structures to adopt, respond to and utilise novel technologies, such as advanced therapy medicinal products as part of regenerative medicine. One work package led by Prof Alex Faulkner, Centre for Global Health Policy, School of

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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 Guidance. We welcome the opportunity to review this Guideline on good pharmacovigilance practices (GVP) ☐Module V – Risk management systems (Rev 2).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Have all imposed PASS (as conditions of the MA or as specific obligations) been included?"
Line		Comment: Proposed change (if any):
Line		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2016

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)' (EMA/838713/2011 Rev 2 draft for public consultation)

Comments from:

Regeneron Pharmaceuticals, Inc.

Global Corporate Headquarters: 777 Old Saw Mill River Rd, Tarrytown, NY, 10591
European Business Office: Europa House, 9 Harcourt Centre, Harcourt Street, Dublin 2, Ireland

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 (if any)
	Consultation Question 1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? The priority of the GVP Module V guidance should be a focused RMP list of safety concerns instead of full alignment with the PSUR content. A focused RMP list would be consistent with the objectives of the RMP, which is intended to provide a focused discussion on important identified and important potential risks, and missing information. The updated terminology and risk definitions also support that only *important* identified risks and *important* potential risks will be in the RMP. Consequently, the RMP will be focused on the subset of risks that are important, and the PSUR content would remain more comprehensive, containing the full list of all identified and potential risks, as well as safety concerns.
	Consultation Question 2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Information on studies conducted by the MAH but neither required nor imposed by the competent authority (category 4 studies) should not have to be included in the RMP annex 2: Tabulated summary of on-going and completed pharmacoepidemiological study programme. The decision to include such information should be up to the discretion of the MAH. Generally, including category 4 studies in the RMP would not provide regulators with any useful and meaningful safety and risk management information. Therefore, requiring RMPs to be updated with information on category 4 studies would levy additional undue burden on MAHs without contributing value to the aim of the RMP, which is to address uncertainties with the safety profile of a medicinal product during its life cycle. **Proposed Change in Lines 1025-1026**: “Studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) can also be included for information in annex 2**, at the discretion of the MAH**.”
	Consultation Question 3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	We do not agree that additional risk minimisation materials as they were distributed in the Member States should be included in the RMP. We believe that the inclusion of the proposed (or approved) draft key messages of the additional minimization activities, as described in RMP annex 6 – part A, sufficiently serves the purpose of providing applicable details of additional risk minimization activities. The actual physical presentation of the distributed materials for each Member State would not add additional value for the purpose of the centralised RMP, and thus should remain within the remit and management of the individual Member States. In the case of products approved through a centralised procedure, the general content of such additional risk minimization materials is endorsed by PRAC during the review.
	Consultation Question 4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? We believe that section V.B 10 should be maintained, as it serves as a useful guide for the MAH to describe the relationship between the RMP and the PSUR, including similarities and differences.

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 V.A.1 Terminology (Lines 221-223)		**Comment**: We request the Agency to ensure consistent and accurate use of terminologies throughout the document. Specifically, in lines 221-223, "important" appears to be missing in the context that the RMP should be a focused discussion on the identification of important identified and important potential risks, and missing information (i.e., safety concerns), as stated in lines 491-492. The omission of the term, "important", as currently written could lead to inconsistencies in interpretation by stakeholders. **Proposed change in Line 222**: "The risk management system shall be proportionate to the **important** identified risks and the **important** potential risks of the medicinal product, and the need for post-authorisation safety data [DIR Art 8(3)]."
Section V.B.4.8 RMP module SVII "Identified and potential risks" (Line 490)		**Comment:** We request the Agency to consider the addition of "Important" to the title heading of the module to avoid confusion and to be consistent with the terminology and risk definitions: **Proposed change in Line 490**: "V.B.4.8. RMP module SVII "**Important** identified and potential risks"
Section V.B.4.8.1.a RMP module SVII sections "Risk considered important for inclusion in the safety specification" and "Risk not considered important		**Comment:** We propose that risks not taken forward as safety concerns should not be included in the RMP. This would dilute the purpose and the focus of the RMP, which is to address important identified and important potential risks as per the new definitions and guideline. Risks not considered important for inclusion in the safety specification of a RMP are already included in the PSUR. An additional justification and summary for these risks should not be duplicated in the RMP. Furthermore, for an initial RMP, the Summary of Clinical Safety (Module 2.7.4) should address the justification for risks not taken forward as safety concerns.

