25 June 2012
EMA/428848/2012
Patient Health Protection

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

GVP Module V – Risk management systems

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

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

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

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

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An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16/Apr/2012

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

Comments from:

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

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
	Will RMP template be available before July 2012? If not, in the interim period, will you publish transitory measures or should applicant/MAH use former EU-RMP template?
	The Agency and Member States shall make publically available public assessment reports and summaries of risk management plans RMP (REG Art 26(1), DIR Art 106). Is this also applicable for products approved before this new legislation came into force? For applicant of a new generic product, it is requested to consider RMP of the reference medicinal product.

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')*
613-616		Comment: Module SVI is Additional EU requirements for the safety specification. Specific risk information is provided on module SVII "Identified and potential risks". Please clarify if reference to module SVI is correct. Proposed change (if any): Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP module SVI but reference should be made in this section as to which risks and populations are affected.
656		Comment: Please specify which module is referenced as Module SVa. Clarify differences between reference to Module SV and Module SVa. Proposed change (if any):
704 718 1357		Comment: Please specify which module is referenced as Module SVIa. Clarify differences between reference to Module SVI and Module SVIa. Proposed change (if any):
742		Comment: Please specify which module is referenced as Module SVIIa. Clarify differences between reference to Module SVII and Module SVIIa. 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')***
1669-1670		Comment: Please clarify how RMP "routine" updates submission should be restarted after the end of procedure. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
AESGP

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	According to the new provisions RMP have to be provided for all new medicines authorised after July 2012 and no exemptions are foreseen for products with a low and well known risk. Only some sections may be omitted (e.g. section SII - SIV, see line 1591). However the legislation states that "Marketing authorisation holders should plan pharmacovigilance measures for each individual medicinal product in the context of a risk management system. The measures should be proportionate to the identified risks, the potential risks, and the need for additional information on the medicinal product". The original intent of the legislator seems partly fulfilled as there appears to be minimal reduction of the regulatory burden for older products. In addition to reducing the number of modules for certain products, it should be possible that the content of submitted modules be downsized as appropriate. The compilation of a RMS is a time and resource intensive process - even if some sections might be omitted - and the expenditure of time is not in balanced proportion to the gain of new knowledge. We therefore propose to further reduce the burden taking into account the factual 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')*
154-206		Comment and proposed change: The definitions should be removed here and cross-references should be made to the definition annex in order to avoid repetition and ensure consistency.
211		Comment: Where this sentence mentions RMP it appears it should actually refer to system rather than plan Proposed change: Although the primary aim and focus of the RMS remains that of risk management,…
328		Comment: It needs to be clarified who decides if module can be "locked". Proposed change: Please include "These RMP modules can be "locked" 'after notification of the competent authority' or 'when the MAH justifies the module ceases changing or has not changed'
331-338 Major		Comment: There appears to be minimal flexibility for 'well established medicinal products,' including non-prescription products. In addition to reducing the number of modules for certain products, the content of submitted modules should also be tailored as appropriate. Proposed change: This proportionality can be achieved in ~~two~~ three ways: by reducing the number of modules or tailoring the content of modules which need to be submitted for products meeting certain conditions (such as well established products – see V.C.3.1) and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the risks and uncertainties of the product.
348		The attachment of published literature may pose a copyright issue. This was already raised in the context of the EC IM Concept paper. Consistency should be ensured with the IM. However nothing further than reference and abstract should have to be provided.
400-401 Major		Comment: The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments, could become a very long section This is a massive amount of duplication of the regulatory status which is included in the PSUR (see lines 311

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 381-384 of the PSUR GVP module) anyway. Proposed change: Therefore this requirement should be deleted entirely, because it contravenes one of the key goals of the new pharmacovigilance legislation, i.e., simplification of pharmacovigilance processes.
470		Comment: it may not be appropriate to use patient years or months for short duration studies Proposed change: patient time (patient-years, patient-months) exposed to the medicinal product, as appropriate.
976-983 Major		Comment: The use of specific AR follow-up questionnaires should not be considered as routine pharmacovigilance, rather it should be an additional measure. These types of questionnaires may be tailored to obtain specific information pertinent to a particular risk and may also be sent with a greater frequency than those used to fulfill routine regulatory requirements. Proposed change: move this paragraph to V.B.9.2
1017-1019		Comment: The sentence "*If, when reviewing a study protocol, a study is thought to be primarily promotional, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP*" is unnecessary as it has already been stated that studies should not be promotional Proposed change: delete this sentence
1156-1232 Major		Comment: The term "Routine minimization" is unsuitable for covering all situations described under this header. If "routine" qualifies activities "which happen with every medicinal product" (line 1157), then a legal status that "controls the conditions under which a medicinal product may be made available" (line 1179), should not be classified as "routine", as it clearly does not apply to every medicinal product. Limiting the pack size (line 1169) should also not be considered as "routine". There should be a distinction between the "true" routine minimization applying to every medicinal product, i.e. the "simple" recommendations and information in the labeling documents (SPC, PIL), and other available regulatory provisions (such as pack size limitation, restricted legal status) that are beyond routine as they clearly aim at limiting the use. This would help

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		harmonization beyond different regions, because these specific EU regulatory provisions may not be available outside the EU, and would therefore not been considered "routine" in such other jurisdictions. Proposed change: please move the sub-sections "pack size limitation" and "legal status" into section V.B.11.2 "Additional risk minimization activities"
1331		Comment: A template for the public summary will be useful to ensure that the public are able to respond to risks associated with a product proportionately and make a fully informed decision. We await the publication of such template for comments. If possible, this template should include standard wording for the patient friendly statements on frequency and severity of safety concerns.
1371-1372		Comment: Timelines and milestones should not be included in the public summary. Even timelines proposed with the best of intentions tend to change for factors beyond industry or regulator control (e.g. slow recruitment; delays to approval; etc). Publication of such discrepancies would devalue the system and reduce public confidence in both industry and regulators. Proposed change: please delete timelines and milestones from the sentence.
1570-72		Comment: There appears to be minimal flexibility for 'well established medicinal products' (including non-prescription products), as the majority of modules are still required. RMPs for well established products should be very targeted and only focus on the new indication/new issues (and not include old data). The safety specification should concentrate on new data for the new indication/population etc and not be a repeat of old data that is part of an accepted and established existing safety profile. Proposed change: Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted or the content of the modules tailored (for example, to concentrate on new data only) unless otherwise requested by the competent authority.
1609		Comment: Most non-prescription medicines contain well-established use substances; by analogy with the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		generics, part II, module SII could be omitted for those well-established use medicines. Proposed change: the symbol ^ should be inserted to indicate that the section may be omitted for well-established use medicines when justified.
258		Comment: The two sentences have different tenses Proposed change: ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation.
283		Comment: Change this bullet for consistency in the wording Proposed change: ensuring the implementation of risk minimisation activities at a national level;
287 - 289		Comment: the following wording is confusing: ensuring marketing authorisation holders of generic and/or similar biological medicinal products make similar changes when changes are made to the reference medicinal product risk minimisation measures; Proposed change: clarify the wording
302		Comment: not well written, cannot identify the safety profile but it can be characterised Proposed change: characterise the safety profile of the medicinal product(s) concerned;
303		Comment: change the order of the words further and characterise for clearer meaning Proposed change: indicate how to further characterise the safety profile of the medicinal product(s) concerned…
527 - 531		Comment: The following sentence is too long and difficult to understand - The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist so the cumulative effect of multiple impairments and multiple medications should be evaluated. Proposed change: rewrite sentence or split it
727		Comment: is this the correct referenced section or should it be SVI? *V.B.8.6.6. RMP module SV section*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"Projected post-authorisation use" Proposed change: check it is the correct section
1415		Comment: Move full stop to after the bracket Proposed change: medicinal product (and a much wider range of (suspected) adverse reactions).
Throughout the document		It would be good to have consistency: - with the use of benefit-risk. It switches between benefit-risk and risk-benefit. - MAH or Companies or Pharmaceutical Companies, but not switch between these names in the document. - Competent Authorities or Regulatory Authorities or Regulatory Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 17 Apr 2012 18:16:00

Submission of comments on 'GVP Module V – Risk Management Plans' (EMA/827661/2011)

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

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

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Declaration:

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In general, Novartis finds the GVP module on RMPs descriptive with improved guidance on given sections of the RMP document. However, in some areas further guidance is still needed and in other areas, the extra detail provided raises additional questions, which in turn require further clarification. While Module V is applicable to all product types, the level of detail is very much aimed at new development compounds. Although Section V.C.3.1 provides some guidance to address differences in product types, some information requested may not be possible to obtain for specific product types, e.g. for OTC products "epidemiology of the indications and target population", lines 433-447, "Clinical trial exposure", lines 465-498, "Post-authorization use in populations not studied in clinical trials", lines 605-614. **<u>Availability of new templates and transitional measures:</u>** According to Stakeholder forum 27 Feb 12, New MAAs will require EU RMPs in the new content and format, yet at same meeting noted that work will start on the new EU RMP template during Q3/Q4 2012. "Clarification will be provided as to what format to use ad interim…" – When will details of the transitional measures be made available? In addition, given that new RMP template is not due for 6-12months, the release should be aligned with new PBRER template for effective transition by MAHs. Once the new template has been developed, we recommend that sample RMPs for different product types should be provided on the Agency's website, e.g. a RMP for new development product in registration and a RMP for a product which is more mature, i.e. OTC or generic product, where a RMP has been requested. **<u>Important Identified / Potential risks:</u>** *An AR observed in well designed CTs (158 & 170)* *A signal arising from a spontaneous AR reporting system (174)* *…any risk which is/is likely to be included in the contraindications or warnings & precautions section… should be included here.* *..e.g. severe nausea and vomiting with chemo (753-760)* *…to add an adverse event to section 4.8 of the SPC is not a sufficient cause per se to include it as a safety concern… (lines 1415-1417)* The module appears to shift between the inclusion of all identified / potential risks vs. important identified / potential risks. In some

Stakeholder number *(To be completed by the Agency)*	General comment
	instances the expectations in terms of the risks to be included, appear to be over and above those considered truly important enough for a defined risk management system, e.g. the inclusion of contraindications (line 754). The inclusion of all these components moves to make the RMP a duplicate of the label, which is not consistent with its purpose as an additional tool to facilitate management of patient safety. Clarification and examples should be provided of "important" identified and potential risks that merit inclusion in the RMP to avoid the RMP becoming a duplicate of the product label. **Educational materials:** Module V lacks detail on expectations regarding expectation and extent of input from "communication experts and… patients and/or HCPs", CHMP approval process, and piloting of educational materials. It will be difficult for MAHs to meet expectations of EMA without clarification and more guidance regarding these topics. **Benefit / Risk assessments, inclusion of Efficacy Studies**: The new module still very much focuses on the risk-management based activities and "benefit" related activities still remain largely undefined. The broad expectations in terms of the need for efficacy studies also needs further clarity. For OTC and/or generic products, it may not be possible for such studies to be conducted or for "true" efficacy assessments to be made by a MAH who is not the innovator of a product and for whom only post marketing data is available. **Parallel Submissions / Procedures:** Guidance has been provided for the provision of RMP updates while a procedure is in progress, but there is no guidance provided on how to handle the RMP and its data if more than one procedure in process at the same time, e.g. applications for a new indication and a new dosage form. How should specific data respective to each new application be handled in this scenario?

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')*
266-267,1241-1252		Comment: Clarification and additional detail is needed Will clarity be provided in Module XVI regarding the expectation and extent of input from "communication experts and… patients and/or HCPs." ("Where possible and appropriate… ") in the development of risk minimization activities (including educational materials)? Will inspectors expect to see evidence of this? Who decides on appropriate experts, patient groups etc.? Should this be agreed with the CHMP? Proposed change: Provide clarification and more detail in Module XVI.
309-311		Comment: How does the EMA expect a MAH to "indicate a level of certainty regarding the efficacy shown in CTs…?" Proposed change: More guidance needs to be provided as to when additional efficacy studies would be expected to be completed by a MAH. Such guidance should make clear that the need for such studies will be determined on a case-by-case basis, between the MAH and EMA. This guidance should also detail how the EMA expects efficacy to be measured
319-327		Comment: Will further guidance be provided in respect of the use and management of the "modular sections" of the RMP template? For example, are all modules candidates to be "locked"? Would modules that are "locked" have a different version number to updated modules? Will modules be submitted within a single document body or would they be submitted individually? Will guidance / examples be provided of given scenarios where certain modules can be "omitted" (line 327)? Proposed change: To ensure clear guidance is provided regarding the use and management of RMP template modules.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
340-341		It is not clear what is meant by "different medicinal products". Does this mean all products with the same active ingredient should be in the same RMP? Can the decision to have a single RMP for more than one product, be made by the MAH or does the CHMP decide? Will there be pre-defined exceptions to a single, shared RMP for products with the same active ingredients? In addition, clarification is needed for how to address combination products in which one or more component(s) is/are not produced by the MAH. Proposed change: Clarification and guidance should be provided for those scenarios when a separate RMP would be expected and for combination products when the individual component(s) may be produced by multiple MAHs.
376		Comment: Need definition of Data Lock Point for new RMPs and RMP Updates. Proposed change: Use CTD DLP for new submissions and DLP of most recent safety data for RMP Updates
379		Comment: More specific guidance is needed on versioning. Situations that need to be addressed are 1) when there are multiple versions submitted during a procedure and 2) when there are multiple procedures on-going, e.g. new indication submission and new formulation submission.
388-396		Comment: Please clarify if the information requested is specific to the EEA
444-447		Comment: Information requested on intended purpose and impact of product does not fit under topic title of Epidemiology of indications and target populations. Product information is already requested in Product Overview section so is redundant. The "normal therapeutic armamentarium" could differ by country. Proposed change: Delete lines 444-447
748		Comment: "Most important" identified and potential risks is not defined. Suggest to not using the term

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"most". Proposed change: Delete the word "most"
974-981		Comment: Use of specific questionnaires as a follow up to a reported adverse reaction should not be considered routine pharmacovigilance if they are created specifically to follow up on a risk in the RMP. While some of the information requested may be applicable for any product, other information may be specific to the product in question (e.g. how the product is used; first dose effect; known interaction with food) and would not necessarily be applicable to all products. Novartis' experience is that the EMA assessor sometimes provides comments on the questionnaires that are very specific to the product in question and are not broadly applicable across the product portfolio. In addition, it is not realistic to expect that MAHs will use the same or similar questionnaires, unless these are managed by a central organization, e.g. EMA, or there is a pharmacovigilance agreement between MAHs who will be using this approach for the same active moiety/marketed product. Proposed change: Questionnaires created specifically to address adverse events of interest should not be considered routine pharmacovigilance.
1246-1266		Comment: Regarding the approval process for educational materials, it is recommended that these are piloted before the final version is agreed, yet it then states that "CHMP will agree to key elements of what should be included in the educational material and these key elements will become, once agreed by the EU Commission, a condition of the MA". Will a formal process for the development of educational materials be clarified in Module XVI? With regard to "piloting" educational materials, would the expectation be to complete this with EMA approved materials before country level use or after the countries have received EMA approved materials and adapted in accordance with local HA requirements, i.e. with country specific materials (which reverts back to the former 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')*
		For products where different MAHs require alignment of educational materials, will this be facilitated by the EMA to ensure fulfilment? Proposed change: That any further guidance regarding the development and use of educational materials (i.e. Module XVI) makes clear the development process and takes into account country specific requirements (which exist even within the EU).
1308-1316		Comment: The inclusion of a broad summary that should be suitable for the "lay reader" is a new component of the RMP. Guidance is needed regarding the level of language required for the "lay reader" in respect of RMPs. Proposed change: That EMA provide very clear guidance in respect of this new section, including examples of text that is appropriate for the 'lay reader". A specific template fore this should be included in the new RMP template.
1317-1329		Comment: It is unclear what is the relationship between the "public assessment report" that will be posted and the summary document. In addition, will the public summary document require updating with each update or could this section be "locked" at a certain point in line with the modular concept?
1639-1641, 1647-1648, 1666-1667		Comment: The module serves to address the appropriate submission of RMP updates, however, the following needs clarification. How would the time schedule for providing RMP updates provided as part of the MAA, differ from the schedule to submit an update with a PSUR? If a routine update is not submitted because a procedure is in progress, when would this RMP update be due? Would this be decided on a case-by-case basis, or will there be definitive timelines for this scenario? The specific scenarios provided in Vol9a as triggers for RMP updates have not been included in this module. Are these scenarios still perceived as RMP update triggers or has this changed?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: To provide a timeline to MAHs as to how submission of RMP updates would look in each of these scenarios, to avoid MAH non-compliance with submission activities.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

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

Comments from:

Name of organisation or individual
AstraZeneca

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

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)
	AstraZeneca welcomes the opportunity to provide feedback to GVP Module V – Risk management systems (EMA/838713/2011). AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to those. Additionally, AstraZeneca would like to provide some further comments which follows below as general and specific comments.
	Within section V.B.12 (line 1310) the scope is unspecified with regards to providing information on any activities which are conditions of the marketing authorisation (line 1330). This section would benefit with added clarity of "activities which are conditions of the marketing authorisation"
	There is a discrepancy in guidelines for when to apply separated or united RMPs when products are authorised under different authorisation routes. Section V.B.7 RMP part I, "Product Overview", line 383, require the authorisation procedure for each medicinal product in the RMP to be specified, while Section V.C.2 Risk management in the EU, lines 1542-44 states that RMPs might be split by procedure. This section would benefit from clarification of the actual situation for united or separated RMPs due to authorisation routes.

2. Specific comments on text

<table>
<tr><th>Line number(s) of the relevant text

(e.g. Lines 20-23)</th><th>Stakeholder number

(To be completed by the Agency)</th><th>Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')</th></tr>
<tr><td>Lines 344-348</td><td></td><td>Comment: The guidance states that "...cross references to other parts of the dossier should be avoided since it is intended that the RMP should be largely a standalone document that is a scientific synopsis of the relevant parts of the dossier". When producing a CTD and RMP in parallel it is important to ensure consistency between the information provided in relevant sections of the RMP and CTD respectively.

Proposed change (if any): Addition of a mapping table indicating overlaps between (sub)-sections in RMP and CTD.

<table>
<tr><th>RRMP</th><th>CTD</th></tr>
<tr><td>Part I Active substance information</td><td>Module 2.3 Quality Overall summary
Module 3 Quality</td></tr>
<tr><td>Module SI Epidemiology of the target population</td><td>Module 2.5 Clinical overview</td></tr>
<tr><td>Module SII Non-clinical part of safety specification</td><td>Module 2.4 Non-clinical overview
Module 2.6 nonclinical written and tabulated summaries
Module 4 Non-clinical study reports</td></tr>
<tr><td>Module SIII Clinical trial exposure</td><td>Module 2.7 Clinical summary - briefly
Module 5 Clinical Study reports</td></tr>
<tr><td>Module SV Post authorisation experience</td><td>Module 2.5 Clinical overview - briefly</td></tr>
<tr><td>Module SIV Populations not studied in clinical trials</td><td>Module 2.5 Clinical overview</td></tr>
<tr><td>Module SVII Identified and potential risks</td><td>Module 2.5 Clinical overview (including benefit risk conclusion)
Module 2.7 Clinical summary (SPC)</td></tr>
<tr><td>Module SVIII Summary of ongoing safety concerns</td><td>Module 2.5 Clinical overview
Module 2.7 Clinical summary</td></tr>
<tr><td>Part III Pharmacovigilance activities</td><td>Module 2.5 Clinical overview
Module 2.7 Clinical summary</td></tr>
<tr><td>Part IV Plans for post authorisation efficacy studies (including presentation of efficacy data)</td><td>Module 2.5 Clinical overview
Module 2.7 Clinical summary</td></tr>
<tr><td>Part V Risk minimisation measures</td><td>Module 2.5 Clinical overview
Module 2.7 Clinical summary</td></tr>
</table>
</td></tr>
<tr><td>Lines 400-401</td><td></td><td>Comment: Definition of "licence status" is not specified. It is not stated if definition covers all applicable categories including 'under review', 'approval ' and 'expired'.

Proposed change (if any): Amend text for clarity to read "… date approved/refusal, date marketed, current licence status (e.g. approved, under review, expired, withdrawn), explanatory comments."</td></tr>
</table>

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 476		**Comment:** The specification for use of ethnic and racial origin is not consistent. In this paragraph, clinical trials exposure should be stratified by racial origin. However, line 437 suggests that epidemiology data should be stratified by racial and/or ethnic origin. Line 563 also refers to racial or ethnic origin in a different context. **Proposed change (if any):** Stratification should be consistently specified to be by "racial and/or ethnic origin".
Line 630		**Comment:** Reference to use in clinical trials should be included in RMP module SIII – not in module SII as stated. There is an error in reference to 'Clinical trial exposure' module. **Proposed change (if any):** "Use in clinical trials conducted as part of the marketing authorisation holder's development programme should be included only in RMP module ~~SII~~ **SIII**
Line 727		**Comment:** This subsection is labelled SV but appears in SVI. **Proposed change (if any):** Change sub-section heading to be in accordance with module numbering.
Lines 754-757		**Comment:** The description what is meant by an important risk should cross-reference that provided on this subject under definitions (183-185). **Proposed change (if any):** Amend the 1st sentence to "....impact on public health (see V.B.1 for definition of important risk)."
Line 1288		**Comment:** Reporting period is referred to but it is not clear whether this is the same as the "The time schedule for "routine updates" to the RMP... "referred to in Section V.C.5. **Proposed change (if any):** Suggest addition of reference for reporting period. Reword line 1288 to read as follows: "In general, the focus should be on information which has emerged during the reporting period **(i.e. the "the routine update" period referred to in Section V.C.5)**...."
Line 1386- 1387		**Comment:** Requirements for provision of SmPC and package leaflet in relation to different marketing authorisation routes are not specified. **Proposed change (if any):** Reword line 1654 as follows; "…the Agency will publish on its website ~~a timescale~~ the latest date by which the RMP should be in the new format. Reword line 1386; "Current (or proposed if product is not authorised) local/MRP/DCP/CP summary of Product Characteristics (SmPC) and package leaflet"
Line 1653-1655		**Comment:** It is presumed that the timescale published will constitute a maiximum allowed time and that the RMP update will be triggered by the earliest planned procedure (e.g. variation, renewal, PSUR) where an RMP would normally be submitted.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Suggest proposal for clarification on relationship between published timescale and other planned procedures. Reword line 1654 as follows; "…the Agency will publish on its website ~~a timescale~~ the latest date by which the RMP should be in the new format.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1543		Comment: The sentence starting on line 1543 refers to substance class authorised under different authorisation routes. It is not clear how to handle products of the same substance class authorised by same authorisation routes. Proposed change (if any):
1519 -1520		Comment: In the section on the legal basis for implementation the following references appear to be incorrectly presented: Directive 2001/83/EC article 21a, article 22a, article 22c, article 106(c), article Proposed change (if any): Should this refer to Directive 2010/84
1521 - 1522		Comment: In the section on the legal basis for implementation the following references appear to be incorrectly presented: Regulation (EC) 726/2004 article 10a, article 23(3), article 26(c). Proposed change (if any): Should this refer to Regulation (EC) 1235/2010

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Bayer HealthCare

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
312		Comment: There are variations of "everyday medical practice" regionally. Proposed change: Suggest adding "according to local variations of medical practice".
980-981		Comment: The Agency encourages the use of the same or similar questionnaires for the same adverse events. Will the Agency provide templates for the common/similar questionnaires?
1240-1242		Comment: As Science is in progress on risk minimization it is our understanding that the MAH can propose an appropriate risk minimization tool based on available literature data and the proposal will usually be acceptable unless clear evidence exists for other tools being more appropriate. Please kindly clarify.
1258		Comment: Piloting of educational material should be applied particularly in exceptional cases, i.e. where illiteracy of the patients could be expected or risk minimization actions outside standard medical practise will be required. Please kindly clarify.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

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

Comments from:

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

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
	There are several references to Modules that have not yet been issued for consultation. As additional guidance is to be given in these Modules, it could compromise the implementation of this guidance and result in differing standards of preparation and assessment of RMPs
	Comment: Many sections/data/information included in the RMP are already included in other sections of the dossier, especially the SmPC and clinical overview for generic products, and the PSMF. How can this duplication of information be avoided? Can cross-references be made to other sections of the dossier?
	Comment: The RMPs for informed consent, generic, hybrid and well established use products should be proportionate to the active and any of other possible risk factors. If the RMP is for what is generally considered a generic product, but the regulatory routes have forced them into another category, can the RMP should reflect this, e.g. when IC is made against a generic product the RMP sections for a generic only should be followed?

