21 October 2013
EMA/646427/2013

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

GVP Module VII – Periodic safety update report (Rev 1)

The draft of this module was released for public consultation between 25 April and 25 June 2013. The module has been revised, taking the comments received into account.

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

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

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

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*).*

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')*
597-600		Comment: For well-established medicinal products available without prescription, it is not routine for the MAH to have access to stratified patient exposure data; particularly relating to age, sex and indication (where product has multiple indications). Proposed change (if any): 'An overall estimation of patient exposure should be provided. In addition, the data should be ~~routinely~~ presented by sex, age, indication, dose, formulation, and region, where applicable.
781-789		The introduction to Section VII.B.5.9 is not aligned to ICH E2C(R2). It refers to areas (e.g. overdose, abuse) which are not covered by the subsection 9.1 and 9.2. Proposed change (if any): Other sources of information may include data collection outside of a ~~study~~ **clinical trial** environment. Information obtained from **other clinical trials/studies or patterns of medication errors and potential medication errors, even when not associated with adverse outcomes should be included in sub-sections VII.B.5.9.1 and VII.B.5.9.2 respectively.** ~~For example, this would include available reports of asymptomatic overdose, abuse, use beyond that recommended in the reference product information, or use in special populations (see Module VI). Such information may be received by spontaneous reports, medical information queries, customer complaints, screening of digital media or via other information sources available to the marketing authorisation holder.~~

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
Biotest

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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')*
1388-1390 and 1391-1395		Comment: Page 40/41: (Flow-chart on page 40 and first chapter on page 41) We do not understand the reason for filing a variation for something that has been decided by the authority and therefore should be present for everybody. Filing variation creates additional work for authorities and MAH without any additional benefit, especially not any benefit for patient's safety. Proposed change (if any): 1388-1390: Adapt without variation 1391-1395: Delete!

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25.06.2013

Submission of comments on GVP Module VII (Rev 1) – Periodic safety update report (EMA/816292/2011 Rev1)

Comments from:

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
No general comments.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
410-411		Comment: Known or emerging important information on the medicinal product's benefits and risks are often matter of opinion. Probably MAH and Regulatory Authority could have different opinions. This content should be formulated more clearly. Proposed change (if any):
464-465		Comment: the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world Proposed change (if any): the date on which the product was first approved for market anywhere in the world
625-628		Comment: "For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorisation holder should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR (e.g. authorised indication, contraindications)." Most likely every MAH takes this for granted. This passage seems to be superfluous. Proposed change (if any):
861-934		According to Article 107h of Directive 2010/84/EC MAH shall inform Agency and NCA in the event of new signals / risks. This responsibility of MAH should be mentioned in the section VII.B.5.16. for completeness.
		According to VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information" It is recommended that the level of detail of the evaluation included in this sub-section **should be proportional to the available evidence on the risk and its medical significance and public health relevance**. This should be defined more in detail, because this could be matter of opinion.
1056-1058		According to section VII.B.5.16.4. "When missing information could constitute an important risk, it 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 as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed." It should be noted that missing information, which could be an important risk, could evolved from for example M&A deals of a medicinal product. Often not all historical data (case report) were available, so that cumulative assessments could not be done, which could have an impact for signal management and risk evaluation.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

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
	Throughout the document two different terms are used: benefit-risk analysis and risk-benefit balance. We suggest to use benefit-risk analysis or benefit-risk balance throughout

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 175-180		**Comment:** Line 178 says “data lock point (day 0) for PSURs. Line 180 says “data lock (day 0) point for PSURs Can this be made consistent language? **Proposed change (if any):** Suggest to use “data lock point (day 0) for PSURs” consistently
Lines 396-404		**Comment:** Throughout the document two different terms are used: benefit-risk analysis and risk-benefit balance. **Proposed change (if any):** The term “benefit-risk” analysis or “benefit-risk” balance to be used consistently throughout the guidance and replace all mentions of “risk-benefit”
Pg 20-VII.B.5.7		**Comment:** **“Summaries of significant findings from clinical trials during the reporting interval”** advises author to create a single appendix for Post-authorisation interventional trials and also provided the information that should be captured. However, this is in conflict with Pg 33-VII.B.5.20 **“Appendices to the PSUR”** which advises the author to create one Appendix listing all of the MAH interventional and non-interventional studies. This would mean combining current Appendices 5 & 6 into one Appendix which would be Appendix 4. **Proposed change (if any):**
Pg 20-VII.B.5.8		**Comment:** **“Findings from non-interventional studies”** advises author to create a single appendix for Post-