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for inclusion in the safety specification" (Lines 615-616)		
Section V.B.4.8.2.a RMP module SVII section "Newly identified risks of the product (Line 623)		**Comment**: Line 623 references section V.B.4.8.1.1, but this section does not exist. Please clarify that the appropriate reference is section V.B.4.8.1.a. **Proposed change in Line 623**: "Data presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1**.a**."

Please add more rows if needed.

31 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

UCB BioPharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	General comment: It would be important to receive more clarity on how to handle existing RMPs of authorized products. Which level of change is required to trigger a change to the new template?
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: 1) The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content? Response: We agree to a focused RMP. The scopes of the two documents are different (although linked) and we should avoid duplications as much as we can, which would also reduce time on maintenance of the documents. Further clarity/guidance should also be provided in the PSUR template due to potential impact of this change, especially regarding definition of 'list of safety concerns'
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: 2) Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2? Response: Category 4 studies in general should not be included, as not all studies will add value to the conclusions mentioned in the RMP. In addition the revised guidance stipulates 'Studies not required by the EU or national competent authority should not be included in the pharmacovigilance plan in the RMP. This is without prejudice to safety concerns arising from any such studies, which should be reported as per the applicable legislation'. However, we propose an optional approach for non-mandated studies that would allow the MAH, should they choose, to include studies that characterises the benefit/risk and provide additional information for a safety concern.

Stakeholder number *(To be completed by the Agency)*	General comment
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: 3) Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)? Response: No, risk minimisation materials distributed in the Member States should not be included. This would make the RMP heavy and cumbersome with little value added. Please confirm whether mock samples (which have been proven to be very useful) are desired as provided in Annex 11 of the current EU-RMP template.
	Answers to Questions on which the Agency seeks specific feedback by means of the public consultation: 4) Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)? Response: We support keeping section V.B.10. Section V.A.1 describes the focused definitions of (important) identified or potential risks and missing information are developed whereas Section V.B.10 is providing guidance on the relationship between the RMP and PSUR and provides a table of common modules between the two documents which is very useful.

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 15		Comment: Please confirm that the revised templates are for initial applications only and that for authorised product RMPs would only need to occur with a major change of an RMP. Proposed change (if any): The guidance is updated in parallel to an amended RMP template for initial marketing authorisation application, which undergoes public consultation in parallel. For authorised products the RMP would only need to be updated to the new template in conjunction with a major change to the RMP.
Line 295		Comment: (1) Our interpretation of the current wording is that we have to include all literature articles in Annex 7, which is a large administrative burden. Instead we propose that references are cited and that articles are made available upon request. (2) Please note that, according to our experience, when managing a modular RMP as distinct documents, it is much easier to manage/maintain reference lists at the end of each module instead of in a separate annex. Proposed change (if any): ~~Literature referenced in the RMP should be included in RMP annex 7. This should be in the format of links if already included elsewhere in eCTD (see V.B.9.).~~ Literature references in the RMP should be cited at the end of each module of the RMP and be available upon request. If there are particular references which need to be provided in full, they can be provided in Annex 7. This could be in the format of links if already included elsewhere in eCTD (see V.B.9.).
Line 670		Comment: Measuring effectiveness of RMin is included here and under Part V (Line 809). Additional clarity on the extent of the details provided in each module is requested.
Line 733		Comment: There is some inconsistency with this statement and elsewhere. It would be helpful to clarify better that a reference to a previous submission is acceptable to reduce the file size of re-attaching protocols. Text in

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		Annex 3 says this would be acceptable.
Line 759-761		Comment: It is our understanding that if a study is conducted to collect data for a missing information item, and it is not required by EMA/NCA, it should not be included in the PV Plan. Instead we propose an optional approach for non-mandated studies that would allow the MAH, should they choose, to include studies that characterises the benefit/risk and provide additional information for a safety concern.