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')*
135-137		Comment: Has the proposed modular format for the RMP been shared with non-EU regulatory agencies for their review and comment? Proposed change (if any):
151 271 1153 1237 1267		Comment: Module XVI has not yet been issued. It does not aid the review of this Module if additional guidance is to be included in other document which have not yet been finalised or issued for consultation Proposed change (if any):
181-183		Comment: This definition is not identical to the one in Annex I. Annex I does not refer to Important missing information Proposed change (if any): Standardise the definitions across the two documents
184-187		Comment: This definition is not identical to the one in Annex I. Annex I does not include "activities" Proposed change (if any): Standardise the definitions across the two documents

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
190-192		Comment: This definition is not identical to the one in Annex I. Annex I includes: These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimisation activities (e.g. healthcare professional or patient communications/educational materials) Proposed change (if any): Standardise the definitions across the two documents
200		Comment: This definition is not identical to the one in Annex I. Annex I uses "second" instead of 2nd Proposed change (if any): Standardise the definitions across the two documents
235		Comment: Consider including dentists
250		Comment: How will "...all appropriate actions..." be defined/determined? This is a vague statement and open to wide interpretation Proposed change (if any):
305 1538		Comment: What is reference IM Annex II.1? It is assumed that it is Annex II of the Implementing Measures issued as a Consultation Paper in September 2011. Does this refer to all of section 1, or specifically to section 1.1? 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')*
318 337 341 1314		Comment: What is reference IM Annex II.2? It is assumed that it is Annex II of the Implementing Measures issued as a Consultation Paper in September 2011, but there is no section 2 to this annex. There is a section 1.2 Proposed change (if any):
328		Comment: "The Agency will make available on its website a template for the RMP". Why is the template not available for review in parallel with the draft guideline? Proposed change (if any):
340		Comment: Under what circumstances would two or more products containing the same active be considered sufficiently different to warrant their own part VI module? Proposed change (if any):
366		Comment: For generic products, and such like, cross-reference to the SmPC and PSMF should be sufficient.
679		Comment: Please clarify what is meant by 'special consideration'? Proposed change (if any):
728		Comment: What is meant by "...market position in the EU."? 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')*
766-744		Comment: Module SVII will be required for a new marketing authorisation application for a generic medicine. However, the risk data listed in this section may not be available to the applicant even though it is in the innovator's RMP. Would such a situation be covered by the "When the information is available..." statement? Proposed change (if any):
766-744		Comment: Module SVII will be required for a new marketing authorisation application for a generic medicine. However, the risk data listed in this section may not be available to the applicant even though it is in the innovator's RMP. Would such a situation be covered by the "When the information is available..." statement? Proposed change (if any):
1156		Comment: Why would "routine" activities form part of the dossier? Surely routine activities should be part of the PSMF and be inspected, rather than assessed.
1159 – 1163		Comment: The SmPC, labelling, PIL, pack size and legal status are all highly regulated via other regulations and guidance. Also, many of these aspects for generics, and such like, are already dictated by the reference product.
1188-1189		Comment: Restricted medical prescription or a special medical prescription may not be applicable to all healthcare systems in the EU. Proposed change (if any): Whilst some guidance follows, a note should be added to indicate that these are not recognised universally across Europe.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1263-1266		Comment: Colour and formatting of documents may be trademarked attributes. Proposed change (if any): Clarification on infringement of intellectual property rights of the innovator should be considered for inclusion.
1359 - 1364		Comment: The RMP summary is supposed to be in lay terms, but this section suggests the actual text of the SmPC should be used. The SmPC is not in lay terms.
1383		Comment: Reference is missing. Proposed change (if any): Add missing reference.
1446-1447		Comment: For a generic application, will the applicant have access to the full RMP from the innovator so that it can be confirmed that safety concerns from the reference medicinal product have been included? Or will they be all included in the summary RMP/EPAR? Proposed change (if any):
1481		Comment: Mock-ups are not provided in the RMP; however, this statement asks is "this has been translated into appropriate product information...and pack design?". This seems to be contradict the "stand alone" nature of the RMP. Pack design and product information are all highly regulated via other guidance and assessed in other parts of the dossier. Also, many of these aspects for generics, and such like, are simpler than branded products and on occasion dictated by the reference product.
1573		Comment: Confirm that this should read "...RMP Modules SII-SV...". Table V.2 states that modules SI – SV may be omitted Proposed change (if any): Correct to read "...RMP Modules SI-SV..."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1577		Comment: Please confirm that the imposed additional activities or efficacy studies will be disclosed publically. Proposed change (if any):
1609		Comment: The asterisk symbol (*) suggests there is a modified requirement for certain sections of the RMP, these are not provided in the guideline text.
1636		Comment: What is reference IM Annex II.3? It is assumed that it is Annex II of the Implementing Measures issued as a Consultation Paper in September 2011, but there is no section 3 to this annex. There is a section 1.3 Proposed change (if any):
1704-1705		Comment: When will this information start to become available, from the 2nd July, or at a later yet to be disclosed date? Proposed change (if any):
1717-1718		Comment: For nationally authorised products, will this information be made available at the same time across the whole of Europe, i.e. from July 2012? Proposed change (if any):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Currently the risk management system is to be submitted together with a marketing authorisation application **where applicable**. That means, in special circumstances, e.g. for traditional herbal medicinal products, no detailed RMS was required. According to the new provisions no exemptions are foreseen for products with a low and well known risk. Only some minor sections may be omitted (e.g. section SII - SIV, see line 1591). The compilation of a RMS with its administrative information is a time consuming process - even if some sections might be omitted - and the expenditure of time is not in balanced proportion to the gain of new knowledge. We therefore propose to reduce the burden taking into account the factual risks.
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.

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 282 - 284		**Comment:** Whenever the communication between an authority and stakeholders is related to a specific product, it should be made sure that this is done in close cooperation with the marketing authorisation holder. For clarification purposes, a respective sentence should be added to the paragraph.
Line 464 ff		**Comment:** This is generally acceptable, however, advice should be given how to proceed in cases where a marketing authorisation is applied for and if no or almost no study data is available (e.g., generic applications). Would it be appropriate to present published data in such situations? A clarifying paragraph is appreciated.
Line 624 - 626		**Comment:** It would be helpful if advice could be given how to prepare such figures to quantify off-label use.
Line 1496 ff		**Comment**: According to Section V.B.16 the final responsibility for the quality, accuracy and scientific integrity of the Risk management plan should be with the QPPV. In line 261 ff it is considered that *"Producing a RMP requires the input of different specialists and departments within an applicant/marketing authorisation holder. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of study planned to address them." From this it is clear that the responsibility cannot be taken by the QPPV alone. As with other documents submitted with a marketing authorisation application the responsibility should be with the applicant/marketing authorisation holder. Furthermore, this requirement would be inconsistent with module I (Quality system). According to module I the QPPV should provide input to the RMP (line 472 and line 552). Nothing is mentioned about the responsibility.

<Date of submission>

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

Comments from:

Name of organisation or individual
Celgene Europe Ltd.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Timeline very short for in depth evaluation.
	Two templates are not yet provided and will be required before MAHs can implement the new RMP structure: • EU-RMP template, • Summary of EU-RMP (Part VI) – to be made publicly available.
	The request that some sections should be written in "lay language" should not be interpreted as requiring systematic testing similar as that performed for Patient Information Leaflets. Further, some points mentioned in the summaries to be presented in lay language are already covered by contraindications, precautions and warnings in the Patient leaflet. Therefore, it should be possible to provide reference to the relevant sections of the patient leaflet.
	Transitional measures: In order to move to the future RMP format, including switching from the previous format to the new one for products with an existing EU-RMP, companies will need to make extensive changes in existing processes for RMPs and PSUR development. Therefore, even given the commonalities with the new PSUR format through the modular approach, it should be clearly stated that all new RMP or RMP updates to be submitted with the next renewal if the EU RMP template has come into force for longer than 6 months or until July 2015.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
122		Comment: the risk-benefit balance Proposed change (if any): the benefit-risk (chance of benefit/risk of harm) balance please use this term throughout the whole document
390		Comment: Indications may vary by country/regions. Proposed change (if any): specify "indications in the EEA"
393		Comment: Dosages may vary by country/regions. Proposed change (if any): specify "Dosage in the EEA"
400-401		Comment: The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments, could become a very long table. Proposed change (if any): This table should be moved to an Annex.
498 - 500		Comment: "When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Suggest that the wording be more specific in how the data should be presented. Proposed change (if any): "When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables representing total pooled data across all indications".
583 - 587		Comment: "These may include age, sex…" Please give examples how these data could be generated. Proposed change (if any):
612 - 613		Comment: "In particular, any information regarding an increased or decreased benefit in a special population should be provided." Be more specific in how the data should be presented. Proposed change (if any): "In particular, any information regarding an increased or decreased benefit in a special population should be provided as a tabulation of adverse drug reactions per each special population sub-group.
624 – 628		Comment: Examples on how the data could be generated would be helpful. Proposed change (if any): Please include examples how these data could be generated
648 - 651		Comment: "Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern and appropriate risk minimisation proposed in RMP part V " Be more specific which data should be presented herein. 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')*
		Only if harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, harm from overdose should be included as a safety concern and appropriate risk minimisation proposed in RMP part V.
750		Comment: Undefined terminus Proposed change (if any): "This RMP section should provide more information on the important identified and potential risks."
769		Comment: "When the information is available, detailed risk data should include the following: " More clear guidance on how the data should be provided should be given Proposed change (if any): "When the information is available, detailed risk data per authorized indication should include the following: "
838 - 839		Comment: Be consistent in termini "..concern with the medicinal product, and hence is not included as an identified or potential risk, the evidence supporting this should be provided. Proposed change (if any): "..concern with the medicinal product, and hence is not included as an important identified or important potential risk, the evidence supporting this should be provided.
925 - 926		Comment: It should be more specific in presentation "At the end of the safety specification a summary should be provided of the safety concerns. A safety concern may be an:.." Proposed change (if any): "At the end of the safety specification a summary table should be provided of the safety concerns. A safety concern may be an:.."
1043		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')*
		A definition would be needed for Drug utilisation studies; does this include non-interventional studies? Proposed change (if any): Please define this term
1117- 1120		Comment: A brief summary of at maximum one page to present efficacy data would be a challenge for complex medicinal products. Further, this would require an additional document with unnecessary burden for MAHs. Indeed, the proposed content is similar to the information already prepared by MAHs in the Clinical Summary Overview. Therefore, the use of the clinical overview summary should be an option and would result in better quality. Proposed change (if any): "As explanation for any efficacy studies proposed and to provide background that can be used in the RMP summary, there should be a summary of the efficacy of the product and what studies and endpoints it was based upon. The robustness of the endpoints on which the efficacy evaluation is based should be briefly discussed. This should be brief (one page maximum). Alternatively, the clinical overview summary in the content as required for renewals can be used.
1563 - 1568		Comment: Why is a justification required when the submission of the RMP is not mandatory? Proposed change (if any): Please clarfy
1584 – 1586		Comment: Who provides the RMP? Is it the Competent Authority or the originator? Proposed change (if any): Please clarify

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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1. General comments

Stakeholder number	General comment
(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')*
V.B.8.4. :RMP module SIV "Populations not studied in clinical trials":548		About " Sub-population carrying known and relevant genetic polymorphism" in section V.B.8.4, It is not clear what should be addressed in this subsection. If polymorphism focuses on the metabolism of the drug which could cause unexpected risk to a certain population, it should be described as such. If biomarker use to select target population is the focus (i.e. personalized health care), it should be described as such. The title of the subsection does not specify its contents. Also, the guidance for the contents should be more specific.
V.B.8.5.1. :RMP module SV section "Regulatory and marketing authorisation holder action for safety reasons":		The list of any action taken in and outside the EU is needed. This sentence should align with the requirements in PSUR (i.e. any significant actions related to safety). The level of the action taken for safety reasons may differ in each country, especially in the case that is initiated by MAH. The list should limit to the significant ones which would affect the safe use of the medicinal products.
V.B.8.5.3. :RMP module SV section "Post-authorisation use in populations not studied in clinical trials":RMP module SV section "Post-authorisation use in populations not studied in clinical trials"		The module SV "post-authorisation experience" has five sub-sections which mainly focus on "exposure". However this subsection V.B.8.5.3 requests not only the exposure in populations not studied in clinical trials but also the safety profile of the products and also increased /decreased benefit in this population. To align with the other subsections in SV, only exposure should be described here. Overall assessment for population not studied in clinical trial should be described in other relevant sections.
V.B.8.5.3. :RMP module SV section "Post-authorisation use in populations not studied in clinical trials":RMP module SV section "Post-authorisation use in populations not studied in clinical trials"		It is requested to provide "any information regarding an increased or decreased benefit in a special population". In general, we cannot claim the increase in benefit unless the clinical study result proves it. This section is dedicated for populations not studied in clinical trials. What is expected to be provided in this section regarding an increased benefit (for off-label use)?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
V.B.8.5.4. :RMP module SV section "Indicated use versus actual use":RMP module SV section "Indicated use versus actual use"		I assume that the linked section in line 628 is not to SII, but to SIII.
V.B.8.6.5. :RMP module SVI section "Specific paediatric issues":Potential for paediatric off-label use		We found RMP module SVI but there is no SVIa section. We may need additional explanation for this.

Please add more rows if needed.

17.04.2012

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

Comments from:

Name of organisation or individual
CIS bio international/IBA

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines141-142 Lines 1655-1656		Comment: When are these transitional arrangements made available? Which time limit will be admitted to update an old format to the new one? Will the next scheduled submission be the time limit? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
CMDh

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1575-1583		Comment: Since a generic product (10(1)) is similar (as proven by bioequivalence) to the reference medicinal product, an extensive RMP should not be required. The CMDh considers that a risk based approach should be applied, in line with requirements for PSURs for generic products. Proposed change (if any): For applications for generic products further guidance should be provided in the GVP (lines 1575-1583) to explain that the modules S VI – S VIII should be drafted concise. This would be appropriate as these should be derived from the corresponding sections in the RMP of the reference medicinal product. In fact, only the safety concerns should be mentioned in the generic RMP without detailed risk data (as these can be found in the RMP of the reference medicina product and will not be different for a generic product). The focus in the RMP of the generic product should be on the (additional) pharmacovigilance and risk minimisation activities which should be in line with those of the reference medicinal product.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, non-profit organization (NGO) established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO). Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. Two major themes for CIOMS within the field of biomedicine have been bioethics and the development and use of drugs. In 1986, CIOMS set up its first pharmacovigilance working group to discuss international reporting of Adverse Drug Reactions (ADRs). Following that several different CIOMS Working Groups (WGs) have published consensus reports covering specific areas of drug development and drug safety such as terms and definitions for vaccine pharmacovigilance, SMQs, the Development Safety Update Report (DSUR), practical aspects of safety signal detection and management. The most recent report (vaccine pharmacovigilance) was published in collaboration with WHO January 2012. Working Groups are presently ongoing covering the area of a harmonized tool kit for risk management and meta-analysis of regulated biopharmaceutical safety data. Each WG has consisted of scientists invited to the group based on their recognized specific expertise and, if required, in consultation with their background institution. Regulatory agencies, health authorities, research-based biopharmaceutical companies and academia have been globally represented. As the CIOMS WGs have no legal jurisdiction or mandate to make binding decisions the goal have been to achieve harmonization and standardization across regulatory jurisdictions. Consequently the CIOMS' reports have served as internationally harmonized recommendations that could be implemented in regional/national legislation. It has also been used as educational material at various training institutes and seminars and in particular for new staff within the pharmaceutical industry and regulatory authorities. The GVP Module V – Risk management systems' is highly relevant, practical and useful guidance related the update of the Community legislation. The EMA is congratulated to a very well elaborated and well formulated document. The overall description of content, functions and responsibilities including the structure with modules are generally endorsed.

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

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	As the objectives of the risk management plan are to reflect the safety profile of the medicinal product concerned DK recommends that further consideration and discussion should take place regarding the extensive requirements requested for generic medical products which have a known safety profile.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Drug Commission of the German Medical Association; D-10623 Berlin, Herbert-Lewin-Platz 1, Germany

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Drug Commission of the German Medical Association (DCGMA) thanks for having given the opportunity to comment on the Guideline on good pharmacovigilance practice. The DCGMA is taking the opportunity to make some general comments to 'Module VIII – Post authorisation safety studies' followed by detailed proposed changes of the text and will also propose changes to the Module V and Module VI.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 469-470		Comment: The patient time exposed to the medicinal product is not as informative as the number of patients treated for different periods (see also lines 477-478). Proposed change (lines 469-470): "...should be detailed both numbers of patients…" skip the reminder of the sentence and insert "…exposed to the medicinal product and duration of treatment. Patient time (patient-years, patient-months) may also be given…".
Line 517		Comment: Multimorbidity is often an exclusion criterion for the selection of patients. Hence, interactions because of co-medication might remain not detected. Proposed change (line 517): Please insert the term "4. co-medication;".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

< 18 April 2012>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module V - Risk management systems) is very comprehensive and provides detailed and helpful guidance on safety risk management systems, concentrating on peri- and post-authorisation risk management in the context of benefit, as applicable to all EU products. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance. Sections related to risks are well detailed and thought through. They take into account the 6 years of experience with previous EU-RMP guidance and template, and clarify a lot of previous difficult interpretations. The new Parts related to benefit are less worked out and not detailed.
	The new RMP template is not yet available. There is no indication as to when this new RMP template will be available on the EMA website. This template is necessary to fully evaluate the impact of the new legislation.
	Summary of RMP (Part VI) – The template is not yet available but it will be necessary to fully evaluate the impact of the new legislation and to assess if there is duplication with the proposal to include information on safety concerns, risk minimisation activities and plans for post-authorisation efficacy and pharmacovigilance development in the EPAR. . The request that this section be written in "lay language" should not be interpreted as requiring systematic testing similar as that performed for Patient Information Leaflets.
	Other provisions are cited as not yet provided and thus prevent to have a full overview of the Risk Management System planned in the EU and fully evaluate the impact of the new legislation: • The Agency RMP repository (lines 1627-31) • The procedure of assessment by PRAC (lines 1673-74) • Module XVI on minimization tools and measurement of their effectiveness.

Stakeholder number *(To be completed by the Agency)*	General comment
	Transitional measures: In order to move to the future RMP format, including switching form the previous format to the new one for products with an existing EU-RMP, companies will need to make extensive changes in existing processes. Given the commonalities with the new PSUR format through the modular approach, EFPIA propose that the new RMP format applies at the same time as the new PSUR format, i.e. to all new RMP or RMP updates to be submitted with a data lock point after January 2013.
	Transparency: EFPIA recommends that EMA guidance on the format of the "public assessment reports" (mentioned line 1707) be subject to stakeholder consultation.
	Guidance/Tools to describe the processes for how to evaluate benefits, subsequently asses benefit - risk evaluation need to be developed and implemented
	We have general concerns related to Section V.C.3.1.a concerning New applications involving generic medicinal products: Although noted that sections of the full RMP may be omitted, there remain sections where, as a generic submission, some of the data will be available only to the innovator product, for example, V.B.8.7 (Identified and potential risks). How would the generic MAA be able to complete such modules, should the newly potential risk only be recently identified by the innovator product? In addition, in the event that there are multiple generic products authorised, with multiple RMPs in place, how will consistency between the RMPs be maintained? In terms of a new RMP being issued for a new generic product, what is the envisioned process to update all other RMPs for a specific generic product (or biosimilar)?
	Comment: There appears to be minimal flexibility for 'well established medicinal' products (Section V.C.3.1.d), as the majority of modules are still required, including all components of the safety specification such as clinical trial exposure. This information may not be valid for a well established product that has >10 years of post marketing exposure and a well defined safety profile. RMPs for well established products should be very targeted and only focus on the new indication/new issues (and not include old data).
	There is a discrepancy in guidelines for when to apply separated or united RMPs when products are authorised under different authorisation routes. Section V.B.7 RMP part I, "Product Overview", line 383, requires the authorisation procedure for each

Stakeholder number *(To be completed by the Agency)*	General comment
	medicinal product in the RMP to be specified, while Section V.C.2 Risk management in the EU, lines 1542-44 states that RMPs might be split by procedure. This section would benefit from clarification of the actual situation.
	It is unclear whether the process for assessing updates to an existing RMP will remain the same under the new legislation i.e. receipt by the MAH of an assessment report and final Adoption of Conclusions fax.
	For some products, currently a Risk Management Plan Progress Report is provided alongside the Risk Management Plan itself. We assume that the new template would make the requirement for a separate Progress Report obsolete by including the indicators of progress made against risk minimisation measures in 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')*
105		Comment (editorial): "affect" used in place of "effect" Proposed change: "…**effect** on individual patients and public health impact"
137-138		Comment: Which elements are considered "common to all"? Proposed change: Insert a reference to table V.2 (line 1609)
134-142		Comment: It is stated here that risk management is a global activity however the rest of the document describes a very EU centric approach. It is suggested that a product may need a different RMP for each region with some common elements achieved via use of modules. As risk management is indeed a global activity it is inefficient to have to create different RMPs for different regions even if some modules are common. Typically a company would have a core global strategy for a given product for consistency and oversight of any risk minimisation activities. It would be preferable to have the option of creating a global core RMP that references the product CCDS with regional specific appendices that account for the required differences. Proposed change: Amend text to read: 'Therefore a product may have a different RMP for each region, or a global core RMP that references the CCDS with regional specific appendices, although there will be several elements that are common to all.
154-206		Comment: Definitions should remain in the definitions module (with cross-reference to this module) to avoid potential discrepancies between the different GVP modules. Should definitions remain in this GVP module despite the above consideration, additional definitions for additional pharmacovigilance activities, risk minimisation activities, routine pharmacovigilance activities and routine risk minimisation activities should be added.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
161		Comment (concerning definitions if maintained in Module V): There is no indication of how large the magnitude of difference must be to suggest a causal relationship. Proposed change : Suggest amending text in line with that in line 172. "….which the magnitude of the difference compared with the comparator group, **on a parameter of interest** is large enough to suggest…."
175		Comment (concerning definitions if maintained in Module V): Many newly developed drugs do not belong to an already existing drug class. The below-indicated text change takes into account that some evidence should be available for a particular drug before it is relevant to include a "similar-class event" as a potential risk Proposed change: an event known to be associated with other active substances within ~~the same~~ **a similar** class or which could be expected to occur based on the properties of the medicinal product**, and where data raises a suspicion of, but is not large enough to suggest a causal relationship**
180		Comment (concerning definitions if maintained in Module V): the below-indicated text addition, provides examples of missing information Proposed change: Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace **such as populations not studied (e.g. pregnant women) or circumstances not encountered (e.g. experience with overdose).**
211-216		**Comment**: The rationale for focusing efforts to address missing information with efficacy studies is not clear.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Usually, the RMP would be expected to focus on the benefit-risk balance in authorised indications. **Proposed change**: Revise to read (line 212): "Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (~~**particularly**~~ **including** those linked to the Safety Specification section on Missing Information) and their integration, where necessary, in the RMP may enable resources to be used more efficiently and for risks to be put into context.
250		**Comment**: it is unclear what 'constantly' monitors means. Suggest new wording to align with signalling: **Proposed change**: [The MAH is responsible for] ensuring that it ~~constantly~~ monitors the risks of its medicinal products **according to periodicity agreed at marketing authorisation or at RMP updates and** in compliance with relevant legislation and reports the results of this, as required, to the appropriate competent authorities
275-276		**Comment**: This paragraph describes the responsibility of the competent authorities with regards to providing information to other regulatory authorities, with a reference to further description in GVP Module I. From the description in Module I, it can be concluded that 'other regulatory authorities' is restricted to other Member States, the Agency and the European Commission. **Proposed change**: Change the description here to refer more precisely to 'other **EU** regulatory authorities'.
290-292		**Comment**: This paragraph defines the responsibility of the competent authority to communicate safety activities in relation to a product to other regulatory authorities, 'including changes to the product information of a **reference** medicinal product'. It is unclear why communication of safety activities should be limited to this type of product, but should not cover communication on other (originator) products.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Explain the specific role of reference medicinal product for the communication activities or consider broadening the statement to cover all relevant products beyond the domain of generic medicinal products.
304-305		**Comment**: It is assumed that the need to 'document post-authorisation obligations' only relates to RM activities, rather than to all post-authorisation obligations. **Proposed change**: Clarify in the text the scope of the post-authorisation obligations to be included.
312		**Comment**: There are variations of "everyday medical practice" regionally. **Proposed change**: … indicate the level of certainty that efficacy shown in clinical trial populations will be seen ~~in everyday medical practice~~ **according to local variations of medical practice** and document the need for studies on efficacy in the post-authorisation phase;
321-324		**Comment**: In some circumstances it may be appropriate to divide the indications for a single medicinal product within each module/section (e.g. for a product which is indicated for prolonged use for an oncology indication (e.g until progression of disease), and which is also indicated for an arthritis indication (given once in a 6 month period). **Proposed change**: Add the proposed scenario outlined above.
319-329		**Comment**: The Modules describe a modular structure for the RMP, but it is not clear whether individual modules must be individually versioned and dated. If so, further clarification is required as to the link between the RMP version number and the different version numbers and dates for the individual components. In addition, if individual modules must be submitted separately, the e-CTD structure will require amendment to allow separate tracking of the modules through the lifecycle of the submission.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
328		**Comment**: It needs to be clarified who decides if module can be "locked". The message here is some of the modules can remain unchanged if no new data needs to be added, and such a static state is effective until the next change is made based on the new data. **Proposed change**: Include: **These modules can be effectively "locked" until new data needs to be added. MAH needs to justify information ceases or has not changed.**
330		**Comment**: "The Agency will make available on its website a template for the RMP". The EU-RMP template is not yet available, yet it is important to better understand what is expected, particularly knowing that the Agency comments on submitted EU-RMPs in the recent years have focused on compliance to the template. A previous suggestion from EFPIA was to decrease repetition and duplication throughout the document, this can only be seen with the template. **Proposed change**: Specify when the template will be available or replace the sentence by the link to the available template.
334		**Comment**: Since the RMP should refer only to "*important*" identified and potential risks and "*important*" missing information, the reference in the text to identified/potential risks can be misleading for both MAHs and competent authorities. This may result, as has happened in the past, in requests for inclusion of non-important risks in some RMPs. **Proposed change**: Line 334 and where appropriate, always qualify risks and missing information as "*important*" throughout the text, including the table of contents and section titles described in Module V. For example, the title of section V.B.8.7. RMP module SVII "*Identified and potential risks*" (Lines 40 and 738) would become "***Important identified and potential risks***."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
331-338		**Comment**: There appears to be minimal flexibility for 'well established medicinal products'. In addition to reducing the number of modules for certain product, the content of submitted modules should also be tailored as appropriate. In addition, t is unclear what the 'certain conditions' are referred to in line 337 and which modules could be reduced. A cross reference to the examples given in V.C.3.1. line 1569. **Proposed change**: This proportionality can be achieved in ~~two~~ three ways: by reducing the number of modules **or tailoring the content of modules** which need to be submitted for products meeting certain conditions **(such as well established products/generics – see V.C.3.1)** and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the risks and uncertainties of the product.
384		**Comment**: In order to keep as many modules as possible applicable globally as possible we would like to include global trade names. **Proposed change**: insert 'invented name(s) in the European Economic Area (EEA) **and other relevant regions'**
400-401		**Comment**: The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments, could become a very long section. This is a duplication of the regulatory status which is included in the PSUR (see lines 311 and 381-384 of the PSUR GVP module). Therefore this requirement should be deleted entirely, because it contravenes one of the key goals of the new legislation, i.e., simplification of PV processes. Of note, licensed status should have been defined (e.g. approved, under review, expired, withdrawn), **Proposed change**: We recommend that topic to be removed from the RMP, and be located only in the PSUR
407-409		**Comment**: This section now specifies off label use and uses non-specific wording which would encompass

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		any further investigation to refine the benefit-risk in any population **Proposed change**: and outstanding safety questions which warrant further investigation to refine the understanding of the risk-benefit profile **within the indicated use** during the post authorisation period.
440		**Comment**: The emphasis on the relevance of the safety profile of the drug (important adverse events) is no longer mentioned **Proposed change**: Information should be provided on the important co-morbidities in the target population **that relate to the safety profile of the product**.
446		**Comment**: The marketing authorisation holder is not always the body responsible for creating the RMP **Proposed change** :~~The marketing authorisation holder~~ The **RMP** should include a statement of the intended purpose and impact of the product
448-449		**Comment**: It is unclear why the short review of where the medicinal product fits into the normal therapeutic armamentarium is required. The proposed SmPC should indicate this. Such a statement may differ from country to country according to medical practice and may require updating as new products are approved and the standards of care change. Suggest this is deleted. **Proposed change**: ~~A very short review of where the medicinal product fits into the normal therapeutic armamentarium should be provided.~~

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463		**Comment**: The below-indicated text addition highlights where the safety concerns should be summarised. **Proposed change**: added text after line 463: **Where the nonclinical safety finding could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.**
519		**Comment**: For some products/indications this information may not be available (due to age of product if a well-established product) or due to the indication (these populations may never be studies or not appropriate). **Proposed change**: Allow for flexibility of inclusion of this information such as products under 'exceptional circumstances' or for indications when these subpopulations are not appropriate'.
537-542		**Comment**: It is not clear that information on why contraceptive measures advised during trials failed, is captured. This is primarily an issue if there are safety reasons why pregnancy should be avoided. **Proposed change**: If the medicinal product is not specifically for use in pregnancy, any pregnancies which have occurred during the development programme and their outcomes should be discussed. ~~If~~ **For products where pregnancy should be avoided for safety reasons** ~~contraception was a condition of trial entry~~, the discussion should also include **an analysis of failure of contraception the reasons w**hy the measures put in place failed (if relevant) and the implications for use in the less controlled conditions of everyday medical practice.
570-71		**Comment**: The wording "… the number of patients included in observational studies where safety data has been collected…" covers a too broad scope of epidemiological studies (see comment Line 632 below).