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		authorisation non-interventional trials and to reference Section VII.B.5.7 for outline of all information that should be captured (this is currently Appendix 6). However, this is in conflict with Pg 33-VII.B.5.20 **"Appendices to the PSUR"** which advises the author to create one Appendix listing all of the MAH interventional and non-interventional studies. This would mean combining current Appendices 5 & 6 into one Appendix which would become Appendix 4. **Proposed change (if any):** Please clarify how this should be handled.
Sub-Section VII.B.5.9.2.PSUR "Medication errors" Lines 797-802		**Comment:** Please confirm that medication error includes the situation when a physician makes a prescribing error however the patient never receives that dose due to detection of prescribing error and there is no administration of drug to patient. **Proposed change (if any):**
VII.B.5.15.PSUR section "Overview of signals: new, ongoing, or closed" Lines 862-867		**Comment:** Line 863 states "figure 1", however Line 1228, Section VII.B.21 (Pg 34) lists this figure as "VII.1". Please clarify/correct. **Proposed change (if any):** Change from figure 1 (see VII.B.21) to figure VII.1(see VII.B.5.21)
Line 904		**Comment:** Line 904 correct typo: the word And should be An. Clarification is required as to what Appendix number this will become Appendix 2 or 3. Line 1215, describes the tabulation of signals as Appendix 3.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Please change And to An. If the tabular summary of safety signals is included in the body of the report instead of in Appendix 3, Appendix 3 should only contain a note as to the location of the tabular summary in the report (with a link). This will maintain consistency in Appendix numbering.
VII.B.5.16.1.PSUR sub-section "Summary of safety concerns" Line 938		**Comment:** The sentence "For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR" Is this saying it **need not match precisely**? This is mentioned in VII.C.4.3.1 PSUR and risk management plan – common modules. This is in conflict with guidance in Lines 1842-1846 regarding interchangeable sections, Table VII.1 Common sections, and Lines 1895-1898 which states the table should be extracted. **Proposed change (if any):**
Lines 986-987		**Comment:** If not included as an appendix, should appendix numbering be altered? **Proposed change (if any):** If the description of safety evaluations is included in the body of the report instead of in Appendix 3, Appendix 3 should only contain a note as to the location of the evaluations in the report (with a link). This will maintain consistency in Appendix numbering.
Lines 1021-1022		**Comment:** If not included as an appendix, should appendix numbering be altered? **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')*
		Appendix numbering should be maintained for consistency, with location references.
VII.B.17.2.PSUR sub-section "Newly identified information on efficacy and effectiveness" Lines 1104-1106		**Comment:** How should indications not approved in the EU but approved elsewhere be handled? **Proposed change (if any):** As this is a global document, all indications should be discussed, with appropriate countries and/or regions identified.
Line 1212-1214		**Comment:** Clarify if the two summary tabulations should be in one appendix and how should the appendix be structured/numbered? **Proposed change (if any):** Suggest to keep the two summary tabulations separate, e.g., 2A SAEs from clinical trials and 2B Serious and non-serious ADRs from PM data sources.
Line 1215		**Comment:** If the tabular summary of safety signals is included in the body of the report, should the appendices be re-numbered? **Proposed change (if any):** As mentioned earlier: If the tabular summary of safety signals is included in the body of the report instead of in Appendix 3, Appendix 3 should only contain a note as to the location of the tabular summary in the report (with a link). This will maintain consistency in Appendix numbering.
Line1216-1219		**Comment:**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		This is not in agreement with Lines 724-734 and 771-772 which state these appendices will remain individual. Clarification required on how to handle. If two listings are included in one appendix how should this be structured/numbered? **Proposed change (if any):** Suggest to have two separate listings: 4A Interventional studies and 4B Non-interventional studies
Line 1438		**Comment:** Change of the phrase benefit-risk profile to risk-benefit balance. **Consistent use of the term “benefit-risk” should be applied throughout the guidance** **Proposed change (if any):** Replace “risk-benefit” with “benefit –risk”
Lines 1879-1886		**Comment:** Confirm that this is no longer a requirement to compare the CCSI with the proposed SmPC. Text which has been removed is not covered by lines 1867-1873. **Proposed change (if any):**

Please add more rows if needed.