Please add more rows if needed.

31st May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual

[redacted] University of Leeds and Luto Research, UK

I am pleased to respond to this consultation on the revision of GVP Module 5 on Risk Management Systems.

My main focus is the **public summary** of the Risk Management Plan (RMP) – a key part of the module. I have submitted detailed comments on the public summary to the related consultation on the RMP template. In my response to this consultation, I focus on some more general issues related to communicating risk information to the public.

In places I have repeated comments made in my response to the previous consultation on Module 5 in 2014.

[redacted]

[redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	'Benefits exceed the risks' The introduction to the consultation says that the goal is to ensure that throughout its life span " ... the benefits of a particular medicine exceed the risks by the greatest achievable margin...". Although this document relates to the regulatory process for deciding whether the benefits outweigh the harms at a population level, it should also be borne in mind that ultimately the patient should decide, for them personally, whether the benefits outweigh possible harms. (Raynor, 2013)
	Terminology and 'benefit-risk' I welcome the increased focus on harm-benefit balance in risk management systems – as we know that people who take medicines want more balanced information (Raynor et al 2007). However, this and other EMA documents continue to use the term 'benefit-risk'. It could be argued that 'benefit-harm' is the more appropriate terminology. 'Risk' and 'Benefit' are not appropriate terms to link together. We should think of this in terms of the *'chance of benefit'* and the *'risk of harm'*. We would not say 'chance-harm' nor should we therefore say 'risk-benefit'. The correct terminology is 'harm-benefit'. **Balance of harm and benefit information** Finally on this topic, the revised RMP lay summary template no longer includes the section 'Summary of treatment benefits'. This means that the focus of the lay summary is exclusively on possible harms. This goes against the desire of patients for information which balances possible benefits and harms. **Involving the user in information development** There are two important but discrete processes for involving patients (and health professionals, where the activity is directed at them) in the development of risk minimisation activities. • The first is alluded to in V.B.7, under 'Additional risk minimisation activities' and this is appropriately a

Stakeholder number *(To be completed by the Agency)*	General comment
	consultation or discussion with patients (and HCPs) about the proposed risk minimisation activities. • However, what people want or like is not necessarily what works (Andre & Wickens 1999) – hence the need for the **testing** of the draft materials on real people (not people from patient or professional organisations). It may be appropriate for the EMA to undertake such user testing on real people (see below).
	Summary of the risk management plan A part of the Module text relates to the summary of the RMP (V.B.8). Related to this, a joint initiative between the University of Leeds and Luto Research in 2014 we 'user tested' two typical RMP Summaries. User-testing is a technique routinely used to assess the patient leaflets supplied with medicines. The aim of this testing was to determine if members of the public can find and understand the key points of the summaries, and to improve the documents accordingly, using best practice in information writing and design. We had previously undertaken a similar process for the 'European Public Assessment Report' public summary (Raynor & Bryant, 2013). Two RMP summaries were tested – chosen as being typical in terms of length and content – not because of any perception of the quality of the summaries. One of the tested summaries was for Latuda (lurasidone) which is used as an example here. An outline of the results of this work was presented at the DIA European Medical Information and Communications Conference in 2014. The slides presented and a copy of the Latuda summary, as revised after the user testing process is attached to the end of this document. These should be read in conjunction with my response to the linked Template consultation.