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		Proposed change: "…the number of patients **in all completed observational studies conducted to further elucidate a safety issue**…"
568-572		**Comment**: This paragraph requests information on 'any regulatory action taken to update information on the safety of the medicinal product'. This is in contrast to GVP Module VII, PSUR section 'Actions taken in the reporting interval for safety reasons', where only those actions need to be listed which had 'either a significant influence on the risk-benefit balance' of the medicinal product 'and/or an impact on the conduct of a specific clinical trial(s) or on the overall clinical programme. **Proposed change**: Align the requirements between the two modules and only request here 'any regulatory action taken to **significantly** update information on the safety of the medicinal product'.
575-577		**Comment**: The requirement to list any regulatory action in any market could lead to excessively long lists, especially when it comprises information on new safety information, which the MAH rolls out to all countries worldwide. It should be possible to summarize roll-out of such new safety issue in one line, instead of capturing each individual submission and/or approval date of such variation worldwide. **Proposed change**: This list should be cumulative, and specify the country, action taken and the date, **as appropriate. Worldwide roll-out of a new safety statement initiated by the MAH can be presented as one action.**
605-616		**Comment**: It is not clear how it would be possible to provide information on post-authorisation use in populations not studied in clinical trials. **Proposed Change**: For the post-authorisation exposure the draft guideline states the exposure by age, sex etc. should be provided **where possible**. It would be better if the same were applied to exposure in populations not studied in clinical trials (i.e. provide this information **where possible or if available**).

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605-616		**Comment:** While routine pharmacovigilance activities may detect the presence of product use for off-label indications or in special populations, a reliable method for the quantification of post-authorisation patient exposure in these patient groups is not always available. The wording "where post-authorisation use has occurred" to describe the circumstances under which quantification of post-authorisation patient exposure within a special population must be provided could be interpreted to imply that market research or drug utilisation studies must be conducted whenever a report is received describing use in a patient belonging to a special population. We propose wording similar to that used in section V.B.8.5.4 to describe conditions under which such quantitative approaches should be used for off-label use. **Proposed change**: Where **there has been a concern raised by the MAH or by the Agencies regarding** post-authorisation use ~~has occurred~~ in the special populations identified in RMP module SIV as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label.
617-630		**Comment**: Section Indicated use versus actual use: 'specific reference should be made as to how the actual pattern of exposure has differed from that predicted in Module SVII, ….'The information does not flow in an ordered manner, as predicted exposure is in a later section (lines 727-737). In addition, there would be repetition of information provided in the two sections. Proposed change: Remove the section in lines 727-737 and combine the information into this section, with a comment on predicted use (see also comment on lines 727-737)
619		**Comment** (editorial)**:** The cross reference is to RMP module SVII, predicted exposure; however predicted exposure is proposed to be discussed in module SVI.
620-625		**Comment**: "*Off-label use*" should be defined in GVP Annex I (definitions) and the pieces of information cited

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		here should be adjusted to be consistent with that definition. **Proposed change**: Define "*Off-label use*" in GVP Annex I (definitions) and ensure the pieces of information cited in this and other relevant sections in all GVP modules are accurate with respect to that definition.
624-625		**Comment**: There seems to be an inconsistencies between module 6 (lines 166-169) and 5 on the definition of misuse regarding off label. In module 6, it seems that when prescribed in non authorised indication, off label use should not been considered while in module 5, all situations where prescriptions are made outside the registered indication should be considered **Proposed change** : Clarify definition of misuse in term of off label use in module 6
624-625		**Comment**: The scope of the following is unclear: "*Off-label use includes, amongst others, use in non-authorised paediatric age categories, and use in other (non EU-authorised) indications outside of the clinical trial setting*." Certain paediatric age categories are mandatory in certain jurisdictions outside the EEA, e.g., Japan, and these categories are sometimes impossible to correlate with EU paediatric age categories. **Proposed change** : Revise to read: "Off-label use, includes, amongst others, use in non-authorised paediatric age categories (**when this can be determined**), and use in other (non EU-authorised) indications outside of the clinical trial setting."
Line 629		Comment on statement: "MAH should provide a listing of epidemiological studies which have included/include the collection of safety data." This is a very broad statement and will include all studies a MAH runs as all studies should collect safety data, such a listing will not add value to risk management planning and could detract from focus on relevant safety studies.

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		Proposed change: MAH should provide a listing of epidemiological studies which ~~have included/include the collection of safety data~~ **are being conducted to further elucidate safety or efficacy issues or measure effectiveness of risk minimisation measures**.
629-630		**Comment**: Reference to use in clinical trials should be included in RMP module SIII – not in module SII as stated **Proposed change:** "Use in clinical trials conducted as part of the marketing authorisation holder's development programme should be included only in RMP module ~~SII~~ **SIII**
632-633		**Comment**: The scope of epidemiology studies to be included ("….epidemiological studies which have included/include the collection of safety data") is too broad, as virtually all epidemiology studies, including for instance those conducted for pricing purposes, collect safety data at some point. We suggest the RMP should focus on the epidemiological studies that have defined safety objectives. **Proposed change:** change to "Marketing authorisation holders should provide a listing of MAH sponsored epidemiological studies **which are being conducted to further elucidate safety or efficacy issues**."
632-639		**Comment:** Epidemiological studies are a very important part of the pharmacovigilance science. However, epidemiological research is also often performed on a smaller, ad-hoc basis to support signal evaluation. It would be important to either explicitly include this type of research in this section or to indicate that such ad-hoc research should not be part of this section. **Proposed change:** Add to line 639: "**this excludes ad-hoc epidemiological research for the purposes of supporting signal evaluation. Results of such research should be part of these respective signal**

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		evaluation reports."
647		**Comment:** proposed text addition to highlight where the safety concern should be mentioned. **Proposed change:** The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern **in module SVIII** and….
702-703		**Comment:** Clarification is needed on whether this section is only applicable where there is an agreed PIP for the same condition or whether this applies even when the PIP(s) related to another condition
727		**Comment** (editorial): in the title, section number should be SVI and not SV
727-737		**Comment**: It is hard to predict projected post-authorisation usage, and it is unclear how supposition will be helpful in the RMP especially in rapidly changing environments. MAH speculation should not be made public. There also would be significant repetition with a previous section 'Indicated use versus actual use'. In addition, the information does not flow in an ordered manner, as actual use versus predicted exposure is discussed in a previous section, before the 'predicted exposure' information has been presented. **Proposed change**: Remove this section (lines 727-327) and present the information in 'indicated versus actual use' (lines 617-630), with the discussion focusing on actual use, and a comment on how this differed from expected use as appropriate.
739-740		**Comment:** Previously this was limited to important identified and potential risks that 'require further characterisation or evaluation'. It is unclear why this topic has been broadened. **Proposed change:** This RMP module provides information on the important identified and potential risks associated with use of the product **that require further characterisation or evaluation.**

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749 - 823		**Comment:** Details of important identified and potential risk: If class effects were considered a 'potential or an identified risk' they should be included in this section, as it would be more appropriate to include all risks in one section, if they are then included in SVII 'Pharmacological Class Effects' there would be duplication of information. **Proposed change:** Include 'class effects' in section SVII Details of important identified and potential risks'. Remove 'Pharmacological class effects' as a separate section of the EU RMP (See comment on line 832).
750		**Comment:** the term 'important' identified and potential risks is defined in the document, but 'most important' is not. We suggest leaving out 'most'. Alternatively, a rationale for the prioritization of risks should be given to explain why certain risks were chosen as the most important identified and potential risks. Proposed change : "This RMP section should provide more information on the ~~**most**~~ important identified and potential risks."
754-755		**Comment:** The description of what is meant by an important risk does not fully match the definition provided earlier (183-185). The description what is meant by an important risk ~~does not fully match what is~~ should cross-refer that provided on this subject under definitions (183-185). **Proposed change:** Amend the sentence line 754-755 to add "....impact on public health **(see V.B.1 for definition of important risk)**."
754-762		**Comment:** Although we agree that importance of a risk could be derived from the fact that it justifies a warning or contraindication in the product labeling, the content of the Warnings and precautions section in the SmPC is not only selected according to significance, but some standard topics are always addressed in this section, even if the information provided may be of minor significance in individual cases. Examples are

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		statements on the absence of information in special populations or excipient warnings, which actually state the absence of a risk (e.g. sodium content below 1 mmol/l). In addition, the section sometimes contains precautionary statements of minor importance, which would not qualify as 'important risks' and would not qualify for inclusion in this labeling section in other regions of the world, e.g. in the USA. **Proposed change:** 'Normally, any risk which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be ~~included~~ **considered** here'
774		**Comment:** 'preventability' of risks is a new inclusion to the detailed risk data. It is not clear what is required for 'preventability (i.e. predictability, avoidability or possibility of detection at an early stage). **Proposed change**: Include further guidance on what is required for this risk characterisation
832-839		**Comment**: see comment on lines 749-823 **Proposed Change:** delete this section
941-948		Comment: For clarity, it would be helpful to retain the previous guidance that this section does not include actions intended to reduce or prevent risks. Proposed change : how important missing information will be sought. **It should be noted that this section does not include actions intended to reduce or prevent risks**.
968		**Comment:** It would be helpful to include the statement from previous guidance, confirming that for products

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		for which no special concerns have arisen, routine pharmacovigilance should be sufficient for post approval monitoring. **Proposed change: For products for which no special concerns have arisen, routine pharmacovigilance should be sufficient for post approval monitoring. However, in certain situations,** the Pharmacovigilance Risk Assessment Committee....
980-981		**Comment:** Whilst the concept of a consistency in the format to follow-up requests is good it is unrealistic in practice for companies to co-ordinate this across companies. Proposed change: It is suggested to add that the Agency would provide an optional template when coordination among applicants/MAHs is needed.
987 - 992		**Comment:** The example used implies that medicinal products for chronic use should have at least 3 years safety data at time of authorisation. This is not in line with ICH E1 which requires a minimum of 100 patients treated for a year. **Proposed change:** For example, ~~a medicinal product intended for chronic use may not have any safety data on use longer than three years at the time of authorisation. Long term follow up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long term follow up of a cohort of patients to confirm that there is not an increased risk of cancer in human use.~~ **limited exposure for a product intended for chronic use, pre-clinical data indicating a need for follow up data in the clinical setting etc**. Another example when additional pharmacovigilance activities should be considered is when .....
1003		**Comment**: Investigating the possibility of a risk should be based on a scientific justification relating to a

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		meaningful safety issue for the patient. **Proposed change:** For important missing information, the objective**, based on a scientific justification**, may simply be to investigate the possibility of a risk or....
1003 1011-1016		**Comment:** This section states that the RMP "should include all studies designed to address the safety concern and those which might provide useful safety information even though the particular safety concern might not have been the primary focus" (emphasis added). The underlined text from the GVP appears to be applying a very broad interpretation of the definition of post-authorisation safety studies (DIR Art 1(15)), with the result that the RMP may need to include almost any clinical trial with safety endpoints, including those in unauthorised indications. This is not consistent with the general principles for PASS described in GVP Module VIII (VIII.B.3, lines 123-137). The applicant/MAH should be allowed some discretion in defining which clinical trials to describe in the RMP in order to address the safety concerns identified in the safety specification. **Proposed change:** The applicant/marketing authorisation holder should include all studies designed to address the safety concern ~~**and those which might provide useful safety information even though the particular safety concern might not have been the primary focus.**~~
1018		**Comment**: "If, when reviewing a study protocol, a study is thought to be primarily **promotional**, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP". The term "promotional", used as qualifier for a PASS, should be defined to avoid mis-interpretation. A definition is actually suggested in Line 1469: a "promotional study" is "a study which does not have a valid scientific question as its primary aim and is designed to increase use of the product". This type of study is actually unethical. Promotional studies, defined as intended to result in a promotional claim, need to have a valid scientific rationale and objective.

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		Proposed change: If, when reviewing a study protocol, **a study is evaluated as not fulfilling one of the objectives of a PASS (as described in Module VIII) or a PAES**, the applicant/….”
1033		**Comment**: To make it evident that protocols do not need to be appended indefinitely: **Proposed change:** ‘…provided in RMP annex 5 **until completion of the study, defined as finalisation of the study report**.’
1043-1052		**Comment**: Role of drug utilisation studies in the pharmacovigilance plan: While the value of results from drug utilisation studies to understand specific safety-related topics, such as extent of product use in a patient sub-population, is appreciated, we would maintain that, based on study objectives and design, some drug utilisation studies may have no relevance to pharmacovigilance or post-authorisation efficacy. It is suggested that the RMP guidance distinguish between drug utilisation studies designed to inform a safety concern or and efficacy issue per the RMP from those that cannot provide any relevant information. These latter studies should not be automatically categorized as PASS or PAES studies, and may not warrant inclusion in the pharmacovigilance plan. **Proposed change:** add at the end of the sentences line 1047 paragraph line 1052: “…the studies should be included [..] **should they provide relevant information to the safety or efficacy concerns addressed in the RMP.”**
1068 – 1076		**Comment:** Definition of registries is inaccurate and inconsistent with that provided in Module VIII PASS. **Proposed change:** The section should be replaced with language consistent with GVP Module VIII App1.1.1.4 Registries.
1094-1095		**Comment:** To avoid overlap and redundancies seen with the current EU-RMP template, the future RMP

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		template (not yet provided, see general comment) should clarify how the requested "Summary table of additional pharmacovigilance activities" will differ from "Action plans for safety concerns with additional pharmacovigilance requirements" in the previous section. **Proposed change:** will be further addressed in commenting the future template
1105		**Comment:** The references to the legal basis for imposition of post-authorisation efficacy studies as a condition of the MA are incomplete. **Proposed change:** In addition, article 10a(1) of Regulation (EC) No 726/2004 and articles **21a(f) and** 22a(1) of Directive 2001/83/EC, provide the legal basis for requiring post-authorisation efficacy studies...
1117-1119		**Comment:** It is unclear if sub-section V.B. 10.1 "presentation of efficacy data" is to be completed even if there are no planned post-authorization efficacy studies (the subject of the entire Part IV per title). This sub-section is considered for two different purposes (line 1117): "as explanation for any efficacy studies proposed" (thus would be not necessary if no PAES) and "to provide background that can be used in the RMP summary", (this would be required for any RMP). The content of this sections mixes the rationale for performing or not PAES, and the presentation of the benefit data for putting all the RMP into context in the RMP summary. In addition, a better alignment with the benefit sections of PSUR/PBRER would facilitate the development of the modular approach. **Proposed change**: This section might be better placed in an earlier part of the EU RMP (Product Overview or Safety Specification), before the Pharmacovigilance Plan. It should be a summary of the PSUR/PBRER sub-section 17.1 "important baseline efficacy and effectiveness information" for a first RMP, or 17.3 "Characterization of benefits" when relevant post-authorization benefit data have been obtained. Lines 1121 to 1125 discussing the need for PAES should be brought in the previous section "Plans for efficacy Studies".

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1118		**Comment:** This should be more explicit in referring to the authorised indication. **Proposed change:** summary of the efficacy of the product in **the authorised indication(s)** and what studies...
1120		**Comment:** It is unrealistic to describe efficacy in one page maximum for large and complex programs. In addition, as proposed, this is the only place for the presentation of efficacy data and these data are requested as summaries that are suitable for inclusion in the RMP public summary. When there are benefits characterised separately by indications, population, and/or route of administration, it is suggested to allow one page per each factor. **Proposed change**: This should be brief (one page maximum **per indication, population, and/or route of administration**).
1156		**Comment:** The term "Routine risk minimization" is unsuitable for covering all situations described under this header. If "routine" qualifies activities "which happen with every medicinal product" (line 1157), then a legal status that "controls the conditions under which a medicinal product may be made available" (line 1179), should not be classified as "routine", as it clearly does not apply to every medicinal product. Limiting the pack size (line 1169) should also not be considered as "routine". There should be a distinction between the "true" routine risk minimization applying to every medicinal product, i.e. the "simple" recommendations and information in the labeling documents (SPC, PIL), and other available regulatory provisions (such as pack size limitation, restricted legal status) that are beyond routine as they clearly aim at limiting the use. This would help harmonization between different regions, because these specific EU regulatory provisions may not be available outside the EU, and would therefore not be considered "routine" in such other jurisdictions. **Proposed change:** Suggest to move the sub-sections "pack size **limitation**" and "legal status" into Part V

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		"Additional risk minimization activities" under a subsection "Methods using EU Regulatory Provisions",
1256		**Comment:** The term "promotional" used as qualifier of (inappropriate) educational material, should be defined, or not used, to avoid mis-interpretation (see above comments on the same term used elsewhere). For educational material, there is an opportunity to make the distinction with the promotional material used by MAHs for their marketing campaigns and which are subject to specific regulations. Of note, promotional materials may include communication of safety information. **Proposed change:** "Any educational material should be ~~non promotional~~ **clearly focused on the risk minimization goals defined to justify their use, and should not be confused or combined with promotional material for marketing campaigns".**
1256		**Comment:** Will piloting of educational material be required for every situation including previously used ones?. **Proposed change:** inclusion of the following text at the end of this paragraph. ***Piloting will not be required if the educational program has been previously piloted and unchanged subsequently.***
1282-1284		**Comment:** Providing detailed wording of the SmPC for routine risk minimisation activities would heavily impact global use of the section (for different countries). In addition, for products under national procedure,

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		there may not be a harmonized SmPC among all CAs. The detailed wording can be checked in the SmPC or the Core Safety Profile, in these cases where there are differences in SPC arising from different CAs, appended to the RMP. Therefore it should be sufficient to provide a meaningful keyword here, e.g. 'warning on special risk group X for safety concern Y included in the product labeling'. The use of a cross-reference to the actual labeling text in Annex could limit the redundancy and the potential for unintentional discrepancies. **Proposed change:** For routine risk minimisation activities, ~~the proposed text in the summary of product characteristics (SmPC)~~ **a meaningful description of how this will be addressed in the product labeling** should be provided along with details of any other routine risk minimisation activities proposed for that safety concern. **Reference should be made to the actual labeling text in Annex 2 (SmPC or Core Safety information, in these cases where there are differences in SPC arising from different CAs)**
1297-1307		**Comment:** this section ("Evaluation of the effectiveness of risk minimization activities") does not include any guidance on how to handle risk minimisation plans which may have been considered reasonable at the time of first marketing but which subsequently are demonstrated to be excessive and an undue burden on the healthcare systems of multiple countries without any demonstrable positive impact on minimising risk. (This issue will be further addressed in Module XVI) **Proposed change:** in line 1304: add text in bold in the following sentence "if a particular risk minimisation strategy proves ineffective **or causing an excessive or undue burden on the healthcare systems**, then alternative **strategy/**activities need to be put in place."
1310 - 1381		**Comment:** The summary of the RMP seems to be very detailed and will be very repetitive of information in the EU RMP. If the Summary of the RMP is targeted for the general public /lay people it could be very difficult for them to understand if it is long/involves tables/discussion of scientific concepts (such as the concepts of identified risks/potential risks etc). The utility of this for the public/lay person is not clear.

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		It appears that this section is serving two purposes, a summary of the RMP and a summary for the general public and these are different target audiences. Further guidance would be very useful as the summary of the RMP will be difficult to author /transpose to lay language.
1313- 1314		**Comment:** Is the 'lack of knowledge' stated here the same as 'missing information'? Proposed change: 'With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as ~~lack of knowledge [IM Annex II.2]~~ **missing information [IM art 311(2)].**
1322-1326		**Comment:** Line 1326 specifically denotes that this should be worded in lay language when in fact so do the other sections (overview of disease epidemiology, summary of benefits/efficacy) **Proposed change:** add to Lines 1322-23 an overarching statement (bold) : "RMP part VI should contain the following information based on RMP modules SI, SVIII and RMP parts 1322 IV and V **(in lay language)**". Remove specific reference to lay language in line 1326
1330		**Comment:** The scope is not specified with regards to providing information on 'any activities which are conditions of the marketing authorisation'. Further guidance in the template would be usefull.
1331		The Summary of EU-RMP is not yet available, yet it is important to understand what the Agency expects as RMP information to be made publicly available. In particular, it will be useful to understand the requirement for the efficacy summary.