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EFPIA appreciates the extent to which the revised PSUR GVP module VII has utilised the content and format of the PSUR/PBRER based on the Step 4 ICH E2C (R2) guideline. This will promote international harmonisation and hence avoid unnecessary duplication and burden on industry. With respect to the date for coming into effect (Q4 2013), we would request that consideration is given to applying the effective date to reports which have data lock points (DLPs) in Q3 2013 rather than PSURs that are due for submission after the effective date. The new format PBRER/PSUR requires planning and preparation well in advance of the DLP (approximately 4 months), therefore it is important that marketing authorisation holders (MAHs) are allowed sufficient time for implementation of updates to templates and procedures to meet the requirements of this first revision. Whilst some deviation from ICH E2C (R2) is expected and understandable due to the constraints of the 2012 PV Legislation, there are nevertheless two significant areas of concern which primarily relate to where EU specific provisions have been included which a) do not support international harmonisation, b) introduce significant confusion when added to the final ICH E2C (R2) guideline text or c) appear to be inconsistent with the provisions of the EU PV legislation and ICH in defining the scope and content of the future periodic report. A final and third general cause for concern relates to the single PSUR assessment procedure and timelines for review, particularly for PSURs on a six monthly cycle. • The first cause for concern relates to **Section VII.B.5.9: Information for other clinical trials and sources.** This section of the GVP guideline has aligned with ICH E2C (R2) to the extent that it has sub- divided the section of the PSUR/PBRER into 5.9.1 “Other Clinical Trials” and 5.9.2 “Medication Errors”. There are, however, significant deviations from the ICH E2C (R2) final text in that there is an additional introductory paragraph which was carried over from the July 2012 B.5.9 text. This text was rejected by the ICH E2C (R2) EWG and no longer reflects the subsections that follow, thus rendering the whole paragraph completely redundant and confusing. This feedback also takes into account the fact that most of the concepts are now covered in the revised section 5.5.2 a) The paragraph refers to other sources of information which may occur outside a study environment and then proceeds to list multiple different patterns of use (overdose, misuse, abuse, off label use or use in special populations when sub-

Stakeholder number *(To be completed by the Agency)*	General comment
	section 5.9.2 ONLY refers to medication errors and near misses. EFPIA recommends that most of this paragraph is removed and refocused on medication errors and near misses to be consistent with ICH and avoid significant confusion. The re-worded section 5.5.2 and, in particular subsection 3, cover the concepts already and is a more appropriate position for mentioning patterns of use to avoid duplication. *b)* In relation to *patterns of use which do not result in suspected ADRs*, EFPIA supports the concept of medication errors and near misses but questions the value of individual case reports with no adverse sequelae as they are unlikely to reveal information relevant to the safety evaluation over and above information obtained from other sources. In particular, EFPIA has significant concerns with the implied need to collect cases of off – label use with no adverse sequelae as this has significant implications with respect to corporate integrity agreements and promotional practices etc., as well as what can and cannot be collected in third countries, notably the US. Furthermore, in the interests of proportionality, EFPIA considers that, if there are patterns of use anticipated e.g. off label use, use in children, then this will need to be included in the RMP and evaluated more systematically where appropriate e.g. with a drug utilisation study. Signals in relation to patterns of use relevant to safety that arise from ICSRs or other sources, should also be managed as appropriate, depending on whether or not the signal becomes a safety concern. EFPIA strongly considers that the terminology in section 5.5.2 subsection 3 (Other post authorisation Use) is a more appropriate, proportionate and accurate description of what is needed, namely ***patterns of use considered relevant to the interpretation of safety data.*** As this aspect is already covered in section 5.5.2, it is unnecessary and redundant to repeat in section 5.9, so EFPIA recommend that the sources of information wording in 5.9 be moved to 5.5.2. *c)* The subsection “Other Clinical Trials “ in the revised Module VII is new and is faithful to the ICH E2C(R2) wording EXCEPT that it has added “ including patient support programmes”. Although PSPs have been proposed in GVP Module VI as a source of “solicited” data, they are neither clinical trials nor clinical studies under prevailing definitions so this should be deleted. This position is consistent with international consensus, including that of CIOMS V. • The second cause for concern relates to requests for information and presentation of data in the future format PSUR where there is no section in which these requests can now be placed. Furthermore, it is not clear from most of the requests made to date, if they have been made because the Assessor or PRAC consider that there is a signal or for other