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 281		**V.B.3. Format and contents of the risk management plan** There is a table with an overview of the RMP 'parts and modules'. The order of these modules and parts appear to be mirrored in the lay summaries. However, it is not necessarily the case that the order that works for professionals will work for lay people. This has been demonstrated recently in relation to the Package Leaflet contents, where our study showed that the order presented currently is not the order preferred or expected by patients (Pander Maat, Lentz & Raynor, 2015). It may be convenient for professionals and policy makers, but such 'mirroring' may present significant barriers to lay people using and accessing lay summaries. (See also response to Template consultation)
Line 827		**V.B.7. RMP part V "Risk minimisation measures":** Routine risk minimisation activities are listed here, including the package leaflet. It is important that there is effective cross-referencing between this leaflet and the RMP lay summaries.
Line 835		The Summary of Product Characteristics (SmPC) and Package Leaflet (PL) are described here as important tools for risk minimisation. It is noted that the guideline on SMPCs provide guidance on how information should be presented. We need to remember that HCPs also want clear and easy to use information (as well as patients) and our recent work has shown that SmPCs performed very poorly in user testing with doctors and 'while meeting regulatory approval standards, contribute little to clinicians' prescribing behaviour' (Raynor, Bryant & De Veene, 2014). Many of the suggested improvements to SmPCs as a result of

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		the testing are similar to those suggested for patient facing documents after testing.
Line 845		Here 'routine risk minimisation activities beyond routine risk communication' are described. It is stated that this is usually found in sections 4.2 and 4.4 of the SmPC. This means that it will also be found in sections 2 and three of the PL. This is a source of considerable confusion to patients, where serious side-effects and the action to take are listed in section 2 of the PL ('What you need to know before'), rather than section 4 ('Possible side effects') where they expect to find it.
Line 975		**V.B.8 RMP part VI "summary of the risk management plan"** The regulation is quoted here: "A summary of the RMP for each authorised medicinal product shall be made publicly available and should include the key elements of the risk management plan". Our user testing of RMP summaries (see slides below) showed that all the 'key elements' may not be wanted by lay people. One option would be to include the elements that people want in the main part of the summary and then include the rest in appendices which interested parties could refer to if necessary.
Line 981		It is stated "Based on the information contained in part V one of the RMP... the agency should publish the RMP summaries..... together with the other documents of the EPAR". Our user testing of both EPAR and RMP summaries shows that such cross-referencing is essential in these documents, for patients to be able to use them successfully.
Line 995		It is stated here that: • "The audience of RMP summary is very broad". This is a welcome confirmation that the audience can range from expert patients to members of the lay public. • "To ensure that the summary can satisfy the different needs, it should be written and presented

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		clearly, using a plain language approach". Again this is welcome, as is the inclusion of references to supporting texts. However, inclusion in the summary template of specifically pertinent plain language advice is advised. (See also response to Template consultation). • "However, this does not mean that technical terms should be avoided". This advice should be re-worded. ○ "Technical terms can be retained where necessary, but with a lay explanation. The lay explanation should come first, with the technical term afterwards (in brackets if necessary). • "The document should clearly explain its purpose and how it relates to other information (particular product information), i.e. the SmPC, the PL and the labelling)". This is very welcome advice, born out by our user testing of EPAR and RMP summaries. However, the proposed explanation of purpose in the template needs improvement (See response to Template consultation).
Line 1,000		The following text needs re-wording, as the four bulleted wordings have been misunderstood as the headings which should be used in the summary. These are not appropriate headings for lay people. (See response to Template consultatation). "The summary of the RMP part V1 should be consistent with the information presented in RMP part II, modules SVII and SVIII and RMP parts III, IV and V. It should contain the following information: • the medicine and what it is used for. • summary of safety concerns and missing information. • routine and additional risk minimisation measures. • additional pharmacovigilance activities.