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		Proposed change: Specify when the template will be available
1336		Comment: The term 'non alarmist' is subjective. Proposed change: in a ~~non alarmist~~ factual manner and in....
Lines 1359-1364		Comment: (see comment to Lines 1282-1284). We are not in favour of providing detailed wording of the SmPC when detailing risk minimisation activities. A meaningful summary of the way a safety concern is addressed in the product labeling should be sufficient, as actual wording can always be checked in the appended version of the SmPC (or the Core safety information, when there is no harmonised SmPC in the EEA). Concerning the Package Leaflet, detailed wording for such document would limit global use of the section. According to the rules governing the creation of Package Leaflets in the EU, the Package Leaflet must reflect the SmPC, and this is regularly evaluated in any new approval procedure or variation. If the authorities wish to obtain information on the patient information in this place, it should also be possible to describe in general terms that and how a safety concern is addressed in such document. Proposed change: When detailing the risk minimisation activities in relation to the summary of product characteristics (SmPC), ~~the actual text of SmPC sections 4.3 and 4.4 (if relevant)~~ **a meaningful summary of how a safety concern is addressed in the product labeling should be used.** ~~However if the SmPC sections are very long, a précis should be provided. For risk minimisation activities involving other parts of the SmPC a summary of what is in each SmPC section should be provided. For SmPC section 4.8, indicating "labelled in section 4.8" is sufficient.~~ The corresponding information in the package leaflet should also be provided.
1384-1400		Comment (minor): In the previous RMP template, it was not clear if all the annexes were needed even if not relevant. We suggest specifying that all the stated annexes should be present and specify if no information is

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		available for a given annex. Proposed change in bold: The RMP should contain the following annexes **(when no information is available for an annex, this should be stated)**
Line 1386- 1387		Comment: Requirements for provision of SmPC and package leaflet in relation to different marketing authorisation routes are not specified. For instance, there may be a common RMP for same active principle authorised to the same MAH but with national procedures resulting in different SmPCs across the EU,. I would be useful then to allow the Core Safety Information to be appended instead of SmPCs. Proposed change: Reword line 1386; "Current (or proposed if product is not authorised) **local/MRP/DCP/CP** summary of Product Characteristics (SmPC) and package leaflet**, or the Core Safety Information in case of non harmonized SmPCs across the EEA**"
1387-8		Comment: follow-up of the comment on Lines 400-401. The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments, could become a very long section Proposed change: add an Annex "Worldwide regulatory status by country"
1393		Comment: Clarification is required as to whether all study reports are needed i.e. including off label clinical development, and whether full study reports, including modular appendices, are required. The inclusion of full study reports for all studies will significantly increase the size of the RMP, with little benefit to companies or assessors: it would be preferable to allow that report synopses be provided (with the full report being available upon request). Proposed change: **Synopses of** Newly available study reports for RMP parts II – V

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1395		Comment: There are practical issues in providing 'actual' materials (publishing runs, languages etc). A more practical approach is proposed. Proposed change: ~~Example(s) of actual~~ **Mock up examples in English (or the National language if the product is only authorised in a single Member State) of the** material provided to healthcare professionals and patients....
1432		Comment: As there is considerable overlap between the content of the RMP and the content of the PSUR/PBRER, it is appreciated that the Agency has given some thought to the idea that some of the content can be shared between these 2 documents. The concept of modularity is attractive; however, the examples given in the guidance are limited, and at times the content requirements from the RMP and PSUR guidances are not the same for a section where the Agency has recommended that content may be "utilised interchangeably." For example, the RMP requires a detailed listing of worldwide regulatory approvals by individual country, whereas the PSUR requires a "brief narrative overview" of regulatory status; the RMP requires a cumulative listing of regulatory actions taken for safety reasons, whereas the PSUR requires an interval listing; the RMP requires the current list of important safety concerns, whereas the PSUR requires the list that was in effect at the beginning of the PSUR reporting period. While the impact of these differences varies, their presence limits the efficiencies achievable through modularity. In addition, the schedule for submissions of RMP updates is not well defined, and may differ from the schedule for submission of PSURs. The data intervals under review may therefore differ between the 2 documents, limiting the "interchangeability" of the overlapping content. It would be appreciated if the preparation of the final versions of the RMP and PSUR guidance documents could include a review of the 2 documents together, to improve the consistency of the requirements for the sections considered to be "interchangeable." One suggestion below is the addition, in Table V.1, of a common modular approach with the efficacy sections of PSUR/PBRER, (see above comment on lines 1117-19)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: RMP Part IV section "presentation of efficacy data" to be matched with PSUR/PBRER sub-section 17.1 "important baseline efficacy and effectiveness information" for a first RMP, or 17.3 "Characterization of benefits" when relevant post-authorization benefit data have been obtained.
1469		Comment: (see comment to Line 1018) A study which does not have a valid scientific question as its primary aim and is designed to increase use of the product is actually unethical. Promotional studies, defined as intended to result in a promotional claim, need to have a valid scientific rationale and objective. The term promotional is ambiguous. Proposed change: "Are any proposed studies ~~promotional (ie. A study which does not have~~ **without** a valid scientific question as its primary aim and ~~is~~ designed to increase use of the 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')*
Lines 1565-1570		Comment : In lines 1565-67 , it is mentioned that for submission of an initial application, a RMP may not be required and that a justification of its non necessity should be provided From all the subsections of V.C.3.1, it can be understood that for all application submission for all products, a RMP must be submitted but that only some parts of it can be included in the RMP document for some type of products or situations Proposed change: If an RMP complete exemption is indeed possible, consider adding a sentence at the beginning of V.C.3.1: "When no exemption of RMP writing is proposed by the Applicant, normally all parts of the RMP…"
1591		Comment: The definition of "well established use" should be included in the definitions in the definitions GVP annex.
1591 - 1621		Comment: There appears to be minimal flexibility for 'well established medicinal' , as the majority of modules are still required. RMPs for well established products should be very targeted and only focus on the new indication/new issues (and not include old data). The safety specification should concentrate on new data for the new indication/population etc and not be a repeat of old data that is part of an accepted and established existing safety profile. See also comments on lines 331-8.
1631-1632		**Comment**: It would be desirable for the RMP to be aligned with the Data Lock Point of the PSUR **Proposed change**: Revise to read (line 1631-1632): "It is *anticipated that this will contain an RMP module, **with timing of the RMP module aligned with that of the 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')*
1639-1641		The submission of RMP updates in track changes may be difficult to achieve due to automated software behaviours such as indicating formatting changes etc and also difficulties in spotting factual changes once whole text passages are cut and pasted. The current RMP template includes an update section which would already be detailing the content-wise changes therewith providing a complete overview or what these are. Proposed change: **When technically feasible,** clean and track change version….
1643		Comment: The expected frequency for updates to RMPs for products which do not have the requirement specified as part of their authorisation should be addressed here.
Line 1653-1655		Comment: It is presumed that the timescale published will constitute a maximum allowed time and that the RMP update will be triggered by the earliest planned procedure (e.g. variation, renewal, PSUR) where an RMP would normally be submitted. Proposed change: Reword line 1654 as follows; "…the Agency will publish on its website ~~a timescale~~ **the latest date** by which the RMP should be in the new format.
1671 – 1679		Further guidance on the PRAC assessment process is eagerly awaited. We suggest that this guidance address at least the following points: the basis of assignment of PRAC Rapporteurship (e.g. the same country as the CHMP Rapporteur or Co-Rapporteur or the best available PRAC expert for that product); whether the assessment takes place in parallel and whether there will be a PRAC assessment report and questions at D120; whether PRAC assess only the RMP or have access to the entire submission; opportunities of meetings with the PRAC Rapporteur during review; the possibility of safety aspects requiring an oral explanation be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		discussed by PRAC, CHMP or both.
1682-1695		Comment: Whilst the intent of this is good (to allow for differences in medical practice/healthcare provisions) there is concern that this could be misinterpreted and ultimately undermine the authority of the PRAC if the discussion between individual national competent authorities and the MAH results in request for additions or significant deviations from the Centrally reviewed and approved RMP. Proposed change: Ensure clarity that the intent of this is restricted to the implementation of risk minimisation activities included in the RMP, and that the scope does not allow for deviations from the risks identified in the EU RMP.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
EGA – European Generic Medicines 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*).*

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 new requirement for RMPs for all products is not considered to be risk based. There are a lot of generic and/or well established use products on the market which are safe in use and for which writing/assessing a risk management plan is a waste of time. The current approach does not fulfil the objectives of the new legislation. The EGA proposes to use the same list as established for PSURs to use as requirements for RMPs. This means that for all products on the list where currently a PSUR is required and a periodicity which is less than 5 years, an RMP should be written.
	According to Guideline Module V, the new modular structure for EU risk management plans will come into force in July 2012 but transitional arrangements whereby either the old or new format can be used will be posted on the Agency's website. Will transitional measures be applied to the compulsory submission of risk managements plans or will only be applicable to the format?
	The requirement for what are still quite detailed RMPs for generic products have potentially not only for huge risk of duplication of effort across generics MAHs, but also for inconsistency of approach and/or duplicative actions between different MAHs. The guidance needs to be clearer on how this will be addressed by the EMA/NCAs both to minimise the impact on generic manufacturers (given the need for risk management systems to be proportionate) and, more importantly, to ensure that patients and healthcare professionals receive clear and consistent messages about the products they are using.
	It seems clear from this GVP that the Agency wishes to move towards a harmonised approach to risk management, with generics mirroring the RMPs of the innovator product, similar educational material and joint studies. However, as it stands, under the GVP there is still huge potential for inconsistency of approach and/or duplicative actions between different MAHs, with the potential therefore for patients and healthcare professionals to receive unclear or inconsistent messages about the products they use (or simply to be overwhelmed with information from multiple MAHs which is then ignored!). The GVP does not clearly set out how the Agency will support/drive/facilitate the harmonised approach; their role in this process needs to be developed and clarified if the vision of a harmonised approach is to be implemented effectively.

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 140		Comment: The new modular structure for EU risk management plans will come into force in July 2012 but transitional arrangements whereby either the old or new format can be used will be put in place and will be posted on the Agency's website Proposed change (if any): What deadline would we need? How will we manage this?
Lines 170-171, 183, 190-192.		Comment: Consistency with definitions in Annex I is required.
Lines 274-299		Comment: According to Line 287, the Competent Authority must ensure that the MAH of generic products make similar changes when changes are made to the reference medicinal product risk minimisation measures. This should hold true also the other way around, i.e. if a safety concern emerges with a biosimilar, innovators should change their RMP unless it can be proven that their products are not affected. Moreover, it should be clarified how the Local Authorities will provide to generic MAH this information and vice versa. Proposed change (if any): Text should be revised to clarify that changes to the RMP of a medicinal product should be harmonized across innovators and generics sharing the same active principle, regardless if the change was firstly implemented by the reference or generic MAH, unless it can be proven that the underlying safety concern is specific to a particular medicinal product. Commitment by Local Health Authorities to share the relevant information after updates/changes.
Line 330		Comment: The Agency will make available on its website a template for the RMP. The EGA would like to stress the urgency of publishing or the Agency providing a draft / final 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')*
Line 378		Comment: The RMP is required to have a 'data lock point' – presumably this is a cut-off point defined by the applicant/MAH, for data on which the RMP will be based. What is the expectation of the EMA/NCAs with regard to the time of submission of the RMP in relation to the DLP for the plan – is there an acceptable maximum gap between DLP and submission? Proposed change (if any): clarify what is meant by the data lock point, and any expectation in relation to the maximum gap between the DLP and submission of the RMP to the EMA/NCAs.
Line 400		Could it be specified what is meant by "world-wide regulatory status"?
Line 676		Comment: The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed. Proposed change (if any): What means other formulations on the market? Reference products? Other products taken at the same time, there can be so many products on the market for one INN strength form. Please clarify
Line 692		Comment: If the formulation or strength of a product is being changed, medication error should be included as a safety concern and the measures the marketing authorisation holder will put in place to reduce confusion between old and new "product" should be discussed in the risk minimisation plan. Similarly, it may be appropriate 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')*
		discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicinal product. Proposed change (if any): How strictly should this be read? How often do compositions slightly change? Will this become a routine request when submitting the related variation to change composition?
Lines 727-30		Please clarify whether the details requested in these lines are necessary for generic products, given that the module SV (post-authorisation experience) does not have to be included in the RMP for generic products, and that at the point of application for a generic MA, the product will already have been on the market for a number of years with pattern of use etc already likely to be understood.
Lines 984-1037		Comment: Studies in the Pharmacovigilance Plan should be done related to clarify safety concerns (PASS studies) identified in the safety specification whether the studies are to identify and characterise risks or assess the effectiveness of RMP activities (PAES studies) by the generic company. Protocols for studies in the Pharmacovigilance Plan should be provided in RMP Annex V. Proposed change (if any): Submit Proposal instead of Protocols.
Line 1033		Comment: Do the study protocols which should be provided in RMP annex 5 require being in English language? Proposed change (if any): Specify whether these will be accepted in local language or are expected to be in English

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 1265-68		Will there be a requirement for the EMA/NCAs or the MAH to provide existing educational/patient material to other applicants/MAHs, in order to facilitate the development of material with similar layout/content etc?
Line 1312		A summary of the RMP for each medicinal product shall be made publically available... Will this principle be applied also to legacy RMPs (i.e. retrospectively) or only to those newly released (prospectively)?
Lines 1378-1379		There is a reference here to the need for a variation for changes to risk minimisation activities, but this is not mentioned elsewhere within the document. More detail is needed – for instance, will a variation be required for a routine update to the RMP; what type of variation will be required etc.
Line 1386		Comment: RMP annex 2: Current (or proposed if product is not authorised) summary of product characteristics (SmPC) and package leaflet Proposed change (if any): Why should this document be in the annex? It is already in Module 1.3
Line 1541		Comment: all products containing the same active substance should be included in one RMP [IM Annex II.1] Proposed change (if any): This will be quite difficult to execute, for cases where you have additional forms or formulations (mergers/acquisitions/old national MA's/licenced in etc…)
Lines 1576-7 / 1574 and 1609		Comment: it is stated here that RMP modules SII – SV may be omitted. This is not consistent with the table V2, which indicates that Module SI is also not required for generic medicine. Proposed change: make section consistent with table, i.e. module SI can be omitted for generic MAs.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 1576-82 / Lines 1707-8		The requirements for generic RMPs are appropriately in part related to the safety concerns for the innovator product. Will there be any provisions of making public summaries of RMPs for RMPs in place before 2 July 2012? As generic drug applications will have to include RMPs and the clinical data is not available to the generic companies, there should be a mechanism how their RMPs can be consistent with the innovators' RMPs.
Line 1584		Comment: For new applications under Article 10c of Directive 2001/83/EC, the RMP should be the same as the RMP of the cross-referred medicinal product. Proposed change (if any): What if the reference product does not have a RMP or an old format RMP?
Line 1587		Comment: For new applications under Article 10(3) or Article 10b of Directive 2001/83/EC, only the data on the fixed combination or data relating to the differences compared with the reference medicinal product need be supplied for RMP modules SII and SIII. Proposed change (if any): There is a rather substantial difference between 10.1 and 10.3 requirements.
Line 1609		Comment: The Generic Companies should consider if this public information (summary of activities make publically available) is enough to make their own RMP (Part I, Part II-SI, SV, SVI, SVII, SVIII, Part III*, Part IV*, Part V, Part VI*, Part VII). Proposed change (if any): If additional information will be required by the Generic Company in order to make their own RMP, should be necessary to establish a procedure with Local Health Authorities to request it.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 1609		Comment: Data in Table V.2. Row 5/Column 3. Part II, Module SI should be ticked according details in Line 1576-1577. Proposed change (if any): Update the Table V.2 with this missing data.
Lines 1611-1621		This refers to RMPs requested for products on the market in the EU for 10 years. Clarification is required as to whether this really is for specific products, or for active substances. If this is PRODUCT specific, this could see anomalies where the innovator has been on the market for >10 years but generics have been on the market for a lesser period of time.
Line 1625		Comment: Currently, for centrally authorised products, the RMP is submitted as PDF files within the eCTD submission. Following a Commission Decision where the procedure has involved the submission of an RMP, marketing authorisation holders submit the RMP annex I in XML format within a specific timescale. RMP annex I provides the key information regarding the RMP in a structured electronic format which, following validation at the Agency, is uploaded into an Agency database which is accessible and searchable by the Agency and national competent authorities. The system for nationally authorised products varies by Member State. Proposed change (if any): Should all be covered in eCTD guidance?
Lines 1628-9; Lines 1632-4		Comment: It would be useful if a consolidated list with submission requirements for Annex I in the member states and RMPs could be published, e.g. on the HMA website
Line 1698		Comment: It would be useful if it could be defined what 'launch' actually means in this context, taking into consideration that products may be available on compassionate use basis before and after granting of the MA and before the details of the national implementation of the risk minimisation measures have been agreed

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012>

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

Comments from:

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

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
	Two templates are not yet provided and will be required before MAHs can implement the new RMP structure: • EU-RMP template, • Summary of EU-RMP (Part VI) – to be made publicly available.
	The request that some sections should be written in "lay language" should not be interpreted as requiring systematic testing similar as that performed for Patient Information Leaflets. Further, some points mentioned in the summaries to be presented in lay language are already covered by contraindications, precautions and warnings in the Patient leaflet. Therefore, it should be possible to provide reference to the relevant sections of the patient leaflet.
	Transitional measures: In order to move to the future RMP format, including switching from the previous format to the new one for products with an existing EU-RMP, companies will need to make extensive changes in existing processes for RMPs and PSUR development. Therefore, even given the commonalities with the new PSUR format through the modular approach, it should be clearly stated that all new RMP or RMP updates to be submitted with the next renewal if the EU RMP template has come into force for longer than 6 months or until July 2015.
	Currently the risk management system is to be submitted together with a marketing authorisation application **where applicable**. That means, in special circumstances, e.g. for traditional herbal medicinal products, no detailed RMS was required. According to the new provisions no exemptions are foreseen for products with a low and well known risk. Only some minor sections may be omitted (e.g. section SII - SIV, see line 1591). The compilation of a RMS with its administrative information is a time consuming process - even if some sections might be omitted - and the expenditure of time is not in balanced proportion to the gain of new knowledge. We therefore propose to reduce the burden taking into account the factual risks.
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
122		**Comment:** the risk-benefit balance Proposed change (if any): the benefit-risk (chance of benefit/risk of harm) balance please use this term throughout the whole document
282 - 284		**Comment:** Whenever the communication between an authority and stakeholders is related to a specific product, it should be made sure that this is done in close cooperation with the marketing authorisation holder. For clarification purposes, a respective sentence should be added to the paragraph.
390		**Comment:** Indications may vary by country/regions. **Proposed change (if any):** specify "indications in the EEA"
393		**Comment:** Dosages may vary by country/regions. **Proposed change (if any):** specify "Dosage in the EEA"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
400-401		**Comment:** The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current license status and explanatory comments, could become a very long table. **Proposed change (if any):** This table should be moved to an Annex.
464 ff		**Comment:** This is generally acceptable, however, advice should be given how to proceed in cases where a marketing authorisation is applied for and if no or almost no study data is available (e.g., generic applications). Would it be appropriate to present published data in such situations? A clarifying paragraph is appreciated.
498 - 500		**Comment:** "When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables". Suggest that the wording be more specific in how the data should be presented. **Proposed change (if any):** "When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables representing total pooled data across all indications".
583 - 587		**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')*
		"These may include age, sex…" Please give examples how these data could be generated. Proposed change (if any):
612 - 613		**Comment:** "In particular, any information regarding an increased or decreased benefit in a special population should be provided." Be more specific in how the data should be presented. **Proposed change (if any):** "In particular, any information regarding an increased or decreased benefit in a special population should be provided as a tabulation of adverse drug events per each special population sub-group.
624 – 628		**Comment:** Examples on how the data could be generated would be helpful. **Proposed change (if any):** Please include examples how these data could be generated
648 - 651		**Comment:** "Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern and appropriate risk minimization proposed in RMP part V " Be more specific which data should be presented herein.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Only if harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, harm from overdose should be included as a safety concern and appropriate risk minimization proposed in RMP part V.
750		**Comment:** Undefined terminus **Proposed change (if any):** "This RMP section should provide more information on the important identified and potential risks."
769		**Comment:** "When the information is available, detailed risk data should include the following: " More clear guidance on how the data should be provided should be given **Proposed change (if any):** "When the information is available, detailed risk data per authorized indication should include the following: "
838 - 839		**Comment:** Be consistent in termini "..concern with the medicinal product, and hence is not included as an identified or potential risk, the evidence supporting this should be provided. **Proposed change (if any):** "..concern with the medicinal product, and hence is not included as an important identified or important potential risk, the evidence supporting this should be provided.
925 - 926		**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')*
		It should be more specific in presentation "At the end of the safety specification a summary should be provided of the safety concerns. A safety concern may be an: ..." **Proposed change (if any):** "At the end of the safety specification a summary table should be provided of the safety concerns. A safety concern may be an: ..."
1043		**Comment:** A definition would be needed for Drug utilization studies; does this include non-interventional studies? **Proposed change (if any):** Please define this term
1117- 1120		**Comment:** A brief summary of at maximum one page to present efficacy data would be a challenge for complex medicinal products. Further, this would require an additional document with unnecessary burden for MAHs. Indeed, the proposed content is similar to the information already prepared by MAHs in the Clinical Summary Overview. Therefore, the use of the clinical overview summary should be an option and would result in better quality. **Proposed change (if any):** "As explanation for any efficacy studies proposed and to provide background that can be used in the RMP summary, there should be a summary of the efficacy of the product and what studies and endpoints it was based upon. The robustness of the endpoints on which the efficacy evaluation is based should be briefly

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		discussed. This should be brief (one page maximum). Alternatively, the clinical overview summary in the content as required for renewals can be used.
1496 ff		**Comment**: According to Section V.B.16 the final responsibility for the quality, accuracy and scientific integrity of the Risk Management Plan should be with the QPPV. In line 261 et seq. it is considered that *"Producing a RMP requires the input of different specialists and departments within an applicant/marketing authorisation holder. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of study planned to address them."* From this it is clear that the responsibility cannot be taken by the QPPV alone. As with other documents submitted with a marketing authorisation application the responsibility should be with the applicant/marketing authorisation holder. Furthermore, this requirement would be inconsistent with module I (Quality system). According to module I the QPPV should provide input to the RMP (line 472 and line 552). Nothing is mentioned about the responsibility.
1563 - 1568		**Comment:** Why is a justification required when the submission of the RMP is not mandatory? **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')*
1584 – 1586		**Comment:** Who provides the RMP? Is it the Competent Authority or the originator? **Proposed change (if any):** Please clarify

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases

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
	Question whether "gender" and not "sex" should be considered in all pharmacovigilance activities. The document sometimes refers to sex (usually defined by phenotype and/or chromosomes), sometimes to gender (usually defined by the concerned person), as if they were synonyms and interchangeable, which is not the case. Or if transgenders should be considered appropriately as subgroups or subpopulations, since their number is increasing, since they are often highly medicated with intensive hormonal treatment and request special attention when using medicines.
	About the use of "race" and "ethnicity' in the agency activities. In these guidelines, not only module V, these concepts are used without being defined, e.g. "Patients of different racial and/or ethnic origins". Our opinion: - We appreciate the EMA values, in particular the above-arching statement that all EMA activities are based on science; - Science has unequivocally demonstrated that unlike animals, human beings cannot be distinguished in terms of races[1]; - The concept of "race" does not belong to a scientific discipline, but to an ideology, and the name of that ideology is "racism". What do we want to catch?

[1] Albert Jacquard (extract from "L'Equation du nénuphar") : "Une race est un ensemble de populations dont les patrimoines génétiques ont des structures semblables et nettement différentes des structures des populations considérées comme appartenant à d'autres races.
Il se révèle impossible de classer les différentes populations humaines en races. Selon le niveau de précision que l'on cherche à respecter, on peut finalement énoncer soit qu'il n'y a pas de races dans notre espèce, soit qu'il n'y en a qu'une : l'Humanité, soit qu'il y en a autant que d'humains, soit que le "concept de race n'est pas opérationnel pour notre espèce." La conséquence la plus claire est que tout raisonnement faisant référence à des races humaines est dépourvu de base scientifique.
Il se trouve qu'aucun des groupes formant aujourd'hui l'humanité n'a connu un isolement suffisamment long et rigoureux pour représenter une véritable race."
See also Albert Jacquard, « La génétique des populations », in MURS, no 5, 1986.

Stakeholder number *(To be completed by the Agency)*	General comment
	- Factors that can explain why different people behave differently with the same drugs - But these factors have to do with genetic characteristics that are to be determined, polymorphism that explains differences in metabolism - Race and ethnicity are poor surrogate for these genetic characteristics, a very bad "ersatz" - In an era where we personalised medicine is developing, categorising groups of patients by "race" or "ethnicity" is even more a non-sense, it goes the exact opposite direction ICH guidelines[2] don't even refer to "race", but to the population where the drug was tested, and to the population where the authorisation application is submitted: "Extrapolation of Foreign Clinical Data: the generalization and application of the safety, efficacy and dose response data generated in a population of a foreign region to the population of the new region". EMA guidelines[3] derive directly from ICH documents and avoid references to race or racial groups. In this respect, the pharmacovigilance modules do not coincide with EMA guidelines on ethnic factors. They refer to "ethnicity", and in their definition, and examples of ethnic factors that could impact the efficacy or safety of a medicine are listed:

[2] ICH HARMONISED TRIPARTITE GUIDELINE ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA E5(R1)
[3] NOTE FOR GUIDANCE ON ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA (CPMP/ICH/289/95)
[4] Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials
[5] Smedley, A. Smedley, B. Race as Biology Is Fiction, Racism as a Social Problem Is Real, January, 2005, American Psychologist, Vol. 60, No. 1, 16-26
[6] Owens, K. et al. Genomic Views of Human History, Science 286, 451, 1999
[7] American Anthropological Association (1998). Statement on 'race'
[8] What we do and don't know about "race", "Ethnicity", genetics and health, at the dawn of the genetic area. Francis S Collins, Nature Genetics Supplement, Volume 36, Number 11, November 2004
[9] Kahn, J. "Beyond BiDil: the Expanding Embrace of Race in Biomedical Research and Product Development", St. Louis University Journal of Health Law & Policy, Vol. 3, pp. 61-92, 2009;
In 2005, the Food and Drug Administration licensed a drug, BiDil, targeted specifically for the treatment of heart disease in African Americans. The recommendation of the drug for "blacks" is criticised because clinical trials were limited only to self-identified African Americans. It has been conceded by the trial investigators that there is no basis to claim the drug works differently in any other population. However, being approved and marketed to African Americans only, that specificity alone has been used in turn to claim genetic differences.