Stakeholder number *(To be completed by the Agency)*	General comment
	reasons. . Although PSURs/PBRERs in the new format have been submitted globally since January 2013, such requests to date, have only arisen from the EU, and invariably involve either narratives or detailed presentations of data vs. the summaries of information and scientific evaluation stipulated by the legislation and proposed in the Module VII/ICH E2C (R2) format. As such, it appears that the principles and scope of the new PSUR are not being taken into account and the mind-set of the former PSUR is being perpetuated. It is also confusing for the MAH, as it is often unclear in which section of the new format PSUR it is most appropriate to address such detailed requests. Accepting that this has been a transition period, it is, nevertheless, a major concern as, either way, if such requests continue, and Assessors or PRAC do not accept the provision of summaries in section 15 (if the results of the analyses etc. are negative which is invariably the case), then the PSUR, as submitted in the EU will cease to conform to the scope and content agreed by consensus at an ICH level. Undoubtedly further discussions on this important implementation point will need to occur outside the context of this commentary on the revised draft Module VII. • This comment has been made before by EFPIA and links to the concern expressed immediately above but provision of additional pharmacovigilance data in relation to requests from competent authorities could potentially lead to multiple ad hoc requests from individual authorities when this may not add materially to the evaluation of benefit risk. In particular, the specific inclusion of a request to analyse cases classified as non -serious is not only scientifically invalid (if there is a signal based on spontaneous cases, all case reports should be analysed) but also runs contrary to the principle of proportionality. The final major cause for concern relates to logistics and timelines of the single PSUR assessment procedure, particularly in relation to reports submitted on a six month cycle and the new stipulation to provide responses to requests that have been made in the PAR by Day 90 of the procedure. For PSURs submitted on a six monthly basis, under the stipulated PSUR procedure timelines, the MAH receives PRAC/MS recommendations after updating the Assessment report at around the time of (and not infrequently after) the Data Lock Point (DLP) of the subsequent PSUR. It is also not unusual to receive the Preliminary Assessment Report (PAR) after Day 60. As a result, it becomes impractical and unreasonable to adequately assess all the requests for information s raised in the PAR either by Day 90 or even in the next PSUR which may well be being written when the PAR is received. This particularly applies if the request(s) are extensive and involve multiple complex reviews and analyses. As PSURs on a six month cycle are generally

Stakeholder number *(To be completed by the Agency)*	General comment
	those in the early years post approval (or post approval of a new indication /population/formulation), this is classically a period when there is a lot of new information arising even in the six month period covered by the report and, hence, when there is a tendency to trigger multiple new regulatory requests in Europe. EFPIA understand that the steps and timelines of the PSUR Assessment procedure are detailed in the legislation and therefore cannot be changed. However in order to ensure that, these requests can be adequately addressed and evaluated to appropriate quality standards, EFPIA request that a proportionate and flexible approach is taken by the Assessor and PRAC when setting timelines for providing additional information, and/or analyses by the MAH. It is recommended that, where PRAC make multiple requests for information or additional analyses in the Preliminary Assessment Report (PAR) at Day 60, that the PAR is clear in what does and does not constitute a new signal from their perspective. This would allow, for example, the MAH to submit proposals for appropriate timeline(s) for response to the various requests by Day 90. As such, relatively straightforward request(s) could be addressed either by Day 90 or in most appropriate section(s) of next PSUR submitted; more complex questions/requests could be addressed in the subsequent PSUR after that. If a request has arisen as the result of a safety concern of a more urgent matter that cannot wait until the next PSUR, it is assumed that the timelines for submission would reside outside the PSUR cycle. Ultimately, EFPIA anticipate that, as the new processes, content and format of the new PSUR become more established, the number and extent of these additional requests will diminish. EFPIA have proposed some additional wording in the detailed comments section below which we consider to be more in keeping with the intent of the PSUR legal framework and guidance, provide clarity and be less open to interpretation and ambiguity

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 417 Lines 468		Comment: The requirement for the PSUR title page to contain "the signature" is inconsistent with the ICH E2C(R2) standard agreed at Step 4, has no legal basis and fails to take into account personal privacy principles as well as current document management standards of electronic " approval " of a document. With increased transparency, PSURs will be released under "Freedom of Information" requests and personal data of the signatory may well not be redacted (it is known that at least one Competent Authority releases all personal information). EFPIA is therefore opposed to this unnecessary stipulation and requests its deletion on the grounds that it is unnecessary, and has personal privacy implications. In additions, any delegation by the EU QPPV should be documented by SOPs and subject to inspection so it is entirely unnecessary to submit a delegation statement with submission of the PSUR. EFPIA would question the utility of this information in the evaluation of a scientific benefit risk evaluation document and how the information is used by the scientific Assessors Proposed change (if any): (Line 417) : Part 1 : Title Page ~~including signature~~ **including a statement that the approval signature is held on file**(5) Footnote 5 should be amended as follows: Remove "~~A statement confirming the designation by the QPPV should be included.~~ Line 468: ~~The title page should also contain the signature.~~
Line 464 - 465		Comment: EFPIA acknowledges that the same definition of IBD can be found in ICH E2C (R2) section 2.8.1. Nevertheless, there is concern that this now relates to the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world. For many old active substances, determining the first marketing authorisation granted to any company anywhere in the world could be extremely difficult, if not impossible. This situation would particularly apply if the MAH is not the innovator, or where there are other products containing the same active substance for which other companies hold the MA. In these circumstances, EFPIA recommend that a pragmatic and flexible approach is applied in