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		Bibliography Andre AD, Wickens CD. When users want is what's not best for them. Ergonomics in Design: The Quarterly of Human Factors Applications 1999; 3: 10-14 Pander Maat HP, Lentz, L, Raynor DK. How to test mandatory text templates: the European patient information leaflet. PLOS ONE 2015; 10: Article number e0139250 Raynor DK, Blenkinsopp A, Knapp P et al. Systematic review of quantitative & qualitative research on role & effectiveness of written information available to patients about individual medicines. Health Technology Assessment 2007; 11 : 1-178 Raynor DK, Knapp P, Silcock J et al."User-testing" as a method for testing fitness-for-purpose of written medicine information. Patient Education & Counseling 2011;83:404-10 Raynor DK. Health literacy –is it time to shift the focus from patient to prescriber?BMJ 2012; 344: 7 Raynor DK. The benefits of medicines outweigh the risks of treatment – says who? MHRA annual Norton lecture, 2013. Pharm J 2013; 290: p616 Raynor & Bryant. EPAR summaries – are they fit for purpose? A user testing study. BMJ Open 2013; 3: e003185 RaynorDK , Bryant D, De Veene P. A study of the effectiveness of SmPCs and recommendations 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')*
		improvement. Ther Innov Reg Sci 2014;48: 255-65.

Please add more rows if needed.

30 May 2016

Submission of comments on GVP Module V – Risk management systems (Rev 2) (EMA/838713/2011)

Comments from:

Name of organisation or individual
Xendo-Vigilex

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Response to Q2 Agency We are in favour of including studies conducted and classified as category 4 in Annex 2, because this gives the possibility to have a good oversight of studies that are being performed. We also think in this way, it is stimulated that also for category 4 studies the study is set up and conducted and data are analysed and presented in line with the guidance that applies to category 1-3 studies.
	Response to Q3 Agency We are not in favour of including a part B in Annex 6 where additional risk minimisation materials (aRMM) as distributed in Member States should be included. It is not really relevant, considering the focus for the RMP itself is on the agreed key messages. Further, the implementation of the agreed key messages in local materials and the assessment thereof by local competent authorities is a process with distinct timelines which will make it difficult to have the right and approved materials included in part B at the time of submissions of the RMP.
	Response to Q4 Agency We think it is important to maintain the description of common modules between RMP and PSUR in section V.B.10. In this respect reference is also made to V.A.1. on terminology where it is stated that for other GVP modules the current definitions of the different types of safety concerns will continue to be applied. For the RMP the choice is now made to update the definitions to make it more clear that the focus of the RMP is to have a safety specification that is subject to change during the life cycle. We think it will be very confusing to have different definitions of the same terms in place. We understand considering the number of GVP modules it may be difficult to change it all at one time, but it is important to decide where we want to go to for the future. We would like to focus this then on what we see in PSUR and RMP. We think it makes most sense to follow the safety specification of the RMP in section 16 of the PSUR as it is now the case. If the safety specification of the RMP is intended to develop over time, then the one in the PSUR will develop accordingly. It does not seem a problem that risks that are not considered an important (identified or potential) risk or do not meet the standards for an important identified or potential risks as described in the rev 2 GVP V are no longer reflected on (in evaluation and characterisation parts) in section 16 of the PSUR. If there are important new issues in relation to these types of risk that will be reflected in section 15 and 16.2 on signals. Section 16.1, 16.3 and 16.4 can then focus on the risks that are also most important to follow and evaluate on a continuous basis in line with the RMP. In this way, PSUR section 16.1 and RMP Part II Module SVIII and PSUR section 16.4 and RMP Part II Module SVII.3 continue to be common