Stakeholder number *(To be completed by the Agency)*	General comment
	Extrinsic Ethnic Factors: ▪ Medical practice ▪ Diet ▪ Use of tobacco ▪ Use of alcohol ▪ Exposure to pollution and sunshine ▪ Socio-economic status ▪ Compliance with prescribed medications ▪ Practices in clinical trial design and conduct **Intrinsic Ethnic Factors:** ▪ Genetic polymorphism ▪ Age ▪ Gender ▪ Height ▪ Weight ▪ Lean body mass ▪ Body composition ▪ Organ dysfunction. These factors may indeed impact efficacy and/or safety, and then lets' do proper science and measure each of them and stratify by each of them. Most of them are already captured as part of the trial data collection. In FDA guidance[4], it is stated that "for example in the US whites are more likely than persons of Asian and African heritage to have abnormally low levels of an important enzyme (CYP2D6) that metabolizes drugs belonging to a variety of therapeutic areas, such as antidepressants, antipsychotics, and beta blockers". In this example, it is clear that what matters is to characterise patients with low levels of CYP2D6, they all metabolise these substances differently. And even if these low levels carriers are more frequent in "white" than in "Asian" or ""African", they still exist in all groups. They are just "more likely" to be found in some groups, but they prevail in all. When using the term of "race", the documents are leaving the field of science, entering in a controversial domain where

Stakeholder number *(To be completed by the Agency)*	General comment
	ideology and dogma prevail, i.e. “racism”. There is no scientific definition of human races; there is only one human race. Race is only defined in political or ideological terms. Anthropologists point out that genomic analysis has shown that racial distinctions are "not genetically discrete, are not reliably measured, and are not scientifically meaningful."[5] Most variations in human genes, in fact, pre-date the time of the migration of Homo sapiens sapiens out of Africa, leading genetic researchers to concluded that the "possibility that human history has been characterised by genetically relatively homogeneous groups ('races'), distinguished by major biological differences, is not consistent with genetic evidence."[6] On May 17, 1998 The American Anthropological Association produced a "Statement on 'Race'": *In the United States both scholars and the general public have been conditioned to viewing human races as natural and separate divisions within the human species based on visible physical differences. With the vast expansion of scientific knowledge in this century, however, it has become clear that human populations are not unambiguous, clearly demarcated, biologically distinct groups. Evidence from the analysis of genetics (e.g., DNA) indicates that most physical variation, about 94%, lies within so-called racial groups. Conventional geographic "racial" groupings differ from one another only in about 6% of their genes. This means that there is greater variation within "racial" groups than between them. In neighbouring populations there is much overlapping of genes and their phenotypic (physical) expressions. Throughout history whenever different groups have come into contact, they have interbred. The continued sharing of genetic materials has maintained all of humankind as a single species*[7]. Race as a surrogate correlating to geographic origins or to genetic differences can be a useful concept for race-based medicine[8], more properly referred to as pharmacogenomics; but even in such a form, the concept can be open to abuse[9]. Thus, EURORDIS proposes to erase any reference to race in this paper, as in any document produced by the European Medicines Agency. No phenotypic or genotypic differences can isolate subgroups of human beings, no such scientific definition of race exist, and therefore it is our opinion that the agency is deriving from the purely scientific domain when referring to this concept and should ban the use of this word in its work. Alternatively, Eurordis would like to ask the agency to explain: - What is the EMA definition of race, what is the definition of ethnicity - What are the racial groups the EMA would like to collect information about when evaluating a medicine - What are the ethnic groups the EMA would like to collect information about when evaluating a medicine - What use can be made of that information for regulatory purposes

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')*
435-439		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age and sex. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU of the proposed indication.
466-476		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: RMP module SIII "Clinical trial exposure" In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include: • age and gender; • indication; • dose.
562-566		Comment: See general comment on the use of "race" and "ethnicity' in the agency 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')*
		Proposed change: Delete paragraph
1706-1721		Comment: Measures may vary by Member States. Some variations may be important and may have consequences when for example patients are travelling (i.e. two and not just one contraceptive method requested to deliver product at pharmacy), therefore major variations across MS should be described. Proposed change: To promote public health, the Agency will make available (either on request or via its web portal): • any questionnaires included in RMPs for centrally authorised products which are used to collect 1714 information on specified adverse reactions; • details, which may include copies, of educational material or other additional risk minimisation activities required as a condition of the marketing authorisation; • details of disease or substance registries requested as part of the pharmacovigilance plan for centrally authorised products; • significant national variations to the recommended risk minimisation measures (significant for the patient).

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 17th, 2012

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

Comments from:

EVM

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

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
	EVM is in agreement with general comments of EFPIA
	The templates are not provided and will be required before industry can implement the new RMP requirements: • The EU-RMP template, and • The Summary of EU-RMP (Part VI) – to be made publicly available.
	Module XVI is referenced throughout the document, however, it was not available for the review.
	The objectives of the RMP are to reduce the risks and maximise the benefits: it seems that the process could be renamed: Benefit Risk Management Plan (BRMP).
	We would like to suggest having a separate module on post-authorization efficacy studies
	The RMP is global but should include regional specificities like epidemiology of the indication, risk minimization activities. However all countries whatever the region should have the same information even if there are country specific risk minimization activities. The modular approach should not result in regional 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')*
Line 131		Comment: "Post-authorization efficacy studies" should be called effectiveness studies (observational in nature), as efficacy applies to clinical trials. Proposed change: Replace word "efficacy" with "effectiveness"
Lines 208-210		Comment: It should be noted that the measure of benefits vs. risks at individual level for vaccines will not be achievable. Proposed change: The agency should propose a separate guidance on benefit-risk evaluation
Lines 235-238		Comment: Maybe vaccine specificities should be discussed in this section as the risk management for vaccines particularly under epidemic situation and government-sponsored vaccination campaign may be different from drug use in clinics. On that note, please note that the European Commission has issued a "Draft concept paper on risk management activities for vaccines used in special circumstances including pandemics" that is currently being discussed.
Line 253		Comment: There is a new concept in this module: the maximization of benefits. This will be challenging for vaccines as the immunization programs and recommendations are country specific: for example in Europe there are at least 3 different paediatric programs for immunization with different regimen. The MAHs have no influence on these decisions which are based on the vaccination policy.
Lines 265-266		Comment: The safety specification may require the relevant expertise in the disease and treatment; it is therefore suggested to add a disease expert in the list of health professionals involved in the safety specification.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Add the text in italic letters ..."pharmacoepidemiologists, ~~and~~ pharmacovigilance experts *and disease experts.*"
Lines 479-482		Comment: Immuno-compromised persons should be added to the list of special populations Proposed change: Add the text in italic letters "sub-populations with relevant genetic polymorphisms, *immuno-compromised)*"
Lines 581-583		Comment: In most instances, MAHs only have a total number of doses (of vaccine) sold in the country. Information on vaccine utilization by age, gender etc. is not available to the MAH unless a special study is done. Such data will only be available if a PPP is set up in order to share this info.
Lines 657		Comment: Please clarify what is meant by "Potential for misuse for illegal purposes"
Line 738		Comment: Only important risks (identified or potential) are addressed in the RMP. Besides, in order to be aligned with the text below, the title of this section should incorporate the word "important" Proposed change: Change the title into "Important identified and potential risks"
Line 881-885		Comment: Risks linked to the storage and distribution of vaccines are well known and part of the organization of vaccination campaign (like cold chain breaks): should it be part of the RMP? Proposed change: This is a GDP issue so not a pharmacovigilance issue. We propose removing this section.
Line 1016		Comment: In order to avoid any confusion, for post marketing "efficacy" studies, it would be better to name these studies as effectiveness studies. It's not clear if efficacy referred to pre or post-approval studies Proposed change: Make a distinction between efficacy and effectiveness studies

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 1037-1038		Comment: We do not agree that PASS is meant to measure the effectiveness of the risk management measure. There should be another mechanism in place to measure the effectiveness of the study. Proposed change: Delete this sentence

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

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

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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
	Can we have consistency with the use of the phrase benefit-risk? It switches between benefit-risk and risk-benefit.
	Can we use MAH or Companies or Pharmaceutical Companies, but not switch between these names in the document?
	Can we use Competent Authorities or Regulatory Authorities or Regulatory Agencies consistently

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 4 – line 136		Comment: In the section "risk minimisation will be tailored to regional specifics." What does the term "regional" refer to Proposed change (if any): Please clarify
Page 6 – line 183		Comment: Safety concern in defined on row 195 and could be included in the definition here Proposed change (if any): Important identified risk, important potential risk or important missing information (also known as safety concern against important identified risk, potential risk or important missing information)
Page 6 – line 211		Comment: Where this sentence mentions RMP it appears it should actually refer to system rather than plan Proposed change (if any): Although the primary aim and focus of the RMS remains that of risk 211 management,
Page 7 – lines 226-240		Comment: This section appears to refer only to prescription medicines – what about OTC medicines? Proposed change (if any): Include reference to OTC medicines
Page 8 – line 258		Comment: The two sentences have different tenses Proposed change (if any): ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 8 – line 270		Comment: the word risk before risk management plan is superfluous - this is not a known phrase Proposed change (if any): Since a risk management plan is primarily a pharmacovigilance document,
Page 8 – line 283		Comment: Change this bullet for consistency in the wording Proposed change (if any): ensuring the implementation of risk minimisation activities at a national level;
Page 8 – lies 287 - 289		Comment: the following wording is confusing and poorly written - ensuring marketing authorisation holders of generic and/or similar biological medicinal products 287 make similar changes when changes are made to the reference medicinal product risk minimisation 288 measures; Proposed change (if any): clarify the wording
Page 9 – line 302		Comment: not well written, can not identify the safety profile but it can be characterised, remove identify or Proposed change (if any): characterise the safety profile of the medicinal product(s) concerned;
Page 9 – line 303		Comment: change the order of the words further and characterise for clearer meaning Proposed change (if any): indicate how to further characterise the safety profile of the medicinal product(s) concerned;
Page 10 – line 334		Comment: would it make more sense to say plan rather than system? Proposed change (if any): The risk management plan shall be proportionate to the identified risks and 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')*
		potential risks of the
Page 14 – line 470		Comment: it may not be appropriate to use patient years or moths for short duration studies Proposed change (if any): patient time (patient-years, patient-months) exposed to the medicinal product, as appropriate.
Page 15 – lines 527 - 531		Comment: The following sentence is too long and difficult to understand - The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist so the cumulative effect of multiple impairments and multiple medications should be evaluated. Proposed change (if any): rewrite sentence or split it
Page 20 – line 727		Comment: is this the correct referenced section or should it be SVI? ***V.B.8.6.6. RMP module SV section "Projected post-authorisation use"*** Proposed change (if any): check it is the correct section
Page 21 – line 750		Comment: what does the most important refer to in the following sentence - This RMP section should provide more information on the most important identified and potential risks. 750 Proposed change (if any): clarify most important
Page 21 – whole section		Comment: do labelled events have to be included as identified risks or not – unclear from this section

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): clarify
Page 21 – paragraph starting line 777		Comment: what if there is no clinical data available? Proposed change (if any): provide clarity
Page 21 – paragraph starting 785		Comment: this section is geared towards Rx medicines, what about OTC medicines? Proposed change (if any): provide information about OTC medicines
Page 26 – line 961		Comment: For the section entitled - **Routine pharmacovigilance (safety) activities –** what should go in this section – would it be more appropriate to remove "routine" from the title? Proposed change (if any): please clarify
Page 27 – line 1017		Comment: The sentence - If, when reviewing a study protocol, a 1017 study is thought to be primarily promotional, the applicant/marketing authorisation holder will be 1018 required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP. – is unnecessary – it has already been stated that studies should not be promotional Proposed change (if any): delete this sentence
Page 27 – lines 1043 to 1076		Comment: These sections are in the PASS module, remove and just cross reference to that module Proposed change (if any): see above
Page 32		Comment: This whole section does not provide guidance - delete

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): see above
Page 38 – line 1415		Comment: Move full stop to after the bracket Proposed change (if any): medicinal product (and a much wider range of (suspected) adverse reactions).
Page 39 – line 1439		Comment: Is the dossier referred to here the submission dossier? Proposed change (if any): clarify

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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
	Issue: situations when a risk management plan should be submitted With the new GVP module V the situations when a risk management plan should be submitted are proposed to be restricted for existing marketing authorisations to 'innovative products' which was not the case with previous Vol 9a. However the term 'innovative' is not defined and this restriction is considered to prevent the submission or update of an RMP for situations when significant changes to the marketing authorisation are applied for. It is not considered that this is in line with the intention of the new legislation and the implementing measures and therefore this restriction should be lifted.

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 974-981		Comment on: Specific adverse reaction follow-up questionnaires Proposed change (if any): These questionnaires should not be considered as "routine pharmacovigilance activities" but as "additional pharmacovigilance (safety) activities" and therefore should be relocated to section V.B.9.2. Rational: As previously defined in the RMP guideline "routine pharmacovigilance" are *"activities as specified in Regulation 726/2004 and Directive 2001/83/EC, as amended, that should be conducted for all medicinal products."* Specific adverse reaction follow-up questionnaires are established to obtain additional structured and defined information on adverse reactions (safety concerns) which are not available via routine PV activities performed by all MAHs including routine follow-up of case reports.
Line 1549		Comment on: "when a risk management plan should be submitted" Proposed change (if any): With the new GVP module V the situations when a risk management plan should be submitted are proposed to be restricted for existing marketing authorisations to 'innovative products' which was not the case with previous Vol 9a. However the term 'innovative' is not defined and this restriction is considered to prevent the submission or update of an RMP for situations when significant changes to the marketing authorisation are applied for. It is not considered that this is in line with the intention of the new legislation and therefore this restriction should be lifted and the sentence in line 1549 reworded as follows also for semantic reasons. ~~Applications for innovative products where an~~ An RMP or RMP update will normally be expected ~~include~~:

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 18th 2012

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

Comments from:

Name of organisation or individual
French Association of Regional Pharmacovigilance Centres

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The RMP must ensure complete knowledge of profile adverse drug reaction profile and resolution of previous safety problems before the product looses its patent rights. (e.g the isotretinoin market is hold only by generics, the original (Ro)Accutane has disappeared from the market ; important safety issues are still present such as pregnancy exposure or psychiatrics disorders; the main difficulty is that MAH of generics may not have founds to conduct epidemiologic studies) The overall impression of this RMP GVP module is that RMP is let to the MAH's initiative, negotiations between MAH and the competent authorities may take a long time (e.g. voriconazole). No time frame is proposed in this document. The problem of lack of compliance is not addressed.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 318 -348		Comment: The proposed structure of the RMP is incomplete. A RMP must provide information about further planned product development such as new indication or new target population (e.g. rivaroxaban and dabigatran were planned to be used in auricular fibrillation from the very early start). What remains unknown must be listed, and actions to be conducted to acquire this knowledge, (e.g. now the marketing authorisation in auricular fibrillation is granted and product used in a population with a higher comorbidity rate, method of therapeutic drug monitoring are still to be developed, information about good interpretation of coagulation tests is lacking, because current RMP did not anticipate it) Proposed change (if any):
Lines 749-823		Comment: Pharmacological predictability of previously unobserved adverse drug reactions is very important to build efficient minimisation risk measures. (e.g. rimonobant a CB1 antagonist was potentially expected to induced cannabis withdrawal in cannabis smokers, to loose is CB1 selectivity in case of high dose utilisation with potential negative consequences on atherosclerosis or immunity because of CB2 antagonism, but the RMP did not mention it at all). An exhaustive review of the pharmacology of the product is expected in this section. All pharmacoepidemiologic or efficacy studies proposed in the RMP should include reporting forms with an exhaustive check-list of such potential pharmacologic risks. Proposed change (if any):
Lines 824-831		Comment : Potential pharmacokinetic drug interaction can only be anticipated if correct pharmacokinetic studies are conducted (e.g. isoforms of CYP, UGT, P-glycoprotein transporter, OATP transporter). Precise knowledge of pharmacokinetics is mandatory to build efficient RMP. Results of theses investigations should mandatory be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		mentioned in this section. All potential pharmacokinetic interactions should be listed. For each couple of drugs the probability of simultaneous exposure must be discussed. If probable, specific human pharmacokinetics studies must be included in the RMP and result should be known before the product is launched (e.g the mibefradil tragic experience should be considered as the worse paradigm that should never occur again)
Lines 1147-1148		Comment : The example of QT prolongation is misleading, and should be withdrawn of the GVP or completely rephrased, because educational material is highly needed even if the product is prescribed by cardiologists. Considering a high neuroleptic prescription risk by non cardiologist physicians, a general dear doctor letter is at least recommended Proposed change : To give another example
Lines 1151-1152		Comment: Risk minimisation measures are wider than what is listed: contraindication in special patient groups, packing inscription, suppression of the over the counter status … Proposed change (if any): A complete list should be given, rather than the communication means of such decisions.
Lines 1233-1269		Comment : Why educational material is considered as additional? Is there no other kind of measures to give as an example?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
154		Comment: It would be helpful to add the definition of an important risk to this section to avoid the implication that every ADR would be listed in the RMP.
191		Comment: It should be clear that an RMP is the description of the RM system **for a given product**.
223		Comment: What is meant by a learned society?
226		Comment: Please clarify if this is a cumulative list of risk minimization actions or an interval list of risk minimization actions during the period of the PSUR.
328		Comment: It is unclear what "locked" will mean in practice given data can be added at any time.
380		Comment: If the RMP is a lifecycle document, updated as required – why is it necessary to maintain details of modules – last updated and submitted – it seems an unnecessary burden.
484-488		Comment: Please consider that it is not currently possible to present post marketing sales data by age, sex, indication, dose, and formulation.
528-573		Comment: Please provide templates for all required cumulative and interval summary tabulations.
624		Comment: Please clarify off-label use – is it the intention to describe authorised use ex-EU as off label use as suggested here? If not 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')*
784		Comment: Please provide guidance on how to estimate relative risk and absolute risk as well as how to determine the precision of the estimates.
1152		Comment: Replace product literature with product labelling. Proposed change (if any): Locally authorised product labelling)
1241		Comment: Why needed/provided? Proposed change (if any): Delete "provided".
1283-1284		Comment: Please note that if listings of individual cases retrieved from the EudraVigilance database are created by the Agency and made available to the PRAC Rapporteur, there is the potential for discrepancies to arise against information included in the PSUR by the MAH.
1354-1355		Comment: Please note that if listings of individual cases, summary tabulations, and other relevant data are created and retrieved from the EudraVigilance database by the Agency and made available to the PRAC Rapporteur or Member State, there is the potential for discrepancies to arise against information included in the PSUR by the MAH. This could be an issue in audits.
1632-1634		Comment: How often is the MAH required to check the list of EU reference dates and frequency of submission published in the European medicines web-portal to ensure compliance with the PSUR reporting requirements? Please clarify the criteria for the submission criteria to be changed.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
H. Lundbeck A/S

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Will RMPs also be required for (very) mature products (e.g. + 20 years on the market)
	Guidance/Tools to describe the processes for how to evaluate benefits, subsequently asses benefit - risk evaluation need to be developed and implemented

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')*
175		Comment: Many newly developed drugs do not belong to an already existing drug class. The below-indicated text change takes into account that some evidence should be available for a particular drug before it is relevant to include a "similar-class event" as a potential risk Proposed change: an event known to be associated with other active substances within ~~the same~~ a similar class or which could be expected to occur based on the properties of the medicinal product, and where data raises a suspicion of, but is not large enough to suggest a causal relationship
178		Comment: the below-indicated text addition, provides examples of missing information Proposed change: Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace such as populations not studied (e.g. pregnant women) or circumstances not encountered (e.g. experience with overdose).
189		Comment: An RMP always refers to a particular drug Proposed change: Risk management plan: A detailed description of the risk management system for a particular medicinal product
266-267		Comment: The design of risk minimisation activities should involve communication experts. Is the involvement of communication experts a requirement – and who is to be considered/defined as communication experts (externals as well as internals)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
449 and 456		Comment: non-clinical findings potentially relevant for humans may be identified in/from several toxicology and nonclinical pharmacology studies. Since the relevance to humans of a particular non-clinical finding is not related to the type of study the issues was identified in, but rather to the organ system that it affected, the nonclinical findings should be presented by target organ system. Proposed change: line 449: This RMP module should present a summary of the important non-clinical safety findings (by target organ system), for example:…. Line 456: Normally significant areas of toxicity (by target organ systems), and the relevance of the findings to the use in humans, should be discussed.
463		Comment: The below-indicated text addition highlights where the safety concerns should be summarised. Proposed change: added text after line 463: Where the nonclinical safety finding could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.
580		Comment to: Line 580: "Where marketing of the medicinal product has occurred, the applicant/marketing authorisation holder should provide cumulative data on patients exposed post-marketing. *Where possible*, the information should be stratified by relevant variables. These may *include age, sex, indication, dose* and region (EU versus non EU)." And Line 496: "Competent authorities may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, marketing authorisation holders should consider routinely providing such data where possible." Although the text states "where possible", it also states that this stratification of exposure should be provided routinely. Data on patient characteristics and dose will only be available via prescription database or clinical studies. However, such studies should according to the guideline be described in section V.B.8.5.4. The guideline

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 provide examples as to what type of information concerning stratified exposure information is proposed to be added in this section of the RMP if not intended to be obtain from prescription databases and/or clinical studies
605		Comment to "Where post-authorisation use has occurred in the special populations identified in RMP module SIV as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label." Calculated estimations of the number of patients exposed off- or in-label will only be available via prescription database studies or non-interventional clinical studies. However, such studies should according to the guideline be described in section V.B.8.5.4. The guideline should provide examples as to what type of information concerning stratified exposure is proposed to be added in this section of the RMP if not intended to be obtain from prescription databases and/or clinical studies
647		Comment: proposed text addition to highlight where the safety concern should be mentioned. Proposed text: The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in module SVIII and….
748 and 851		Comment: This RMP section should provide more information on the most important identified and potential risks Will tools/description be available to define what should be considered most important Proposed change (if any): should "most" be deleted? The same is applicable for line 851 mentioning most important identified and potential risks for ATMPs

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
April 16th, 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	1. What are the transitory measures allowing putting in place this new template of RMP? 2. It should be specified if it would be one RMP by product or one RMP by indication for a product? 3. The Will the summary of RMP that the CA will publish on their portal be the part 6 of the RMP written by the MAH or a document written by the CA?

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Clarify what mechanism will be in place for MAH's to discuss any questions with the PRAC? Will there be a framework for providing advice?
	The term 'public health impact' appears throughout the document with no guidance in terms of scope and measurement. Please provide guidance in terms of scope and measurement.
	The "modular" structure of the RMP and PSUR documents is referred to throughout the guideline, including language describing the potential to "reuse" modules. Should the MAH take this literally, and should we expect CAs to have the authority to request updates to and/or submission of individual modules?
	The template should address some of the repetitiveness of the old template – e.g. describe the relevant epidemiology in RMP module SI, and provide cross-reference in subsequent sections rather than repeat it (potentially) for the individual risks in RMP module SVII – or vice versa.