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		setting the EURD. Proposed change: The title page should include the name of the medicinal product(s)6 and substance, international birth date (IBD) (the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world)**7**, **Add footnote 7: Where there is no existing EURD for the active substance or where the IBD cannot be determined by the MAH based on the authorisation for any product containing the same active substance granted to any company in any country in the world, the MAH should propose an IBD based on international harmonisation principles.**
Line 616-628		Comment: As noted in the general comments in section 1 of this commentary, EFPIA consider that this section (sub -section 3 of B.5.5.2) is the most appropriate section to describe patterns of use relevant to the interpretation of safety data and not section B. 5.9 (Clinical Trials and Other Sources) which is confined to medication errors and near misses in other sources" per ICH E2C (R2). In order to avoid confusion and align with the ICH E2C(R2) guideline in section 5.9 (as noted above), we propose to modify the paragraph in lines 781 – 787 but move wording from lines 785 – 787 regarding sources of information to section 5.5.2 in order to retain the information. Although this now means that additional wording is introduced in section B.5.5.2 (subsection 3), it is nevertheless consistent with E2C (R2). Proposed change: If the marketing authorisation holder becomes aware of patterns of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. **Such information may be received via spontaneous reports, medical information queries, customer complaints, screening of digital media or via other information sources available to the marketing authorisation holder.** Examples of patterns of use may include overdose, abuse, misuse, and use beyond the recommendation(s) in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/ or prophylaxis of migraine headaches

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Line 780		Comment: There appears to be a typographical error in the section heading for VII.B.5.9 which needs to be corrected in order to be consistent with the table of contents i.e. in the section heading title “for” should be amended to “from”. Proposed change : **Information ~~for~~ from other clinical trials and sources**
Lines 781-787		Comment: As noted above in section 1, the introductory paragraph of this section is a major EFPIA concern as it has been carried over from the GVP Module VII finalised in July 2012, when the content that followed was different. The new subsections relate purely to other CTs and medication errors/near misses and not to all the other patterns of use situations listed. This is considered to be not only a deviation from the ICH E2C (R2) guideline but also very confusing. Furthermore, patterns of use relevant to the interpretation of safety data for all the listed conditions are already covered in section B.5.5.2 and therefore this would be duplicative as well. The amendments proposed take these points into account Proposed change (if any): Other sources of information may include data collection outside of a ~~study~~ **clinical trial** environment. Information obtained from **other clinical trials/studies or patterns of medication errors and potential medication errors, even when not associated with adverse outcomes should be included in sub-sections VII.B.5.9.1 and VII.B.5.9.2 respectively.** ~~For example, this would include available reports of asymptomatic overdose, abuse, use beyond that recommended in the reference product information, or use in special populations (see Module VI). Such information may be received by spontaneous reports, medical information queries, customer complaints, screening of digital media or via other information sources available to the marketing authorisation holder.~~ **Note: EFPIA propose that the highlighted section be moved to section 5.5.2.**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 792		Comment: This new subsection (B.5.9.1) relates to other clinical trials /studies only. Contrary to the ICH E2C (R2) wording, the sentence includes patient support programmes as an example of a CT/study, when clearly PSPs are neither clinical trials nor clinical studies. This verbiage has probably been carried over from the July 2012 Module VII when this section was not subdivided; with the current placement and context, however, it is confusing and incorrect so should be deleted. Proposed change : This PSUR subsection should summarise information relevant to the benefit risk assessment of the medicinal product from other clinical trials/study sources, ~~including patient support programmes,~~ which are accessible…..
Lines 1203 - 1208		Comment: EFPIA appreciates the requirements under IR Art 34(5) to refer to conclusions in the PSUR as to the need for changes and/or actions including implications for the approved SmPC with those proposals for changes included in a regional appendix. The conclusions however will actually be written for submission to global regulators so in the main body of the PSUR in the Conclusions section, the conclusions should relate to proposed changes to the **Reference Product Information** with those specific to the SmPC in the regional Appendix. EFPIA propose that this is clarified as follows : Proposed change: Based on the evaluation of the cumulative safety data……..including implications for the approved summary of product characteristics(SmPC) for the product(s) for which the PSUR is submitted ((IR Art 34(5)) **For this section of the PSUR, any proposed changes to the reference product information should be described. Proposed changes to the SmPC should be included in** T **t**he regional appendix ~~should include proposals for product information (SmPC)~~ together with information on on-going changes when applicable.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1203-1208 and 1864-1866		Comment: It is clear that the regional appendix should include proposals for product information if, during the evaluation of the cumulative safety data and risk benefit analysis, that the marketing authorisation holder (MAH) identifies changes to the SmPC. However, if the MAH does not propose any changes, EFPIA consider that it would be helpful to both the MAH and Assessor if MAHs just state this point in the cover letter and omit this regional appendix. Proposed change: In this sub-section, the marketing authorisation holder should provide the proposals for product information (SmPC and package leaflet) based on the above mentioned evaluation. These should be based on all EU authorised indications**. If the MAH does not propose any changes to the product information, this point may be included in the cover letter accompanying submission of the PSUR and the regional appendix "Proposed Product Information" can be omitted. .**
Lines 1247 – 1250 Line 1567 (commented on later)		Comments: In line with comments in section 1, early experience of EU regulatory review of PSURs in the new format and content, is indicating that they are being treated no differently to the previous PSUR, e.g. MAHs continue to be requested to provide detailed information on individual cases, additional tabulations and presentation of breakdowns of data without apparent signals and when previous similar analyses or data presentations have repeatedly failed to identify an issue. In many cases, the information requested has no section for placement in the new format per ICH E2C (R2). Moreover, it is not usually made clear to MAHs if such requests relate to a new safety signal arising from a PSUR assessment or for another reason. This is becoming very difficult to manage in practice and, to the point, where the EU PSUR is already increasingly diverging from the international consensus agreed in November 2012 which negates the whole point of an ICH standard. The ICH Expert Working Group attempted to address this issue by making provision for the negative results of requested analyses to be summarised in section 15 of the new report. However, as a result of multiple and repeated EU requests for more detailed presentation of data , section 15 is rapidly becoming very long which