Stakeholder number *(To be completed by the Agency)*	General comment
	modules and should thus also be reflected as such in Table V.4 (line 1106). Considering the addition of missing information to the Module RMP Part II SVII.3 it makes sense to then also present that information in PSUR section 16.4. We currently often present cumulative information on missing information in section PSUR section 16.3 (as focus of 16.4 is on important identified and potential risks).
	Response to Q1 Agency This question relates to Q4 and therefore our response is presented below the response to Q4. We are in favour of the current decision to have a focussed list of safety concerns in the RMP. At the same time we think it makes sense to then also focus the evaluation in the PSUR on this focussed list of safety concerns (see also above). So, instead of full alignment of the RMP with PSUR content, we suggest full alignment of the PSUR with RMP focus. In the end, there is always the product information that gives the whole picture of the risks related to a product. Further, considering the more dynamic nature of the safety specification that is foreseen we think it is important to have a place in the RMP (for instance an Annex) where the development of the list of safety concerns is clearly tracked. In case there is a signal in a PSUR later on that is related to a risk that used to be considered one of the safety concerns but not anymore, then it can still be made clear this is the history of this risk in relation to the RMP and this can be taken into account in further actions and decisions related to the signal. In relation to the changes in the safety specification over time also the newly introduced section V.B.4.8.2. RMP module SVII section “Identification of safety concerns with a submission of an updated RMP” is important. However, at this stage it is not fully clear what will be included here over time, but it seems the focus is on the changes made in a specific update of the RMP. If this is correctly interpreted, an additional Annex to track the history of this process may be very worthwhile. This is also in line with research by Vermeer et al. (Clinical Pharmacology & Therapeutics 2014) that also showed that some changes observed over time are also due to regulatory requirements and/or dynamics between regulatory authorities and industry rather than resulting from knowledge gain.

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')*
1106		Comment: It seems there is an error in table V.4. RMP section Part II, module SV is now stated to correspond to PSUR Section 3. Proposed change (if any): Change PSUR Section 3 into Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”
		Comment: Proposed change (if any):

Please add more rows if needed.

30 May 2016

Submission of comments on 'Draft guidance on format of the risk management plan (RMP) in the EU – in integrated format- Revision 2 (EMA/PRAC/613102/2015)

Comments from:

Name of organisation or individual
ZEINCRO HELLAS S.A

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 (if any)
	Due to the complexity of GVP documents, it would be considered helpful for reviewers to have a list of changes provided with every new draft thus guiding the reviewer to concentrate on all changes.
	Response to question 1 (page 2, before line 19): We consider that the justification of the updated risk definitions is valid. We agree that the aim of RMP is to focus on important identified risks and therefore support the proposal of having a focused RMP list of safety concerns. However, we propose the consideration of a final aim to harmonise all relevant documents with the new definitions (ICH guidelines, GVP Module VII etc.).
	Response to question 2 (page 2, before line 19): We do not believe that non-imposed studies should be listed in annex 2 as the results of such studies will already be discussed in the core RMP document (clinical trial exposure section) when applicable. Therefore, we agree with the revised verbatim as nominated in this draft document.
	Response to question 3 (page 2, before line 19): We do not consider necessary the reference of all “local” risk minimisation materials within annex 6- part B. Although this may be practical sometimes from the MAH point of view, the full materials are not in any way assessed by EMA or Member States and therefore should not be part of the annex. All Member State materials should be kept separately by MAH and where applicable, specific material for specific Member State shall be agreed with the concerned Member State.
	Response to question 4 (page 2, before line 19): We propose the maintenance of section V.B.10 because this is an extra helpful guidance and it is not necessarily repetitive of section V.A.1. Size of the Module will not be considerably affected by its maintenance and this section will possible aid smaller Pharma companies in the creation of RMPs.

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')*
393-396		Comment: Please clarify if the “target population” in line 393/394 involves information on EU patients only (i.e. to correspond to reference for emphasis to the proposed indication in EU made in line 390-391) or global data Proposed change (if any):-
1214-1218		Comment: A spontaneous response to the situation where originator does not have an RMP and the safety profile of the originator is not published on the CMDh website, is that an RMP shall not be required for the Generic applicant. However, it is understood that there are cases (e.g. when originator is not in the market) where an RMP may be required. Please clarify as to be apparent that a harmonisation is always desired (e.g. someone could conclude that it is possible that an RMP is requested from the Generic applicant and not from the MAH that markets the originator). Proposed change (if any):-

Please add more rows if needed.