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 98		Comment: The document mentions that the numbers of patients are small relative to the intended population of treatment. However, for some clinical programmes, thousands of patients may be treated. Proposed change: "This is due to many factors, including the relatively small numbers of subjects in clinical trials compared to the intended population of treatment…,"
Line 105		Comment: Typo: "affect on individual patients..." Proposed change: "~~affect~~ effect on individual patients..."
Lines 127, 1124		Comment: "efficacy of the medicinal product in everyday medical practice" Effectiveness is a more appropriate term for the context of everyday medical practice, and use of this term provides a useful distinction between what was observed in rigorous randomised clinical trials (efficacy) versus what may be expected in everyday medical practice (effectiveness), acknowledging that the two will typically not be the same. In *Dictionary of Epidemiology*, John M. Last (4th Edition, 2001), efficacy is defined as follows: "*Efficacy in clinical epidemiology is the extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions....ideally the determination of efficacy is based on the results of a randomized controlled trial...*"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 is distinguished from effectiveness: "*Effectiveness is a measure of the extent to which a specific intervention, procedure, regimen or service when deployed in the field in routine circumstances does what it is intended to do for a specific population; ...a measure of the extent to which a healthcare intervention fulfils its objectives, to be distinguished from efficacy and efficiency*..." Proposed change: "~~efficacy~~ effectiveness of the medicinal product in everyday medical practice"
Lines 137-138		Comment: "Therefore a product may have a different RMP for each region...". It appears that EMA is attempting to make it easier to reformat the document for submission outside the EU, but this should be clarified. If this is a proposal for regional EU RMPs (i.e. different RMPs for different parts of the EU), we strongly oppose this. Proposed change: Clarify that the regional differences are not intended to produce different RMPs for different parts of the EU.
Lines 139 – 142		Comment: There will need to be a reasonable transition period to enable industry to switch to the new template, i.e. to allow update of internal processes/templates and training. The transition period should start only after this GVP Module and the RMP templates are available (including the RMP Summary Part VI). Proposed change: Please provide clarification on when the new template will be available, and from when it will become 'effective', and specify a reasonable and practical period of transition that will allow companies time to develop and implement the new template that is compliant with the requirements.
Line 140		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')*
		Will CAs have the authority to request updates to, or submissions of, individual modules? How will this be handled in practice? Proposed change: Please clarify this.
Lines 143-144		Comment: The meaning of "this module" is not clear. The new EU RMP is itself modular, so this is confusing. Proposed change: "this GVP module"
Lines 170-171		Comment: Definition of potential risk – slightly divergent from Volume 9a and DSUR guidance: "an adverse reaction which was seen in non-clinical safety studies" in the GVP module vs. "non-clinical safety concerns" in Volume 9a and the DSUR guidance. Proposed change: To ensure alignment between documents, the rationale for the difference in definitions in ADRs and potential risks in the RMP should be clarified.
Lines 180–182		Comment: It would be helpful if some examples of missing information representing a limitation of the safety data could be included here. Are there any examples (e.g. pregnancy) that EMA would consider should be included automatically, unless there is evidence to the contrary? 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')*
		Clarify what is meant by missing information, and whether anything should be included routinely under "Missing information".
Lines 205-206		Comment: "The patients who might be treated by the medicinal product according to the indication(s) and contraindications in the authorised product information." This may be misunderstood as patients with contraindications are not part of the target population. Proposed change: "The patients who might be treated ~~by~~ with the medicinal product according to the indication(s) ~~and contraindications in the authorised product information~~, in whom the use of the product is not contraindicated. "
Line 222		Comment: "Other players may be involved in risk-benefit management..." Colloquial language. Proposed change: "Other ~~players~~ stakeholders may be involved in risk-benefit management..."
Line 242		Comment: "The principle organisations..." Wrong spelling. Proposed change: "The ~~principle~~ principal organisations..."
Lines 268-269 Lines 1243-1247		Comment: Further clarity is needed around the involvement of patients and healthcare professionals in the design of 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')*
		minimisation activities and summaries for the public. Specific details should be provided. Is EMA proposing something like 'user testing' or focus groups? Should this be via formal patient organisations? Presumably the healthcare professionals involved will be the ones who are likely to prescribe/administer the product. How much scope will the company have to incorporate such feedback, given that those external contributors will often not be trained in PV. Proposed change: Clarify the involvement of patients and HCP in the design of risk minimisation activities and summaries for the public.
Line 314		Comment: Editorial change – a document cannot plan Proposed change: '**outline** ~~plan~~ how the effectiveness of …'
Line 328		Comment: It is not clear what is meant by the term 'effectively locked' or what the benefit of this is when it is subsequently stated that the RMP will need to be updated when new data becomes available. Proposed change: Delete the relevant sentence, or clarify what is meant by this and what the benefits are.
Line 337		Comment: It is not clear what is meant by "products meeting certain conditions". Proposed change: Please clarify what is meant by "products 'meeting certain conditions" (e.g. refer again to V.C.3.1)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 342		Comment: If a company markets a combination product without marketing the individual components, is a separate part VI summary of the RMP still required? Proposed change: Please provide clarification.
Line 376		Comment: Mention is made here (and in several other places) that the RMP may span several products. Proposed change: Please define a medicinal product here – is it a brand name of the same active ingredient, or a combination product?
Lines 379-381		Comment: For practical reasons it is not possible to include the actual date of submission in the RMP. Documents may be finalised several days prior to submission. Proposed change: Suggest change actual date of submission in the RMP to reflect the date of RMP finalisation by the applicant/MAH.
Lines 400-401		Comment: There is potential for considerable duplication with the MA application form for pre-approval RMP submissions and PSURs for post-approval RMPs.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Remove this requirement.
Line 420		Comment: "Identified and potential risks" Proposed change: "Important ~~I~~identified and potential risks"
Lines 440-445		Comment: This particular example was difficult to follow – does it refer to MI as a risk for prostate cancer patients over 50 years or males over 50 years? The latter would be very broad. Furthermore, there is already a section on co-morbidities in section V.B.8.4. Proposed change: Amend the example to clarify this, and also explain how this would differ from the information discussed in section V.B.8.4.
Lines 450-465		Comment: The language in Volume 9a instructing to "present non-clinical safety findings that have not been adequately addressed by clinical data" has been removed, and the current section suggests that this module "should present a summary of the important non-clinical safety findings". Proposed change: Please clarify whether all non-clinical findings should be discussed, or only those not adequately addressed by clinical data.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 502-510		Comment: There should be clarification as to the type of inclusion/exclusion criteria that need to be considered here. Many such criteria are applied simply to facilitate recruitment or observe response of a particular population, and have no relevance to the safety of the product in clinical practice. Proposed change: Clarify that this relates to those criteria that have an impact on the safety of the product.
Line 516		Comment: Is there a threshold or example as to what may be considered long term? Proposed change: Please provide additional guidance.
Lines 573-574		Comment: The distinction between "Regulatory" and "Marketing Authorisation Holder" Action is not clear. Proposed change: "Action taken by Regulatory Agency and marketing authorisation holder ~~action~~ for safety reasons".
Lines 582-583		Comment: Editorial change for clarity Proposed change: '~~Where marketing of the medicinal product has occurred,~~ Post-approval, the applicant/marketing authorisation holder should provide cumulative data on the number of patients exposed to the product ~~post marketing~~.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		,
Lines 648-649		Comment: Add clarifying comment that the statement refers to products where there is an increased risk of overdose. Proposed change: "For these products, where ~~Where~~ harm from overdose…"
Lines 661-698 Section V.B.8.6.4. Potential for Medication Errors		Comment: It is not clear why there is reference to routine measures such as the naming convention or readability of the label and package leaflet in this section when these are enshrined in regulatory practice and are part of the regulatory approval process. Proposed change: This should be more objective. In keeping with RMP principle, it could be more clearly stated upfront that this section should focus on those products where there is most need, i.e. where a medication error has potential for most serious harm.
Lines 701-706		Comment: The scope of "issues identified in paediatric investigational plans" is not clear. Does this refer to regulatory issues, Safety issues, and/or open issues with the health authorities? Proposed change: Please provide clarification.
Lines 727-737		Comment: Incorrect positioning of a section.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: This should actually be V.B.8.5.6 and is in the wrong place.
Lines 738		Comment: "V.B.8.7. RMP module SVII "Identified and potential risks" Proposed change: V.B.8.7. RMP module SVII "Important ~~I~~identified and potential risks"
Line 740		Comment: "These include the identified and potential adverse events/reactions..." suggests inclusion of all/any identified and potential risks, even if not considered important. Proposed change: "These include the important identified and potential adverse events/reactions...
Line 743		Comment: It is not clear where RMP module SVIIa is discussed. Proposed change: Please include consistent cross-references throughout the GVP document.
Line 771		Comment: As with prior RMP guidance, the definition of public health impact is poor and open to interpretation. Proposed change: Public health impact should be clearly defined, particularly with respect to any requirement for quantitative measurements and the scope of any applied measures.
Line 772		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')*
		Impact on individual patient is a new criterion and appears to be based on patient reported outcomes and measure of quality of life. Proposed change: Given that this is a new criterion, further guidance in this area is needed.
Lines 777-793		Comment: The current RMP template does not include a section for presentation of postmarketing safety data. This absence leads to uncertainty about whether, when and how to present these data. Proposed change: Include a proposal for a format for presentation of postmarketing safety in the future RMP template.
Lines 778-784 (and Table V.1)		Comment: Does the reference to reporting rate and the commonality between RMP module SVII and Sub-section 16.4 of the newly proposed PSUR format suggest that RMPs should routinely include postmarketing safety information, whether or not this information has an impact on the risk assessment? Proposed change: Please include guidance on whether postmarketing safety information should routinely be included in RMP module SVII.
Lines 794-797		Comment: The instruction to include time to event data only appears to apply to important identified risks. Proposed change: Please confirm that this is not applicable to important potential risks.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 798-799		Comment: This has already have proposed in RMP module SI? Proposed change: Please remove this repetitive requirement
Line 840		Comment: Presumably this is meant to refer to RMP module VIIa. Proposed change: Amend to "RMP module ~~SVII~~ SVIIa"
Line 947		Comment: It is not clear what is meant by a "potential safety concern" the definition of a safety concern includes important potential risks. Proposed change: Please clarify the terminology.
Line 961-983		Comment: Is the title an accurate reflection of the information that follows on recommendations for specific activities requested by the PRAC? If the PRAC recommends additional activities, surely they are not routine. Proposed change: Consider changing the title to reflect the fact that this would not be routine pharmacovigilance, or move the proposal to another section of the GVP module.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 993-996		Comment: The newly presented example of conduct of a pharmacovigilance study to determine attribution of a potential risk when the potential risk has a significant background rate is highly problematic given the size of the studies required to sufficiently power this level of difference. Proposed change: Please clarify that these studies should be requested only under limited circumstances.
Line 997		Comment: The mechanism for consultation with a competent authority is not clear. Proposed change: Please clarify the mechanism for this consultation.
Line 1013-1014		Comment: This refers to all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders. Proposed change: Please clarify whether this also includes studies initiated, managed or financed by the MAH's marketing partners.
Line 1016-1017		Comment: Studies requested by other regulatory authorities to investigate a specific safety concern should also be included.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: It should be clarified whether the scope is restricted to regulatory authorities within the EEA, or whether it applies worldwide.
Line 1053-1067		Comment: Are additional details regarding the criteria that will be used by the CAs/PRAC to establish the need to work across companies to execute joint studies forthcoming in another GVP module? This would be difficult in practice due to sponsorship, confidentiality, budgeting. Proposed change: Removal is preferred, but if retained, please provide additional clarification, either in this module or as a reference to another relevant module.
Line 1092-1095		Comment: In the procedural announcements of the June and October 2011 CHMP meetings, it states that the practice of a Letter of Undertaking, in which all such measures (formerly follow up measures) were summarized, ceased to exist as of November 2011. Any new or changed post-authorisation measures will be classified either as Conditions in Annex II (Obligations to fulfil post-authorisation measures), as Additional Pharmacovigilance Activities in the RMP, or as Recommendations for further development, which will be reflected in a cumulative letter to be signed by the applicant. Proposed change: Please clarify whether V.B.9.4 replaces the Letter of Undertaking, or explain the impact that this would have on the Letter of Undertaking and tracking of follow up measures and commitments?
Line 1112		Comment: "Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		included in this part of the RMP." Proposed change: Please clarify the level of detail that is required here, and whether the inclusion of this information is limited only to certain defined situations (post-approval efficacy commitments) and therefore in most cases will not be applicable.
Lines 1116-1131 V.B.10.1 Presentation of efficacy data		Comment: The legislation specifies the following as the reasons for requesting post-approval efficacy studies: At authorisation: "where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed"; and Post-authorisation: "where the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised." It is not clear what criteria will be used to review this section compared to how this section will be reviewed in relation to the summary of clinical efficacy in the MAA, for example. It is concerning that this section may result in duplicative review of summary of efficacy data that has already been reviewed in the original MAA. Furthermore, that based on the data provided there is potential for requests for PAES to be broader in scope than that foreseen in the legislation. Proposed change: This section should outline the concerns (if any) relating to lack of efficacy data rather than be a summary of efficacy data already reviewed and approved for the product during MAA review.
Lines 1141-1143		Comment: This part of the guideline states that it may be required to have a risk minimisation plan specific to individual products containing the same active substance but substantially different indications or target populations.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Please clarify whether this will be requested by the Agency on a product-by-product basis, or whether appropriate criteria or a decision tree will be published.
Lines 1256-1258		Comment: This implies one core version of the educational material in different local languages. The local advertising requirements vary between country to country and in practice it would be difficult to get a common core text. What is the scope of a pilot, for how long does it continue, and how is it evaluated? It would be appear to be more advantageous to do something everywhere and revise it later than to do nothing in most areas pending the outcome of the pilot? Proposed change: Recommend developing the materials in consultation with HCPs/patients and then implementing them, rather than doing nothing in those areas in which there is no pilot.
Line 1336		Comment: "language appropriate to the target population" is unclear Proposed change: Please clarify this statement.
Line 1373		Comment: Summary of changes to RMP in chronological order. Proposed change: For existing RMPs, it should be clarified that these changes should start from the date the GVP module comes

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		into effect.
Line 1393		Comment: Will there be a standard format and timing for study synopses to be included in Annex 8? Is the information included in this section intended to be cumulative over the lifecycle of the product? Proposed change: Please provide additional guidance.
Lines 1395-1399		Comment: Websites becoming more frequently used for this. Proposed change: Please clarify how websites should be presented here.
Lines 1426-1432		Comment: The common modules between the RMP and PSUR have different titles. Proposed change: The common modules should have common titles so that if PSURs and RMPs are submitted together in eCTD format, linking between the two documents for identical modules can occur and duplication of wording is avoided. Please provide more guidance on the maintenance of modular aspects of the RMP.
Lines 1499-1507		Comment: This section mandates tracking, including submission dates to EU CAs, and significant changes between RMP versions.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 clarify that this is intended prospectively from the implementation of the GVP module
Line 1556		Comment: The meaning of new manufacturing process of a biotechnology derived product is not explained. Proposed change: Please clarify the term "new manufacturing process"
Line 1710		Comment: Will these be verbatim RMP summaries? Proposed change: Please provide clarity on whether the MAH will have sight of the summaries, and the opportunity to review and comment, before publication, and what this process will involve.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19.04.2012

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

Comments from:

Name of organisation or individual
la Roche

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
	Roche supports the comments EFPIA has sent in. The modules are in general well written but would benefit from consistency checks across in terms of definitions and requirements for the quality system. In particular Module I describes that, in each module, particular quality aspects will be discussed, and as this is clearly the case in a number of modules, it is less obvious in other modules. A few additional comments are provided here as well as in the questions for clarification that were raised while reviewing the draft modules. General comment: consistent terminology should be used (and defined): risk mitigation vs risk minimisation vs prevention Would the agency be able to provide more clarity on the transitional measures: older, well established products suddenly requiring an RMP: should this a fully worked-out RMP or can it remain focused on the safety hazard requiring the Risk management activities?

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')*
179		Question: Missing information is not always a simple definition to apply, therefore suggest giving examples of common types of missing information.
279		Question: Does 'other sources of information' include 'literature monitoring'?
287		Question: Clarify the timelines by when changes to the reference medicinal product risk minimisation measures must be included for the generic/similar biological medicinal products (e.g. 3-6 months following approval)
290		Question: Specify what 'other regulatory authorities' are in scope (e.g. those with a confidentiality agreement in place?)
Line 304-305		Comment: It is assumed that the need to 'document post-authorisation obligations' only relates to RM activities, rather than to all post-authorisation obligations. Proposed change (if any): Clarify in the text the scope of the post-authorisation obligations to be included.
340		Question: Clarify the header where 'missing information' should be included.
1547		Question: Clarify what period of time 'pre-' refers to?
Line 831:		Important risks believed to be common to the pharmacological class should be discussed here. Recommended change: **also include similar MoA (e.g., ACEi and ARB are different clases but share a similar final efefct on the RAS leading to angioedema).**
Lines 752-760		**It would be useful to have a more detailed definition of important risks, at least some key criteria (e.g., Incidence (affecting a large proportion of pts), Severity, Long duration, Fatal outcome, Disability (social and health care cost implications), Require treatment and/or additional monitoring (social and health care cost implications), Preventable and/or manageable, Permanent or reversible, Vulnerable subgroups?, New**

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Medical Products Agency, Sweden

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We have an overarching question in relation additional pharmacovigilance measures (i.e. Post Authorisation Safety Studies) and what could be considered as part of the 'conditions' in Annex II of the Module. For additional risk minimisation measures (e.g. educational material), it is clearly specified that they should be included as 'conditions' in Annex II:*"Additional risk minimisation activities will become, once agreed by the European Commission, conditions of the marketing authorisation and detailed in annex II and annex 127a of the CHMP Opinion as appropriate*" (line 1251). On the other hand, when it concerns additional pharmacovigilance measures, it is suggested that the MAH include all planned safety studies in the pharmacovigilance plan. We find that it is paramount to clearly identify and separate which studies are initiated by the MAH on its own and which studies are initiated as a result of conditions imposed by the competent authorities.

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 1011-1016		Comment: From our general comments, the following modifications are proposed: *The MAH should in the RMP include all studies designated to address the safety concern; safety studies pursuant to obligations imposed by a competent authority as well as safety studies initiated by MAH.* ***To improve clarity, the studies which are imposed by CAs as conditions (annex II) need to be clearly identified.*** Proposed change (if any): ***Adding on line 1016: To improve clarity, the studies which are imposed by CAs as conditions (annex II) need to be clearly identified****.*
Line 1454 -1465		Comment: *The comment and additional text above should also be mentioned as a principle point to be considered when preparing or reviewing a RMP, i.e. in V.B.15 (Principles for assessment of RMP), e.g. between 1460 and 1461.* Proposed change (if any): ***Are the safety studies which have been imposed by CAs as conditions (Post Authorisation Safety Studies) clearly identified?***
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 April 2012

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

Comments from:

Name of organisation or individual
Medicines Evaluation Board, the Netherlands - Pharmacovigilance department

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Throughout the GVP, the terms "Risk Management Plan" and "Benefit-Risk Management Plan" are used inconsistently.
	Within the GPV, cross-references to modules are incorrect. For example line 619, line 630, line 704.
	Reference is frequently made to "identified and potential risks". As only important identified and potentials risks should be addressed in the RMP, we suggest adding the word "important" throughout the GVP (for example line 738 and 744).
	It is very confusing that "risk minimisation activities" and "risk minimisation measures" are used synonymously throughout the GVP, especially because this is only explained in lines 1299-1300. We suggest explaining this already earlier in the GVP (e.g. in section V.B.1).
	In addition the references to the directive it would be very useful to refer to the implementing measures as well.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 287-289		Comment: Not in all cases it is warranted that all MAH's of generic medicinal products adapt their risk minimisation activities. For example in case it may decided that only the MAH of the innovator product provides educational material for HCPs. Proposed change (if any): "When considered necessary" should be added to this paragraph.
Lines 295-296		Comment: It is not necessary to state in the GVP exactly what type of expertise is considered necessary in the assessment team of the RMP. It is the responsibility of the national competent authorities to compose a team with sufficient knowledge to provide an adequate assessment report. Proposed change (if any): Delete the sentence "The different parts of the RMP need different areas of expertise so ideally assessment of risk management plans should be performed by a multi-disciplinary team."
Line 301-317		Comment: It is unclear why the enumeration of the objectives of a RMP, which starts at line 301, contains a section of so-called "implicit requirements". We feel that these "implicit requirements" are an important part of the RMP (e.g. plan of measuring effectiveness of the RMP, line 314) should not be referred to as "implicit requirements". Proposed change (if any): Delete line 308. Merge line 309-310 with line 302.
Lines 624-628 and 732-737		Comment: Off-label use (potential and actual) is now addressed in two separate sections (V.B.8.5.4 and V.B.8.6.6). It is more logical to have all information regarding off-label use together in one section.

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		Proposed change (if any): Merge the information on off-label use into one section.
Lines 692-694		Comment: It is not necessary to include "medication error" as a safety concern with any change in formulation or strength of a medicinal product, or to discuss risk minimisation activities to prevent confusion between the old and new strength. Proposed change (if any): Change the sentence into "if the strength or formulation of a product is being changed the MAH should discuss whether medication error should be included as a safety concern in the RMP and if specific risk minimisation activities are warranted to prevent confusion between the old and new "product"."
Lines 707-711		Comment: In case this section refers to PIPs, it is not necessary to request a justification of the necessity of long-term safety studies in paediatrics. It is sufficient to make reference to the PIP. Proposed change (if any):
Lines 755-758		Comment: It is not necessary to add all risks that are mentioned in the SmPC to this section. It is preferred to request the MAH to discuss whether the risks that are included in the SmPC should be considered <u>important</u> (identified or potential) risks that may affect the benefit-risk balance of the product. Only if that is true, these risks should be discussed in this section. This will help to prevent the RMP being an simple enumeration of the risks that are listed in the SmPC rather than an overview of important risks that may affect the risk-benefit balance and which need a thorough assessment. Proposed change (if any): Delete sentences 755-758 "Normally, any risk which…pharmacological class effects should also be included".
Line 950-952 and lines 996-997		Comment: Here is stated that early discussions between competent authorities and applicants are recommended to identify whether and which additional pharmacovigilance activities are necessary. Please provide more guidance on how these early discussions are expected to be organised, e.g. should this be part

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		of the pre-submission meeting (which may be to early as the details of the dossier are not under assessment), or at Day 80 of the application procedure? Or will there be an additional point in time where this should be discussed?
Line 961 and 984		Comment: Not necessary to add "(safety)" to the heading of this section, as it refers to pharmacovigilance activities Proposed change (if any): Delete "(safety)" in the headings
Lines 1039-1041		Comment: Section on studies to evaluate the effectiveness of risk minimisation activities (RMAs) is very brief, while this is becoming an important tool to improve the quality of the RMAs. This is also not addressed in other sections of the GVP.
Line 1085		Comment: It is stated that routine pharmacovigilance is "nearly" always necessary. We consider routine pharmacovigilance always necessary and additional pharmacovigilance on a case-by-case basis. Proposed change (if any): Delete "nearly" in line 1085.
Lines 1178-1232		Comment: The section on "legal status" consists of almost 1.5 pages, which is unnecessary long and detailed. The decision on the legal status is not primarily made in the RMP and therefore this section can be much more concise and to-the point. For example, the section on additional risk minimisation activities, which are a very important part of the RMP, is only about one page. The length of the section on legal status in unbalance compared to other sections of the RMP. Proposed change (if any): Shorten the section on legal status and make it comparable in length to the section on "pack size".
Lines 1233-1269		Comment: In this section, only educational material is described as possible risk minimisation activity, while there are many more options. It would be very useful to provide an overview of the possible additional RMAs,

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 to focus on educational material only.
Lines 1248-1254		Comment: This paragraph addresses the responsibility of the CHMP in determining risk minimisation activities, while the PRAC is not mentioned here. Proposed change (if any): Add information on the role of the PRAC regarding the determination of risk miminisation activities.
Lines 1251-1252		Comment: We suggest to include in annex II and annex 127a only key elements of the RMAs.
Lines 1243-1247 and 1256-1258		Comment: It states that it is recommended to consult experts and competent authorities (CAs) during the development phase of RMAs, and to pilot educational material. We consider this very useful, but it is unclear how this type of early consultation with CAs should be performed. In addition, it is unclear whether the results of the consultation with experts and the piloting should be submitted to the authorities and if these are subject to formal assessment.
Line 1271-1272		Comment: For all safety concerns, routine risk minimisation is required. Therefore "none proposed" will never be entered against the objective. Proposed change (if any): Delete the sentence "If no risk minimisation activity is proposed then "none proposed" should be entered against the objective."
Line 1285-1294		Comment: the aim of this section is unclear. This section seems to refer to the results of the studies measuring the effectiveness of RMAs, but this is also being addressed in the next section. Proposed change (if any): Merge this section with the next and be clearer on the aim of the section.
Lines 1297-1300		Comment: This reads as an introductory paragraph to risk minimisation activities in general.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Consider to relocate this these sentences to section V.B.11, which provides a general description on risk minimisation measures.
Lines 1295-1309		Comment: Section V.B.11.5 refers to studies that evaluate the effectiveness of RMAs. According to section V.B.9.2 (lines 1010-1011) this type of studies should be part of the Pharmacovigilance plan. Proposed change (if any): Please consider to relocate this section V.B.11.5 to section V.B.9.2.
Lines 1295-1309		Comment: More guidance is needed regarding the development of the objectives for the studies measuring the effectiveness of RMAs.
Lines 1332-1372		Comment: Line 1342 clearly states that this information should be provided by the MAH in lay language. According to section V.C.8, all information to which reference is made in lines 1332-1372, should be in lay language, as this will be made publically available in PARs.
Lines 1382-1400		Comment: In case a single study addresses both safety and efficacy endpoints, cross-reference should be made in the annexes of the RMP. There is no need to include the same study protocol twice (both in annex 5 and annex 7).
Line 1460 and line 1480		Comment: Not necessary to specifically address medication errors here. Only in those cases that the risk of medication errors is considered a safety concern, this should be included in the pharmacovigilance plan. Proposed change (if any): Delete line 1460
Lines 1563-1564		Comment: the example given for the absence of a mandatory legal requirement for the submission of an RMP "(e.g. significant change to a marketing authorisation)" is very confusing, since this is contradictory to line 1553, where is stated that an RMP or RMP update is expected include with an application involving a significant change to an existing marketing authorisation

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 1609 Table V.2		Comment 1: RMP module SI includes "Epidemiology of the indications and target population" and should only be required for New active substances. The requirement to submit Module SI should be deleted for the other types of new application Comment 2: The 'modified requirement' for 'same active substance' should be better specified. Comment 3: Module SIV (Populations not studied in clinical trials) can not be mandatory for hybrid medicinal products and fixed combination products, because Module SIII (Clinical trial exposure) may be omitted. If the MAH does not have clinical trial exposure, there is no need to provide information on 'Populations not studied in clinical trials'
Lines 1642-1643		Comment: it is unclear what the need is of including the time schedule of routine RMP updated as a condition of marketing authorisation. This will create many unnecessary updates where no relevant changes to the RMP are made, thereby creating a lot of work for both MAHs and NCAs. Proposed change (if any): Delete lines 1642-1643 ("The time schedule for providing "routine" updates to the RMP will be included as a condition of the marketing authorisation.") and restructure the text (lines 1642-1651) as follows: *"Unless specified otherwise, when both PSURs and RMPs are required for a product, routine updates to the RMP should be submitted at the same time as the PSUR.* *These are the maximum times between updates and do not remove the responsibility of the marketing authorisation holder to monitor the safety profile of the products nor the requirement for an updated RMP 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')*
		be submitted if there is a significant change to the benefit-risk profile of one or more medicinal products included in the RMP. *If there has been no change to the RMP since the previous submission (i.e. if a "routine" update is due shortly after the end of a procedure), the marketing authorisation holder may submit a letter explaining that there is no change and not submit an RMP update."*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
Medicines and Healthcare Products Regulatory Agency (Inspection, Enforcement & Standards Division)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The citation of the different parts of the RMP is not clear. In order to make it clearer ,when citing modules of Part II, it should state " Part II, Module SI, Part II module SII, etc as it will also help to differentiate them from the GVP Modules (which are cited as Module I, Module II, etc)	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
100		Comment: Follow-up sometimes appears with an hyphen in this GVP and sometimes without. There should be consistency.	
114		Proposed change (if any): Planning of pharmacovigilance activities to characterise known risks and identify new potential risks and increase the knowledge in general about the safety profile of the medicinal product.	
118-121		Comment: This reflects the history of the document. It might not be relevant to include this in a document intended as practical guidance Proposed change (if any): ~~The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit.~~ Delete text	
95-99 and 121-124		Comment: These paragraphs reiterate the same idea Proposed change (if any): Delete paragraph 95-99 ~~It is recognised that at the time of authorisation, information~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~on the safety of a medicinal product is relatively limited. This is due to many factors including the small numbers of subjects in clinical trials, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.~~	
163		Comment: "such as anaphylactic reactions or application site reactions" The examples suggest only infusion or application relations may show strong causal relationship in a spontaneous setting Proposed change (if any): Delete text or add another type or drug related reaction (e.g drug induced hepatitis or other)	
164		Comment: In a clinical trial, the comparator may be placebo, active substance or non exposure. – Related to paragraph 158-160 Proposed change (if any): Move to the paragraph it relates to	
176		Suggest adding, "which requires further monitoring, investigation and evaluation".	
232		Comment: "the majority of medicinal products will be	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		prescribed by doctors and dispensed by pharmacists so that" This might not be the situation in all Member states Proposed change (if any): Delete text For patients, ~~the majority of medicinal products will be prescribed by doctors and dispensed by pharmacists so that~~ management of benefits and risks will primarily involve complying with treatment schedules and recommendations….	
254		Suggest the word "promptly" should be included, because delays in communication can be an issue and have been observed.	
257-260		Comment: incomplete section cited Proposed change (if any): Details of how the safety specification and pharmacovigilance plan are integrated within the RMP and the detailed structure and format are provided in V.B.5	
266		Comment: There might be other activities that are not specifically studies Proposed change (if any): The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of ~~study~~ activities planned to address them.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
283		Comment: Proposed change (if any): Grammatical error - "ensure" should read "ensuring".	
317-319		Comment: This is confusing. Seems to indicate there are more parts divided in modules Proposed change (if any): ~~Certain parts of the RMP, in particular~~ the safety specification is ~~are~~ subdivided into modules [IM Annex II.2] so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs).	
333-336		Comment: "Uncertainties" might be misleading Proposed change (if any): (…) and risk minimisation activities reflect the risks and ~~uncertainties~~ missing information about the 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')*	Outcome *(To be completed by the Agency)*
338		Comment: Part VII should contain an outline of the Annexes as they are referred frequently Proposed change (if any):	
376		Comment: Data lock point for RMPs should be defined Proposed change (if any):	
408		There should be consistency across the GVPs and within the GVP for the term used i.e. "risk-benefit" or "benefit-risk".	
420		Comment: The concept "Limitations of the human safety database" it is not described in this guideline Proposed change (if any):	
654		Comment: RMP module SVa - it is unclear which module this is as it has not been mentioned before Proposed change (if any):	
676-678		Comment: Is this relevant for all products? Proposed change (if any): When relevant, ~~In addition,~~ if there are other products containing the same active substance on the market with formulations which are not proven to be	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.	
683		And appropriate risk minimisation should be proposed to address the possibility of medication error due to visual impairment.	
699		Comment: "Paediatric investigation plan". This concept needs to be clarified Proposed change (if any)	
724		Comment: Module SV section "Indicated versus actual use" V.B.8.5.4 should also be cross referenced Proposed change (if any):	
843-844		Comment: This paragraph should be move under the heading V.B.8.8.2 Proposed change (if any):	
857-863		Duplicate text which has been included earlier in the document. Is this necessary?	
1003-1006		Comment: What is this paragraph trying to achieve in the guideline?	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
1014		Comment: When referring to "other regulatory authorities" it needs to be clarified if it means WORLWIDE authorities Proposed change (if any):	
1176		Comment: It is not clear if this section of part V (Legal status) will require national approval. Perhaps this will be covered in section V.C.6 once it is completed? Proposed change (if any):	
1441		The use of contractions (haven't) is not recommended for official guidance.	
1393-1397		Comment: If material the provided to HCPs and patients is different (due to the fact that it requires national approval) which copy should be provided in RMP Annex 10? Proposed change (if any):	
1502		This is not a legal obligation for the QPPV (in the new legislation). However, the QPPV should have an awareness of RMPs and the processes used to produce RMPs, in order to ensure that an appropriate and compliant system is in place to meet regulatory obligations. Including this as a specific QPPV obligation may be impracticable, because under the new legislation many more RMPs will be required (including for generic products). The QPPV should not be spending all of their time reviewing and authorising RMPs and RMP updates. Instead, the MAH's responsibility for ensuring adequate QC in order to provide assurance of quality, accuracy and scientific	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		integrity should be emphasised.	
1546		Comment: Article 8(3)(iaa) – the referred piece of legislation needs to be mentioned Proposed change (if any):	
1579		What happens if the authorisation for the reference medicinal product has been cancelled?	
1606		Comment: Table footnote 2 does not have a corresponding reference in the table Proposed change (if any):	
1656-1662		Comment: "If several updates to the RMP are submitted during the course of a procedure, the version considered as the "current" RMP for future updates and track changes purposes, shall be the last one submitted before the Opinion. For example, in the final weeks before the Opinion, the RMP may be updated several times to reflect ongoing CHMP discussions, e.g. changed indications, changes in SmPC wording which affect risk minimisation. The last version submitted before the Opinion, shall be considered the "current version" whether or not a formal assessment report of the RMP is provided to the applicant/marketing authorisation holder." This could potentially be misused by companies Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
National Authority of Medicines and Health Products INFARMED, I.P. Portugal