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		goes completely against the legal basis and principle of succinct summaries of information and scientific evaluation as opposed to. a "data dump". Furthermore, provision of information in the next PSUR may not be possible, particularly when the PSUR is on a six monthly cycle, when the additional information/analyses requested are complex and when the Assessment Report (AR) is received by the MAH close to or after the DLP of the next PSUR. The proposed new wording in line 1247 "to be addressed in the PSUR" only serves to perpetuate and reinforce this old practice; there may also be compliance issues by implying that the requests can always be included in the next PSUR when , for reasons already highlighted for PSURs on a six monthly cycle this may simply not be feasible. Under such circumstances, timelines for submission of additional analyses may need further discussion and agreement in line with proportionality principles. . Proposed change: The PSUR should also contain **summaries of** the **evaluation** ~~assessment~~ of ~~specific~~ **closed** safety ~~issues~~ **signals or summary evaluations of other regulatory requests for information that are not signals raised during the time of the PSUR assessment** ~~requested to be addressed in the PSUR~~ by competent authorities (worldwide). ~~for inclusion with the next PSUR.~~ **Provision of this information should be in accordance with agreed timelines e.g. with the next PSUR and with instructed content for sections B.5.15 and B.5.16., as appropriate.** The marketing authorisation holder should have mechanisms in place to ensure that the requests made by the competent authorities (worldwide) ~~during the time of their PSUR assessment~~ are properly addressed, **in accordance with the content and format determined by ICH E2C (R2) and this Module**.
1527-1533		Comment: This section covers MAHs submitting the "relevant" variation to align with the EU Reference date list but there is no guidance on identifying the "relevant" variation. In addition the sentence about submitting a relevant variation is repeated. Proposed change: Cross-reference to the following: • Implementation plan for the update to annex II of the Quality Review of Documents template for

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		centrally authorised products • HMA Questions and Answers on **PSURs (Transitional arrangements for nationally authorised products)** Delete the following sentence on lines 1531 and 1532 as it is a duplicate: *Where appropriate, marketing authorisation holders shall submit the relevant variation in order to reflect the new information in their marketing authorisations [DIR 107c(6)]*
1565-1572		Comment: This section relates to a new provision for the MAH to provide "detailed "information if new ADRs are proposed for inclusion in Section 4.8, or if modifications in the description, frequency or severity of known reactions to allow the adequate description and classification of the frequency of the ADRs. It also indicates that if other sections of the SmPC are to be updated (e.g. section 4.4) clear proposals should be provided for consideration during the PSUR assessment. The wording in the proposed new paragraph, as currently written is unclear and fails to take into account different scenarios : • If the new ADR is the result of a closed signal that was classified as a risk in the reporting period, then the results of the evaluation of this signal (whether or not classified as important) would already have been included in section 16.2 of the PSUR. The instructions for this section (lines 974 – 979) are very clear that the level of detail provided should reflect the medical significance of the signal and extent of available evidence; it is also clear (lines 971-973) that the level of information included in the signal evaluation should be sufficient to describe the basis on which a signal became a risk by the MAH. The same principles apply for new information on a known risk (ADR). It therefore seems duplicative to include more information in a regional appendix, at least for risks and new information not classified as important. If it is the intent that, in these circumstances of proposed amendments to the Reference Safety Information and, hence SmPC, the full assessment report is included in the regional appendix, then this should be made clear. EFPIA consider that a full assessment report would only be needed for risks/new information classified as important.

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		• This comment also applies to modifications of other sections of the SmPC, with the understanding that some risks will warrant inclusion in both 4.4 and 4.8. In the latter circumstance, the MAH is unlikely to wait for the PSUR to notify the authorities • Taking into account the fact that some PSURs may cover intervals of up to several years, there will be circumstances when a variation to amend the SmPC has already been submitted and being processed as the MAH considered that it was inappropriate to wait until submission of the PSUR. In such circumstances, it should be clear that it is not necessary for the MAH to submit the same information again with the PSUR but noted, for example in sections 16.2 or 16.3 (for example) Proposed changes to this new paragraph take into account the points made above, to be consistent with instructions in the relevant sections of the PSUR and proportionality principles. Proposed changes: When the proposals for the product information include new adverse reactions in section 4.8 (Undesirable Effects) of the SmPC or modifications in the description, frequency and severity of the existing reactions, marketing authorisation holders should provide in the PSUR, ~~detailed information~~ **an evaluation of the closed signal that became a risk (ADR) or new information on a known risk (ADR) in sections 16.2 or section 16.3, as appropriate. It is recommended that the level of the evaluation should be proportional to the available evidence on the risk and its medical significance and public health impact. The level of detail in these sections should be concise but sufficient to clearly describe the basis on which the signal was considered to be a risk and included in the adverse effects section (4.8) of the SmPC. For risks not classified as important or new information on a known risk not classified as a signal, the evaluation summaries in 16.2 and 16.3 should provide an appropriate level of detail for assessment. For new ADRs considered to be important risks (e.g. involve a new or modified warning /precaution or where analyses indicate a clinically meaningful change in severity or frequency of a known risk), detailed information should be provided by the MAH** ~~the adequate description and classification of the frequency of the adverse reactions~~. If other sections of the SmPC

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		(e.g. SmPC section 4.4 Special Warnings and Precautions for use) are considered to be updated, clear proposals should be provided for the competent authorities in the Member States to consider during the PSUR assessment. The **detailed analyses and** proposals should be included in the PSUR regional appendix(VII.C.5**.1**)
1298-1305 1597–1598 1654-1655 1623-1626 1693-1696		Comment: This links to previous comments made in relation to the stipulated timelines for review of the PSUR, particularly for reports on a six month submission cycle. For such reports, it is logistically very challenging, if not impossible, to adequately address multiple requests for additional analyses/reviews and still be in compliance with the submission deadline for the next PSUR as this will already be in preparation at the time of receipt of the final AR. Furthermore, MAHs may not receive the PAR until after Day 60 which compounds the situation further. The new statements in lines 1622-1626 and 1693-1696 appear to impose an additional requirement on MAHs to provide responses (in addition to comments) to outstanding issues and questions raised by the PRAC Rapporteur/MS in the preliminary assessment report *and which can be addressed within the timeframe of the comments phase*. Therefore, responses would need to occur in a 30 day timeline or even less if the PAR is delayed; in practice MAHs may actually only have 1-2 weeks to respond. Irrespective of the period covered by the next PSUR, this is an unrealistic expectation unless the requests are few, relatively straightforward and of a non urgent nature. In these circumstances, for PSURs on a six month cycle, it would be more efficient to address with the next PSUR under preparation at the time of receipt of the final AR. EFPIA appreciate that a caveat ("can be addressed") is implicit in the wording but is concerned that, as currently written, it will set an expectation that **all** issues and questions raised should be addressed by the MAH in this short time line. It is important, that analyses provided in response to questions are robust and conducted to appropriate quality standards so an expectation for all responses to be routinely provided in a 30 day or shorter timeline would be inappropriate. Clearly timely receipt of the PAR on Day 60 will facilitate a timely response by the MAH.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed changes: By day 90, the marketing authorisation holder and members of the PRAC may send comments on the PRAC Rapporteur`s preliminary assessment report to the Agency and the PRAC Rapporteur. Those comments **may, if possible,** ~~should~~ also include responses to outstanding issues or questions raised by the PRAC Rapporteur in the preliminary assessment report**.** ~~which can be addressed within the timeframe of the comments phase.~~ **or proposals for alternative submission timelines by the MAH for consideration by PRAC e.g. for PSURs on a six monthly submission cycle it may be more efficient to respond to routine and limited requests in the next PSUR. Consideration of response timelines should take into account proportionality principles including medical significance, the extent and complexity of the requests and need to provide a quality analysis.** **Note : Equivalent changes are proposed for lines 1693-1696**
1856-1858		Comment: Taking into account comments made earlier with respect to documentation needed to be submitted to support proposed changes to the SmPC, the following amendment is needed to these lines Proposed change : Marketing Authorisation Holders should provide the necessary supportive documentation and references within the **relevant sections of the** PSUR **or in this appendix, as appropriate.** to facilitate this **assessment.**
1871-1873		Comment: This new wording indicates that all the SmPCs and package leaflets should be reviewed to ensure that they reflect the appropriate information according to the cumulative data included an analysed in the PSUR. This wording is very vague and ambiguous, especially if the time interval covered by the PSUR is several years. In these circumstances, changes may well have already been submitted and reflected in the SmPC in place at the DLP. 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')*
		All the SmPCs and package leaflets covered by the PSUR **and in effect at the DLP** should ~~be reviewed to ensure that they~~ reflect the appropriate information according to the cumulative data included and analysed in the PSUR. **If a variation to amend the SmPC has already been submitted to reflect new information included in analyses summarised in the PSUR but is not approved at the time of the DLP or is approved after the DLP but before submission of the PSUR, this point should be noted.**
1925- 1926		Comment: The wording in this section is not consistent with the intent of section VII.B.5.16.5 which should reflect broad global experience on effectiveness of risk minimisation activities where this is applicable and have utility across regions. This point takes into account that effectiveness of any measure is specifically linked to the local healthcare system. Proposed changes: In accordance with section VII.B.5.16.5, evaluation of broad global experience should be reflected in the body of the report, **when insights into the effectiveness of risk minimisation activities in any country or region may have utility in other countries or regions.**
2125-2127		Comments: This section relates to submission and availability of documents before the Agency`s repository is in place. The lines highlighted originally only included provision for comments on the preliminary assessment report submitted by MAHs and members of PRAC to be circulated by Day 90. The new wording stipulates that these comments should also be circulated to all members of PRAC by the MAH. As currently worded, this could be interpreted that the MAH(s) should circulate all comments from all sources to all members of the PRAC. EFPIA assume that this is not the intent of this statement. If the intent is that it is only the comments of an individual MAH should be submitted to all members of the PRAC by that MAH, then this needs clarification. It should also be borne in mind that, as a transitional arrangement this may be acceptable to MAHs but PRAC members would equally need to understand that they are likely to receive multiple comments through multiple channels at different times by many different MAHs. This is hardly efficient and EFPIA consider that MAH comments are better collated and circulated by EMA at one