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
126-127		Comment: Proposed change (if any): replace "true efficacy" for "effectiveness"
143		Comment: remove the coma Proposed change (if any): in "Risk management, is applicable"
199		Comment: Proposed change (if any): Propose to replace by "differs significantly"
235		Proposed change (if any): add " … doctors, administered by nurses and dispensed…"
237		Proposed change (if any): add “nurse” in the sentence “reporting to their doctor, nurse, pharmacist”
237		Proposed change (if any): replace "and" for "or" in the sentence pharmacist, and national"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
242		Proposed change (if any): replace "principle" for "main"
352		Proposed change (if any): add the sentence "The exclusion of a specific part or module must be justified." after "but are not mentioned."
569		Proposed change (if any): add the following text "labelled and off-label use and" after "has been used in practice, including"
635		Proposed change (if any): add the text "should be given" after "Information"
638		Proposed change (if any): add the text "The synopsis of the study programme should be included in annex 4 and" in the sentence begining with "If the study"
1124		Proposed change (if any): replace "efficacy" for "effectiveness"
1219		Proposed change (if any): typo: replace "he meaning" for "the meaning"
1572		Proposed change (if any): add "(see Table V.2)" after "otherwise requested by the competent authority"
1705		Proposed change (if any): the meaning of "source of the product" is not clear and should be rephrased

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module V – Risk management systems) is very comprehensive and provides detailed and helpful guidance on risk management systems, concentrating on peri- and post-authorisation in the context of benefit, as applicable to EU medicinal products for human use. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.

2. Specific comments on text

311-313		**Comment**: There are no internationally-accepted, evidence-based rules that would allow MAHs to accurately and consistently "*...indicate the level of certainty that efficacy shown in clinical trial populations will be seen in everyday medical practice.*" Thus, this remains a philosophical exercise to be avoided. **Proposed change**: Delete this phrase: "~~*indicate the level of certainty that efficacy shown in clinical trial populations will be seen in everyday medical practice and document*~~ ***assesss*** *the need for studies on efficacy in the post-authorisation phase;"*
624-625		**Comment**: The scope of the following is unclear: "*Off-label use includes, amongst others, use in non-authorised paediatric age categories, and use in other (non EU-authorised) indications outside of the clinical trial setting*." Certain paediatric age categories are mandatory in certain jurisdictions outside the EEA, e.g., Japan, and these categories are sometimes impossible to correlate with EU paediatric age categories. **Proposed change**: Revise to read: "*Off-label use, includes, amongst others, use in non-authorised paediatric age categories (****when this can be determined****), and use in other (non EU-authorised) indications outside of the clinical trial setting*."
1432 (Table V.1 4th block)		**Comment**: It would be desirable for the RMP to be aligned with the Data Lock Point of the PSUR. **Proposed change**: Revise 4th block in Table V.1 to read: "*Part II, module SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval****; it is anticipated that timing of the RMP module will be aligned with that of the PSUR****.)"* Also, see comment and proposed change for Line 1631.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Pharmaceutical Information and Pharmacovigilance Association (PIPA)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	For many generic MAH the requirement even for an abbreviated RMP will be significant additional workload and the importance of being consistent with the innovator RMP, and even having a common approach etc. to targeted safety questionnaires will need to be facilitated by the EMA.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 9, 2012

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

Comments from:

Name of organisation or individual
Pharmiceutics LLC

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Pharmiceutics LLC is an established consulting firm specialized in biopharmaceutical Core, EU and US labelling, with particular expertise in all aspects of safety labelling and safety evaluation for labelling. Pharmiceutics LLC has numerous clients in all ICH regions. It provides labelling services, management consulting on global labelling processes, and conducts public and in-house seminars on topics like global labelling governance by means of Company Core Data Sheets. Principle consultant is Dr. med. Leander Fontaine. The company is located in Pennsylvania, USA.

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')*
573 - 578		Comment: We believe this request is excessive. While not as such a new element of the EU RMP, the interpretation presented here appears to request that reporting of regulatory actions includes reporting of all actions that were initiated by the MAH as the result of, for example, adding a statement to the Warnings and Precautions section of a CCDS. The number of markets for which labelling updates have to be initiated is very large (close to 200, if we equate markets with countries), often with interdependencies between markets that require staggered roll out in complex patterns. MAH-internal governance systems for such a roll out do not necessarily make use of formal implementation tracking systems, which would provide MAH headquarters with ready-to-access data as they might be expected by the agency; governance systems may use other mechanisms (often not centralized) to ensure complete and appropriately expeditious roll out. We suggest that the EU limit the set of information it wants to be reported, and the resulting administrative reporting burden, to what is necessary in the interest of patient safety in the EU, and therefore legitimate. This will likely NOT include, for example, information on the roll out of labelling content that, by the time of submission of an (updated) RMP is already present in EU labelling or has already been submitted for labelling updates. In addition, the concept "regulatory action" is not sufficiently defined. Would it be expected that both - regulatory submission of labelling changes, - significant modifications to submitted content arising during discussion with local agencies, and - the final regulatory approval of a labelling change be reported? We suggest that the only reportable items are regulatory submissions and outcomes that are substantially different from what has been submitted or approved in the EU.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Furthermore, such differences in locally submitted labelling content or outcome should only be considered reportable if they reflect a substantially different understanding of the adverse effect and/or can be reasonably believed to cause substantially different patient selection, precautionary measures or interventions when compared with labelling information for the EU. Proposed change (if any): See above.
1117 - 1120		Comment: This text does NOT express an expectation that a "summary of the efficacy of the product and what studies and endpoints it was based upon" or equivalent information is also found in a MAH's CCDS. The expectation that such information is found in a CCDS is expressed in draft ICH E2C(R2) (Section 3.17.1), and is implied or expressed in draft Module VII, lines 252 - 253, 824 - 825, and 829 - 830. In our comments to these lines of Module VII, we explain that the assumption that such information, or even only a complete list of locally approved indications and uses, is routinely found in CCDSs is not correct. Proposed change (if any): -

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

Submission of comments on 'GVP Module V – Risk management systems' (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, would like to thank for the opportunity to comment on GVP Module V – Risk management systems.
	In general we want to point out that the overall timeframe of the consultation was very short for an in-depth analysis and commenting on this comprehensive guidance documentation.
	Two templates are not yet provided and will be required before MAHs can implement the new RMP structure: • EU-RMP template, • Summary of EU-RMP (Part VI) – to be made publicly available.
	The request that some sections should be written in "lay language" should not be interpreted as requiring systematic testing similar as that performed for Patient Information Leaflets. Further, some points mentioned in the summaries to be presented in lay language are already covered by contraindications, precautions and warnings in the Patient leaflet. Therefore, it should be possible to provide reference to the relevant sections of the patient leaflet.
	Transitional measures: In order to move to the future RMP format, including switching from the previous format to the new one for products with an existing EU-RMP, companies will need to make extensive changes in existing processes for RMPs and PSUR development. Therefore, even given the commonalities with the new PSUR format through the modular approach, it should be clearly stated that all new RMP or RMP updates to be submitted with the next renewal if the EU RMP template has come into force for longer than 6 months or until July 2015.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
122		Comment: the risk-benefit balance Proposed change (if any): the benefit-risk balance, please use this term throughout the whole document
390		Comment: Indications may vary by country/regions. Proposed change (if any): specify "indications in the EEA"
393		Comment: Dosages may vary by country/regions. Proposed change (if any): specify "Dosage in the EEA"
400 - 401		Comment: The worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments, could become a very long table Proposed change (if any): This table should be moved to an Annex
498 – 500		Comment: "When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables" Be more specific in how the data should be presented

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables representing total pooled data across all indications"
583 - 587		Comment: "These may include age, sex…" Please give examples how these data could be generated. Proposed change (if any):
612 - 613		Comment: "In particular, any information regarding an increased or decreased benefit in a special population should be provided." Be more specific in how the data should be presented Proposed change (if any): "In particular, any information regarding an increased or decreased benefit in a special population should be provided as a tabulation of adverse drug reactions per each special population sub-group.
624 – 628		Comment: Please give examples how these data could be generated Proposed change (if any):
648 - 651		Comment: "Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern and appropriate risk minimisation proposed in RMP part V " Be more specific which data should be presented herein.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Only if harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, harm from overdose should be included as a safety concern and appropriate risk minimisation proposed in RMP part V
750		Comment: Undefined terminus Proposed change (if any): "This RMP section should provide more information on the ~~most~~ important identified and potential risks."
769		Comment: "When the information is available, detailed risk data should include the following: " More clear guidance on how the data should be provided should be given Proposed change (if any): "When the information is available, detailed risk data per authorized indication should include the following: "
838 - 839		Comment: Be consistent in termini "..concern with the medicinal product, and hence is not included as an identified or potential risk, the evidence supporting this should be provided. Proposed change (if any): "..concern with the medicinal product, and hence is not included as an important identified or important potential risk, the evidence supporting this should be provided.
925 - 926		Comment: It should be more specific in presentation "At the end of the safety specification a summary should be provided of the safety concerns. A safety concern may be an:.."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): "At the end of the safety specification a summary table should be provided of the safety concerns. A safety concern may be an:.."
1043		Comment: Drug utilisation studies Please define this term. Does this include non-interventional studies? Proposed change (if any):
1117 - 1120		Comment: A brief summary of at maximum one page to present efficacy data would be a challenge for complex medicinal products. Further, this would require an additional document with unnecessary burden for MAHs. Indeed, the proposed content is similar to the already by MAHs prepared Clinical Summary Overview. Therefore, the use of the clinical overview summary should be an option and would result in better quality. Proposed change (if any): "As explanation for any efficacy studies proposed and to provide background that can be used in the RMP summary, there should be a summary of the efficacy of the product and what studies and endpoints it was based upon. The robustness of the endpoints on which the efficacy evaluation is based should be briefly discussed. This should be brief (one page maximum). Alternatively, the clinical overview summary in the content as required for renewals can be used.
1265 - 1268		Comment: Due to copyright and intellectual property reasons this would be not feasible in real world situation. Further, the cost-intensive printing, distribution, exchange due to Variations, maintenance and retirement of the Educational Materials should be considered. If the educational materials are similar as possible in layout, content, colour and format to avoid patient confusion which MAH will be responsible for printing, distribution, exchange, maintenance and retirement and is responsible for taking the costs while other MAHs can refer to the provided educational materials by another MAH. Will the printing, distribution etc. be done, paid and handled by the competent authority? The content is specified by the key elements in Annex IIb.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		A possible solution would be to encourage MAHs to pay a license fee for the by the initial MAH developed and implemented educational materials and processes. Further, the term required is not mentioned in the legislation and goes beyond the Directive and Regulation Proposed change (if any): For public health reasons, applicants/marketing authorisation holders for the same active substance should be encouraged by the competent authority to have educational material with as similar as possible format to avoid patient confusion. This obligation may also be encouraged for other patient material e.g. patient alert cards and patient monitoring cards. It should be considered to pay i.e. a license fee for already implemented educational materials.
1365 - 1366		Comment: This section is in contradiction with the required "non alarmist manner". It does not provide relevant information for patients but could significantly contribute to cause uncertainty among patients.
1500-1502		Comment: It seems to be an impossible task to be a scientific expert on upwards of hundreds of compounds in a large company even though delegation is allowed and many parts of the RMP will be submitted elsewhere in the world, which cannot be claimed as an EUQPPV responsibility. Proposed change (if any): "although many experts may be involved in the writing the RMP, the EU-QPPV requires sufficient authority and knowledge about its development to provide oversight of the EU RMP. The EU QPPV should be the single contact of the MAH for the competent authority related to the RMP.
1563 - 1568		Comment: Why is a justification required when the submission of the RMP is not mandatory?
1584 – 1586		Comment: Who provides the RMP? Is it the Competent Authority or the originator?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

< **17 March 2012**>

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

Comments from: Pierre Fabre Group

Name of organisation or individual
Pierre Fabre 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
	The EU-RMP template and the Summary of EU-RMP (Part VI) are not provided and will be required before the companies can organise and implement the new RMP requirements. It is to be emphazised that the current template leads to too much repetitions and it is at the utmost importance that the new template could decrease repetition and duplication throughout the document. This would increase the lisibility and decrease risks of "typing errors or missing updates" when the RMP is to be updated. The new parts of the RMP related to benefit may be more detailed. Transitional measures: In order to move to the future RMP format, including switching form the previous format to the new one for products with an existing EU-RMP, companies will need to make extensive changes in existing processes. Given the commonalities with the new PSUR format through the modular approach, EFPIA propose that the new RMP format applies at the same time as the new PSUR format, i.e. to all new RMP or RMP updates to be submitted after January 2013. The addition of a specific section could be planned for risks associated with a Medical Device necessary for the use of the Medicinal Product (Drug Delivery Systems) which evaluation however follows different methodologies.

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 328		Comment: The definition of "locked module" is not totally clear . It should be clarified if it will be possible to have different data lock points for the same document depending on modules and it needs to be clarified who decides if module can be "locked" Proposed change: Add a definition of locked module and specify that " ***RMP modules can be "locked" by the MAH when information ceases or has not changed***'
Line 378		Comment: Definition of Data Lock Point for RMP is missing . Furthermore it should be made clear that different DLPs can coexist in the RMP (see previous comment above) Proposed change : Suggest to be the DLP of the CTD for an RMP included in a submission file, or the DLP of the most recent available post-marketing safety data , such as the most recent PSUR
Line 384		Comment: Company often face difficulties to apply as much as possible for the same RMP in different regions. In order to make the RMP as global as possible it would be useful to include trade names in use in non EU countries. Proposed change :Add '*invented name(s) in the European Economic Area (EEA)* ***and other relevant global regions'***
Lines 400-401		Comment: The worldwide regulatory status by country with date approval/refusal, date marketed, current licence status and explanatory comments, could represent a very long section . In the product overview, a short summary of the number of countries/regions where the product has been approved and is currently marketed could be more lisible. Proposed change: This table could be better located as an Annex

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 570-71		Comment: The wording "*… the number of patients included in observational studies where safety data has been collected…*" can cover all types of epidemiological studies, including marketing research studies (see comment Line 632 below). Proposed change: "…*the number of patients* ***in all completed observational studies conducted to further elucidate a safety issue****…*"
624-625		Comment: There seems to be inconsistencies between module 6 (lines 166-169) and 5 in the definition of misuse regarding off label use In module 6, it seems that when intentionnally prescribed in non authorised indication, off label use should not been considered while in module 5, all situations where prescriptions are made outside the registered indication should be considered Proposed change : Clarify definition of misuse and add definition of off label use and harmonise their utilisation and meaning in annexe of definitions, module 5 and module 6
Lines 632-633		Comment: The scope of epidemiology studies to be included ("….*epidemiological studies which have included/include the collection of safety data*") is too broad, and nearly all epidemiology studies, including for instance those conducted for pricing purposes, could collect safety data at some point. It would seem appropritate for the RMP to focus on the epidemiological studies that have defined safety objectives. Proposed change: change to "*Marketing authorisation holders should provide a listing of ~~epidemiological studies which have included/include the collection of safety data~~* ***non interventionnal PASS****."*
Line 750		Comment: the term 'important' for identified and potential risks is defined in the document, but 'most important' is not. Proposed change : "*This RMP section should provide more information on the* ***~~most~~*** *important identified and potential risks."*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 803-823		Comment: A specific section could be planned for risks associated with Drug Delivery Systems, as their malfunctioning or misuse may lead to specific risks, even if these Medical Devices' risk management follows methodologies different than Medicinal Products (ISO 14971: Medical devices – Application of risk management to medical devices). Proposed change : add after line 816 a new category "***Risks related to a Drug Delivery System*** (when needed)"
Lines 1009-1019		Comment: the type of situations covered by "*those which might provide useful safety information even though the particular safety concerns might not have been the primary focus*" is not clear, probably very broad as it could virtually cover all epidemiological marketing studies in which the possibility to report ADRs is given. Moreover, few lines below it is said :"*If, when reviewing a study protocol, a study is thought to be primarily* ***promotional****, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP*". Proposed change : In order to avoid any misunderstanding , it is suggested to modify the two sentences as below: "*The applicant/marketing authorisation holder should include all studies designed to adress the safety concern* ~~***and those which might provide useful safety information even though the particular safety concerns might not have been the primary focus"***~~ *"If, when reviewing a study protocol,* ***a study is not evaluated as fulfilling one of the objectives of a PASS (as described in Module VIII)****, the applicant/…."*
Line 1033		Comment: It should be specified if protocols need to be annexed to the RMP even after completion and analysis of the study

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 1094-95		Comment: Within the current EU-RMP template, duplications and repetitions have been evidenced. It seems that sections 5 B 9 3 and V B 9 4 would carry a great part of identical data. Proposed change: It may be suggested to combine both sections in only one which should essentiallly include the summary table that would mention in its template all types of information currently detailed and requested in section 5 B 9 3
Lines 1117-1131		Comment: It is understood that current sub-section V.B. 10.1 "*presentation of efficacy data*" is to be completed even if there are no planned post-authorization efficacy studies . This sub-section seems to mix two different aims : the rationale for performing or not PAES with their presentation (if judged necessary) in a table and the synthetic presentation of the benefit data available. Proposed change : It is suggested to start by current section V B 10 1 "*presentation of efficacy data"* which would include data requested in current lines 1117-1129 and to follow with current section V B 10 "*Plans for efficacy Studies*" resulting from the analysis performed above with its current text and including lines 1130 to 1131
Line 1156		Comment: The term "Routine minimization" seems unsuitable for covering all situations described under this header. As "routine" activities have been defined as "which happen with every medicinal product" (line 1157), then it is deemed that specific legal status and limiting the pack size should not be considered as "routine". This would help harmonization beyond different regions, because these specific EU regulatory provisions may not be equally available outside the EU, and could for exemple be part of a REMS in USA Proposed change : It is suggested to move the sub-sections "pack size **limitation**" and "legal status" into Part V B 11 2 "Additional risk minimization 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')*
Lines 1282-1283		Comment : The text of the SPC is to be provided for routine risk minimisations activities . However , in some cases of medicinal products with national product authorisations, the CA may have disagreed on for ex a contraindication, leading to different texts in SPCs. Proposed change : Addition of a sentence mentionning the implementation of the routine risk minimisation activities based on the CCDS. In these cases , the MAH may add a sentence highlighting the differences in SPCs resulting from different positions of national CAs
Line 1386		Comment : In case of common RMP for same active principle authorised to the same MAH but in both national procedure and MRP procedure, should all SPCs be inserted in Annex 2 or could the CCDS be inserted if differences impacting the table on routine minimisation activities exist ? (see comment above for Line 1282)
Line 1432		Comment: There should be a common modular approach with the efficacy sections of PSUR, which is not mentioned in table V.1 Proposed change : RMP Part IV sub-section section "presentation of efficacy data" should be matched with PSUR sub-section 7 B V17 1
Lines 1565-1568		Comment : In these lines , it is mentionned that for submission of an initial application, a RMP may not be required and that a justification of its non necessity should be provided However from wording of article 8 3 (iaa) and from all the subsections of V.C.3.1, it could be understood that for **all** application submission for **all** products, a RMP must be submitted but that only some parts of it can be included in the RMP document for some type of products or situations Proposed change : If an RMP complete exemption is indeed possible for some MAs, consider adding a sentence at the beginning of V.C.3.1 : "***When no exemption of RMP writing is proposed by the Applicant*** *, normally all parts of the RMP…*" and in the title of table V 2 : "*Requirement for new marketing application* ***when no RMP exemption is considered***"
Line 1638		Comment: "*Each submission of the RMP shall have a distinct version number and shall be dated*." (IM Annex

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		II.3) Guidance should be provided regarding intermediate version numbers when the document is subject to discussions with the competent authority/PRAC and several versions are submitted until the document is finally approved. Proposed change : version number can be composed of two figures X.Y The first would be incremented when a change is submitted, the second for each change during a procedure/review until agreement in reached. As the EU RMP template is accepted and submitted outside EU (for ex in Australia) but sometines including a different PI compared to EU SPC, it should be specified how these versions should be considered.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Procter & Gamble

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
	Can we have consistency with the use of the phrase benefit-risk? It switches between benefit-risk and risk-benefit.
	Can we use MAH or Companies or Pharmaceutical Companies, but not switch between these names in the document?
	Can we use Competent Authorities or Regulatory Authorities or Regulatory Agencies consistently

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 4 – line 136		Comment: In the section "risk minimisation will be tailored to regional specifics." What does the term "regional" refer to Proposed change (if any): Please clarify
Page 6 – line 183		Comment: Safety concern in defined on row 195 and could be included in the definition here Proposed change (if any): Important identified risk, important potential risk or important missing information (also known as safety concern against important identified risk, potential risk or important missing information)
Page 6 – line 211		Comment: Where this sentence mentions RMP it appears it should actually refer to system rather than plan Proposed change (if any): Although the primary aim and focus of the RMS remains that of risk 211 management,
Page 7 – lines 226-240		Comment: This section appears to refer only to prescription medicines – what about OTC medicines? Proposed change (if any): Include reference to OTC medicines
Page 8 – line 258		Comment: The two sentences have different tenses Proposed change (if any): ICH-E2E defines two basic parts of a RMP: the safety specification and 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')*
		pharmacovigilance plan. It does not include risk minimisation.
Page 8 – line 270		Comment: the word risk before risk management plan is superfluous - this is not a known phrase Proposed change (if any): Since a risk management plan is primarily a pharmacovigilance document,
Page 8 – line 283		Comment: Change this bullet for consistency in the wording Proposed change (if any): ensuring the implementation of risk minimisation activities at a national level;
Page 8 – lies 287 - 289		Comment: the following wording is confusing and poorly written - ensuring marketing authorisation holders of generic and/or similar biological medicinal products 287 make similar changes when changes are made to the reference medicinal product risk minimisation 288 measures; Proposed change (if any): clarify the wording
Page 9 – line 302		Comment: not well written, can not identify the safety profile but it can be characterised, remove identify or Proposed change (if any): characterise the safety profile of the medicinal product(s) concerned;
Page 9 – line 303		Comment: change the order of the words further and characterise for clearer meaning Proposed change (if any): indicate how to further characterise the safety profile of the medicinal product(s) concerned;
Page 10 – line		Comment: would it make more sense to say plan rather than 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')*
334		Proposed change (if any): The risk management plan shall be proportionate to the identified risks and the potential risks of the
Page 14 – line 470		Comment: it may not be appropriate to use patient years or moths for short duration studies Proposed change (if any): patient time (patient-years, patient-months) exposed to the medicinal product, as appropriate.
Page 15 – lines 527 - 531		Comment: The following sentence is too long and difficult to understand - The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist so the cumulative effect of multiple impairments and multiple medications should be evaluated. Proposed change (if any): rewrite sentence or split it
Page 20 – line 727		Comment: is this the correct referenced section or should it be SVI? ***V.B.8.6.6. RMP module SV section "Projected post-authorisation use"*** Proposed change (if any): check it is the correct section
Page 21 – line 750		Comment: what does the most important refer to in the following sentence - This RMP section should provide more information on the most important identified and potential risks. 750 Proposed change (if any): clarify most important

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 21 – whole section		Comment: do labelled events have to be included as identified risks or not – unclear from this section Proposed change (if any): clarify
Page 21 – paragraph starting line 777		Comment: what if there is no clinical data available? Proposed change (if any): provide clarity
Page 21 – paragraph starting 785		Comment: this section is geared towards Rx medicines, what about OTC medicines? Proposed change (if any): provide information about OTC medicines
Page 26 – line 961		Comment: For the section entitled - **Routine pharmacovigilance (safety) activities –** what should go in this section – would it be more appropriate to remove "routine" from the title? Proposed change (if any): please clarify
Page 27 – line 1017		Comment: The sentence - If, when reviewing a study protocol, a 1017 study is thought to be primarily promotional, the applicant/marketing authorisation holder will be 1018 required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP. – is unnecessary – it has already been stated that studies should not be promotional Proposed change (if any): delete this sentence
Page 27 – lines		Comment: These sections are in the PASS module, remove and just cross reference to that module

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1043 to 1076		Proposed change (if any): see above
Page 32		Comment: This whole section does not provide guidance - delete Proposed change (if any): see above
Page 38 – line 1415		Comment: Move full stop to after the bracket Proposed change (if any): medicinal product (and a much wider range of (suspected) adverse reactions).
Page 39 – line 1439		Comment: Is the dossier referred to here the submission dossier? Proposed change (if any): clarify

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

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

Comments from:

Name of organisation or individual
Professor DK Theo Raynor, University of Leeds and Luto Research, UK

I am please to respond to this consultation on **Risk Management Systems**, as part of the wider consultation on Good Pharmacovigilance Practice.

I focus my comments on risk minimisation materials and their need to be accessible, readable and understandable for the target readers (whether patients or professionals)

Statement of Interest
Professor Raynor is a part-time director of LUTO Research Ltd which provides patient information development and testing services to the pharmaceutical industry and other health information providers.

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
	Harm-Benefit balance I welcome the increased focus on harm-benefit balance in risk management systems. Harms do indeed "need to be understood in the context of benefit" and this applies to the wider pharmaco-vigilance process, but also to any additional material to patients. People who take medicines want more balanced information (Raynor et al 2007), and the previous focus on harms had the potential to give the patient an inaccurate picture. This is likely to have prevented them from making an informed decision when reading risk minimisation materials. I use the term 'harm-benefit' as this is the most 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'.
	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.11.2 – and this is appropriately a **discussion** about what information the experts from the readership group would like, and how it should be presented. • 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). See specific comment below under "Additional risk minimisation activities" (V.B.11.2 RMP part V section)

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')*
1156-1169		Comment: **"Routine risk minimisation" (V.B.11.1 RMP part V)** It is true that routine activities such as the labelling and package leaflet are in themselves important tools for risk minimisation. However, it is important that any additional 'non-routine' materials produced to minimise risk complement and make reference to the label and package leaflet. Patients prefer consolidated information, rather than separate pieces of information (Raynor et al 2007). If this is not possible, it is important that the documents are consistent in the information they provide. It is also particularly important that they are appropriately cross-referenced. This cross-referencing may currently appear in the additional materials, but not in the package leaflet – this needs remedying Proposed change (addition): Risk minimisation materials should complement the information in the label and package leaflet. There should be cross-referencing in both directions, as appropriate.
1233-1258		Comment: **"Additional risk minimisation activities" (V.B.11.2 RMP part V section)** Under sub-heading "*Educational material*", it is recommended that communication experts, patients and professionals are consulted, and that the material is 'piloted' before the final version is agreed. It could be argued that this is 'user consultation' and that it could be made a more explicit requirement – as for package leaflets. Indeed in the section "Potential for medication errors"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		(V.B.8.6.4 RMP module SVI) particular reference (in relation to Instructions for Use and labelling) is made to the "Guideline on readability (EMA 2009) which describes the need for such user consultation to demonstrate the readability of package leaflets. The Guideline describes one way of demonstrating this, using the 'user testing' method. This method is now widely used for package leaflets (Raynor 2012), and has also been successfully used for Instructions for Use and other written materials linked to medicines and devices. (Raynor et al 2011) It has also been used to test risk minimisation materials, but this has not yet become routine. Proposed change (amendment and addition): Any educational material should be non promotional. It is recommended that input is obtained from communication experts, patients and healthcare professionals on the design and wording of educational material. It is then recommended that 'user consultation' is undertaken, one method being 'user testing' as described in the Guideline on the Readability of the Label and Package Leaflet , before the final version is agreed.
1310-1331		Comment: **"Summary of the activities in risk management plan" (V.B. 12. RMP part VI)** The idea of a summary of the Risk Management Plan (RMP) for each product to be publicly available is welcome. This will be an important contribution to the risk management system becoming more transparent. There are clear parallels with the European Public Assessment Report Summaries (EPAR Summaries) – which involve discussion with patients through the "Patients and Consumer Organisations Working Party". As noted above, as well as such discussion with expert patients, it is necessary to see if the documents produced actually work with real people, such as through testing. Our recent user testing of EPAR Summaries showed that they did not currently meet people's needs and allowed us to make recommendations for improving EPAR Summaries (evidence submitted to the EMA in confidence in advance of academic publication). It would seem, therefore, appropriate that such user testing should be utilised during the development of a template for an RMP Summary. I note that "*Further details and a template for this section will be developed*" – we would be happy to input our experience with EPAR Summary testing. These sentiments also apply to the development of the "Summary of safety concerns in lay language" (V.B.12.3. RMP part VI).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: This should await the further details and template for this section – which are being developed.
		Comment: **"Additional risk minimisation activities" (V.B.11.2 RMP part V")** I agree that additional risk minimisation activities need to be based on information which goes beyond the SmPC and PL – I look forward to the consultation on Module XVI " *Risk-minimisation measures: selection of tools and effectiveness indicators*" later in 2012 Proposed change (if any): None

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 Apr 2012

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

Comments from:

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Templates: The availability of the below templates would facilitate the MAHs on the implementation of the new RMP requirements. • EU-RMP Template • Summary of the EU-RMP (Part VI) (incl. more guidance on the preparation)
	Transitional Measures: Transitional measures should take into consideration the extensive changes required to update the existing EU-RMPs to the new template. Given that the RMP template is not due until 2012, guidance should be provided as to the Interim period.
	Use of similar risk minimizations measures/ documents between MAHs: There is a mention of using similar risk minimizations measures/ documents between MAHs. Would there be more guidance to the CAs and MAHs as to how this would be implemented practically? Would there be a harmonization process?
	Version control/ Change management: More guidance is required as to implementation of the version control for the whole document and modular updates.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 287-289		Comment: 'ensuring MAHs of generic or similar biological medicines make similar changes' Are the changes to the reference medicinal product risk minimizations communicated to all the generic/ similar biologic medicinal products MAHs? Will the CAs be more transparent in these communications? Will there be a harmonization process? Proposed change (if any):
Lines 319-329		Comment: 'Modular Concept' Will further guidance be provided in respect of the use and management of the modular sections of the RMP? For example, are all modules candidates to be 'locked'? How would the version number of modules be controlled? Would modules that are 'locked' have a different version number to updated modules? Will modules be submitted within a single document body or would they be submitted individually? Proposed change (if any):
Lines 342-343		Comment: 'RMP concerns different medical products' Does this mean all products with the same active ingredient should be in the same RMP? Can this decision be made by the MAH or does the CHMP decide? Will there be perceived exceptions to a single, shared RMP for products with the same active ingredients? 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')*
Lines 400-401		Comment: 'worldwide regulatory status by country (including EEA) with date approval/refusal, date marketed, current licence status and explanatory comments) This is a lot of information and is changing periodically. Proposed change (if any): This should be an Annex, so that it can easily updated without changes to the Part 1
Lines 631-639		Comment: 'Epidemiological study exposure' The RMP should focus on epidemiological studies that have defined safety objectives. Proposed change (if any): epidemiological studies which are being conducted to further elucidate safety issues.
Lines 676-680		Comment: 'Visual differentiation' How is this implemented practically? Individual MAHs might not have the comprehensive knowledge on all the products. The CAs have more knowledge on this and should guide the MAHs on the visual differentiation. Proposed change (if any):
Lines 692-696		Comment: 'Medication error as safety concern for formulation or strength changes' How is this interpreted in regulatory language? Will this become a standard requirement with a variation to change composition? 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')*
Lines 976-981		Comment: 'Specific adverse reaction follow-up questionnaires' How do the different MAHs get to use same or similar questionnaires? Would there be more guidance on 'publicly available upon request'. Proposed change (if any):
Lines 1162 -1163		Comment: 'Routine risk minimization' Not all activities described in this header are routine. Pack size(s) 'limitation' and the 'legal status' should not be considered as 'routine'. There should be a clear differentiation of the 'routine' risk minimization via the labelling documents (SmPC, PIL) and other regulatory measures aimed at limiting the use of the product. Proposed change (if any): Sub-sections pack size(s) 'limitation' and legal status of the product should be 'additional' risk minimization activities.
Lines 1243-1247		Comment: 'Additional risk minimization activities' Would there be more guidance in Module XVI on the involvement of patients & HCPs in the discussion of the proposed risk minimization measures. Proposed change (if any):
Lines 1255-1269 Line 1569		Comment: 'Educational material' Would there be more guidance in Module XVI on the involvement of patients & HCPs in the preparation of 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')*
		educational material and piloting of the educational material? Will there be harmonization process to ensure MAHs for the same substance have educational material as similar as possible? Proposed change (if any):
Lines 1635-1656		Comment: 'Updates to the RMP' The specific scenarios provided in Vol9a as triggers for RMP updates have not been included in this module. Are these scenarios still perceived as RMP update triggers or has this changed? Proposed change (if any):

Please add more rows if needed.

17.04.2012

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

Comments from:

Name of organisation or individual
SciencePharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Could you please precise, or give any example of possible measures (apart from labelling) that could prevent patients from administration a particular medicinal product by an incorrect route (v 672)? Should such measures always be described in Risk Minimisation Plan?
	In reference to v 1420, could you please specify whether each PSUR should refer to the (lack of) need of RMP actualisation?
	In reference to v 1645-46, could you please explain whether any updating of RMP will require a submission of a variation?

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The requirement to submit Risk Management Plans for every new application as submitted after July (or as much later as the implementing measures will define), is not risk-based. Although some parts of the safety specifications can be omitted in the modular system, the compilation and the assessment of RMPs on all products is not an efficient use of private and public funds. The proposed systems also creates a task for CA assessors to check consistency between all submitted generic/OTC RMPs – a task which will be very time consuming, with questionable impact on the safety of the patients. A solution for this might be that for a lot of active ingredients there will be a risk-based approach as for PSUR writing which resulted in the URD list. This list should also be used for the purpose of RMP writing. For products on the list with a periodicity of >=5 years the requirement for writing an RMP should be witdrawn.
	It is generally anticipated that an MAH for a generic product would implement the same risk minimisation activities as the innovator product. However, this is not applicable for some well-established products that have been in the market for a long time, for which safety concerns have been well characterised, and there is no expectation that new safety issues will emerge. A PSUR alone seems a better and proportionate tool for an ongoing benefit-risk assessment for these products.
	To avoid differences in the appearance and content of educational packs from different MAHs which poses additional risks to the patients, authorities should coordinate the production of these materials such that there is just one educational pack per active substance/product, to be distributed by the Member States together with the MAH.
	Clarity is needed regarding the transition period. As this is a period of adjustment to the new legislative regime, MAHs should be able to submit according to the previous guidelines and new requirements should not be imposed. At the same time, adoption of certain components of the new template during the transition period should be allowed where appropriate. An example of this would be situations in which the new guidelines do not mandate certain components of the RMP that were previously required (e.g. certain modules in a new RMP for a product that has been in the market >10 years); in these situations, the MAH should state clearly that the change from the previous guideline is related to the new guideline.

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')*
287-289		Comment: It is stated that competent authorities should ensure that MAHs of generic and similar biological products should make similar changes when changes are made to reference product risk minimisation measures. It is not described however how the MAHs will be made aware of any changes. This shall be a task of the competent authorities. Proposed change (if any): A bullet point should be added before 287 which should read "*Providing marketing authorisation holders of generic and/or similar biological products with changes are made to the reference medicinal product risk minimisation measures.*"
330		Comment: The agency will provide a template. If this template has to be used for submissions in July 2012, it should be available at the beginning of May at the latest.
334-338		Comment: There is a third way to make sure the risk management system is proportional to risk and that is when there is minimal risk presented by a product, no RMP submission is needed. Proposal: The requirement for RMP submission for every new application should be reconsidered in the interests of the primary intentions of the legislation; reduction of bureaucracy, simplification, reduction of duplicated efforts on behalf of MAH and CAs and sufficient use of resource to address real risks.
409-410		Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The definitions for pharmacovigilance plan and risk minimisation plan are missing from Annex 1 Proposal Add the above definitions.
692-696		Comment: If the formulation or strength of a product is being changed…. Most formulation changes do not influence any of the characteristics of the product so medication error is not an issue. Changing the strength of a product is in principle impossible – either a strength will be added or will be withdrawn. Proposal: rewrite the sentence: If a formulation ~~or strength~~ of a product is being changed *which significantly changes the characteristics of the product, or if a strength is added or withdrawn which could potentially lead to prescribing or administration mistakes,* medication error should be included…..
727-730		Comment: the first part of section "Projected post authorisation use" is not relevant for well established use products, since the pattern of use, estimated population and market position of the active will not change with generic substitution. Proposal: Indicate that these estimates are not needed for well established use products.
1067-1068		Comment: A registry is defined as a prospective non interventional study. This is incorrect. A registry is not a study. The definition should be corrected and added to the annex 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')*
		Correct definition and add to annex I
1116		Comment: It is not clear if the presentation of efficacy data will be mandatory even if no PAES is planned? Proposed change (if any): Since efficacy is an important part of future RMPs and benefit-risk analysis, more detailed explanation is needed on what is expected to be presented in this section, especially for generic RMPs, i.e. is this section also needed for generic RMPs.
1265-1268		Comment: In the interests of public health, educational material should be the same for all companies. The MS should coordinate this. Educational material should be non company specific when there are multiple MA holders and should be available from MS webportals and websites from pharmacy and physician associations. DHPC should also be coordinated by the MS, to ensssure that only one communication goes to the HCPs. The DHPC should be distributed by the MS to reduce the risk of the HCP considering the letter as marketing information.
1426-1432		Comment: Regarding the modular approach of the RMP and PSUR - it is still not efficient to repeat and maintain the same information in 2 documents. It should be stated that cross-referencing is permitted. Proposed change (if any): Instead of copying sections between documents, it should be sufficient just to make a cross-reference to the appropriate document.
1609		Comment: Data in table V.2 (line 1609); fifth row "Generic medicine", third column "Part II Module SI" is not consistent with text in lines 1576-1577 (It is stated that for new application for a new application for a generic medicine

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		modules SII-SV may be omitted). Proposed change (if any): Box should be checked for Part II Module SI in table V.2.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: The Module does not adequately distinguish between "ADR" and "risk". The terms should not be used interchangeably.
	Recommendation regarding Comment 1: The definitions set out in Annex 1 and the terminology of Module II should be considered in light of the legislation and rationalised/clarified.
	Comment 2: It is not clear what should be done by Marketing Authorisation Holders in relation to risk management plans until the new requirements apply (according to the draft Implementing Regulation, Article 39) and templates are available.
	Recommendation regarding Comment 2: Provide transitional guidance on what will be expected of Marketing Authorisation Holders as to timing, action and documentation. In particular, clear guidance should be provided for: a) risk management plans in the 'old' format and by what date they should be converted into the 'new' format and whether this applies to all products (well established vs. recently approved ones) and b) what should be done in the case where a post-authorisation safety studies is requested for a product which has been on the market for e.g. over 10 year, i.e. whether a full-blown risk management plan should be prepared or an risk management plan that focuses on the safety hazard being investigated.
	Comment 3: In Module V it appears that drug utilisation studies are treated as post-authorisation safety studies and it is therefore advised (line 619-21) that they be included in risk management plans. However, as is also recognised (line 1042-43), drug utilisation studies are often requested in relation to reimbursement discussions and do not investigate a safety hazard; and therefore, should not be considered post-authorisation safety studies.

Stakeholder number *(To be completed by the Agency)*	General comment
	Recommendation regarding Comment 3: Drug utilisation studies should be clearly distinguished from post-authorisation safety studies. As these studies are not post-authorisation safety studies strictu sensu, the paragraph contained in lines 1043-1052 should be placed in another part of the guideline (not in section VB9.2.1 a relation to post-authorisation safety studies) or, at least it should be made clear that these are not post-authorisation safety studies at the beginning of the paragraph.
	Comment 4: The Module does not address the "regionality" of some risk management strategies/outcomes. Therefore, if a particular risk minimisation strategy proves ineffective in for example, only one country, there is no guidance on how the Marketing Authorisation Holder should proceed.
	Recommendation regarding Comment 4: Guidance should be included to deal with differing outcomes in different countries to risk minimisation strategies including whether a Marketing Authorisation Holder should put alternative activities in place and apply to all EEA countries, sacrificing the accumulated outcomes in other countries.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<18 April 2012>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In view of the overlaps / common sections of RMP and PSUR, and since Module V suggests that the RMP be updated and submitted synchronously with the PSUR, it should be taken into consideration **for the future** to combine those two documents to one single document which is updated and submitted according to both sets of requirements. The same could apply to RMP and DSUR for the time until first authorisation is granted.

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 138		The transitional measures do not specify a timeframe for implementation of the requirements form this GVP module post finalisation. This timeframe should be a minimum of two years due to the complexities of creating new company internal templates and insertion of additional data requiring involvement of multiple different departments at the MAH site.
Line 154ff		Definitions should remain in the definitions module (annex) only in order to avoid potential discrepancies between the different GVP modules. Should definitions remain in this GVP despite the above consideration, additional definitions for additional pharmacovigilance activities, risk minimisation activities, routine pharmacovigilance activities and routine risk minimisation activities should be added.
Line 340		Although "medicinal products" are included in the definitions module the description of this term is insufficient here. It is unclear whether this refers to a single active moiety, or whether the same active moiety licensed in different indications or formulations may be considered as a separate medicinal product. This should be clarified and the definition included in this document. The same comment applies to line 374.
Lines 388-396		Suggestion: As to indications, dosage and pharmaceutical forms / strengths the details to be given should be categorised as follows: *- current in the procedure(s) within the EEA to which the RMP is submitted* *- current elsewhere in the EEA* *- current elsewhere outside the EEA* *- proposed in the procedure(s) within the EEA to which the RMP is submitted*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 elsewhere in the EEA *- proposed elsewhere outside the EEA* Rationale: In these subsections, without any structure of data, confusion and misunderstandings are inevitable. The proposed categorisation refers in the best possible way to the extent of information to be provided and, at the same time, to the respective grade of relevance for assessment.
Line 725		Correction of a typo. Proposed change: The line should read: "V.B.8.6.6. RMP module SVI section ..."
Lines 753-760		Proposed change: "Normally, any risk which is / is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be considered for inclusion here. Interactions which are of significant clinical importance and important pharmacological class effects should also be included. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but ,affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered for inclusion**,** e.g. severe dizziness in the context of operating machinery. Rationale: The definition of what constitutes an important risk is regarded to be very broad and preventing to focus on the main safety topics of concern. Especially adding "risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life" and "any risk which is / is likely to be included in the contraindications or warnings and precautions section" of the SmPC will increase the number of safety

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		concerns of a compound substantially and therefore does not allow appropriate prioritisation of the most important risks. Furthermore, if the extent of the presentation of data in RMP module SVII is planned to be similar to what was previously included in the section 1.5.2 "Details of important identified and potential risks" of the CHMP RMP template, the increase in the number of safety concerns will result in an extensive module with work-intense generation of data (e.g. NNH from clinical trials), which are frequently not helpful due to very low absolute numbers. Overall, the lower threshold for an identified or potential risk to be important seems to prevent focusing on the relevant safety topics for a given compound.
Line 868 - 878		Proposed change: The following bullet point should be added: "- risks related to new or unusual inactive ingredients with which little experience exists only**;**" Rationale: This point is not sufficiently covered in the draft.
Line 974ff		The use of specific follow-up questionnaires should not be considered as routine pharmacovigilance, rather it should be an additional measure. These types of questionnaires may be tailored to obtain specific information pertinent to a particular risk and may also be sent with a greater frequency than those used to fulfil routine regulatory requirements.
Line 978		Whilst the concept of a consistency in the format to follow-up requests is good it is unrealistic in practice for companies to co-ordinate this across companies. Suggestion: could the Agency please provide an optional template for such requests.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 1316		Proposed change: After "... medicinal product." the following two sentences should be added: "In order to be understandable in the best possible way to the lay reader, for the whole part VI 'lay language' should be used. In this context 'lay language' means avoiding technical terms, abbreviations and acronyms, whenever they can be replaced without loss of meaning by non-technical terms of not more than four (4) words. Unavoidable technical terms, abbreviations and acronyms have to be explained accurately and in detail in a glossary within part VI." Rationale: Since the summary of the RMP is intended to be publicly available, not only concerning the summary of safety concerns, but as a whole, lay language has to be used throughout this part, and it also has to be made clear what lay language is.
Line 1324		Suggestion: The addition "(in lay language)" should be deleted. Rationale: The whole part VI has to be suitable for lay readers, not only this section. See comment on line 1316.
Lines 1340-1341		Suggestion: The addition "(in lay language)" should be deleted. Rationale: The whole part VI has to be suitable for lay readers, not only this section. See comment on line 1316.
Line 1342ff		The template for the public summary is vital to ensure that the public is able to respond to risks associated with a product proportionately and make a fully informed decision.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 template for the public summary should include standard wording for the patient friendly statements on frequency and severity of safety concerns.
Line 1370		Timelines and milestones should not be included in the public summary. Even timelines proposed with the best of intentions tend to change for factors beyond industry or regulator control (e.g. slow recruitment; delays to approval; etc). Publication of such discrepancies would devalue the system and reduce public confidence in both industry and regulators.
Lines 1376-1377		The statement "*Since changes to risk minimisation activities involve a variation*" is confusing. Elsewhere in the GVP module it is stated that the RMP should be submitted with the PSUR avoiding the need for a variation unless there is a significant change. This statement should be clarified so that it is transparent under what circumstances a variation is required.
Lines 1567-1571		Proposed change: "Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted unless otherwise agreed between the competent authority and the MAH." Rationale: Even in specific situations most modules of the RMP have to be submitted. To be in line with the concept of proportionality and to assure planning reliability, the provision of additional modules should be mutually agreed between the competent authority and the MAH.
Line 1588		The definition of "well established use" should be included in the definitions in the definitions GVP annex.
Lines 1636-1638		The submission of RMP updates in track changes is administrative and difficult to achieve due to automated

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		software behaviours such as indicating formatting changes etc and also difficulties in spotting factual changes once whole text passages are cut and pasted. Alternative proposal: The RMP template includes an updates section which should already be detailing the contentwise changes therewith providing a complete overview on what these are.
Line 1643		The expected frequency for updates to RMPs for products which do not have the requirement specified as part of their authorisation should be addressed here.
Line 1652		The sentence regarding transitional arrangements should be clarified. Do RMPs have to be submitted by a given date in the new template or should they be in the new template when submitted for their next routine update?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

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

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

1. General comments

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

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')*
134 - 138		Comment: it is stated here that because of differences in indication and healthcare systems, as well as differences in disease prevalence and severity, risk minimisation and benefits of a medicinal product may vary between regions and therefore a product may have a different RMP for each region although there will be several elements which are common to all. Proposed change (if any): One global RMP in which region specific information (such as risk minimisation) is presented by region.
1033		Comment: Do the study protocols which should be provided in RMP annex 5 need to be in English language? Proposed change (if any): Specify whether these will be accepted in local language or are expected to be in English, or whether an English synopsis will be satisfactory.
1384		Comment: Will the RMP annex 1 be needed for generics? Proposed change (if any): Specify that this includes/excludes RMPs for generic products
1628 - 1629		Comment: It would be useful if a consolidated list with submission requirements for Annex I in the member states for RMPs could be published, e.g. on the HMA website Proposed change (if any):
1632 -1634		Comment: It would be useful, if a consolidated list with submission requirements for RMPs for the member states could be published, e.g. on the HMA website
1576 – 1577 and		Comment: it is stated here that RMP modules SII – SV may be omitted. This is not consistent with the table

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1609		V2, which indicates that Module SI is also not required for generic medicine. Proposed change: make section consistent with table, i.e. module SI can be omitted for generic MAs.
1698		Comment: It would be useful if it could be defined what 'launch' actually means in this context, taking into consideration that products may be available on compassionate use basis before and after granting of the MA and before the details of the national implementation of the risk minimisation measures have been agreed
1707 – 1708		Will there be any provisions of making public summaries of RMPs for RMPs in place before 2 July 2012? As generic drug applications will have to include RMPs and the clinical data is not available to the generic companies, there should be a mechanism how their RMPs can be consistent with the innovators' RMPs.

Please add more rows if needed.