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		time to PRAC members. As a result, EFPIA`s preference is that this new sentence is deleted altogether. Proposed changes: Preference 1: comments submitted by the marketing authorisation holder(s) and members of PRAC by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report. ~~These comments should also be circulated to all members of the PRAC by the marketing authorisation holder~~ Preference 2: comments submitted by the marketing authorisation holder(s) and members of PRAC by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report. ~~These~~ ~~c~~ **C**omments **from an MAH during this transition period only** should also be circulated to all members of the PRAC by **that**~~-c~~marketing authorisation holder.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on 'GVP Module VII – Periodic safety update report' (EMA/816292/2011 Rev 1)

Comments from:

Name of organisation or individual
EGA - EUROPEAN GENERIC MEDICINES ASSOCIATION Rue D'Arlon 50 B-1000 Brussels Belgium

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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	The EGA welcomes this opportunity to comment on the first revision of the GVP on periodic safety update reports. Although we fully understand and support the intention of proposed module, the EGA members would like to advice and have a few comments.
	Is there a possibility to create a list of abbreviations that can be used for all GVP modules?

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')*
226		"comprehensive" or "concise" Proposal: "comprehensive and precise"
303		As the PSUR should be a single stand–alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will only ~~not~~ be accepted in exceptional circumstances.
433		Add also "Terminated clinical trials"
440		It is not plausible why "medication errors" should be a subtitle of "Information from other clinical trials and sources". "Medication errors" should have an own title
619		…may include overdose, abuse, addictions, misuse….
755		Additional PSUR sub-section: "safety aspects related to medical devices packed to the drug"
823		asymptomatic overdose, abuse, addictions or misuse;
902		plans for further evaluation, when relevant; and
1791		detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable [DIR Art 107g(2)]. Where appropriate, the Agency may request for raw data from clinical studies to reinforce a scientific conclusion.
1867-1870		A molecule that is registered in a DCP can have hundreds of MAs connected with this molecule for which a PSUR is written. If a safety related change to the product information is proposed based

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		on the PSUR data, this may refer to hundreds of SmPCs & PILs worldwide that need to be updated. Since time is limited for PSUR submission to 70/90d, it may be impossible to arrange and collect all the SmPC & PIL updates in time for inclusion in the PSUR. Therefore, we propose to rephrase the requirement to: “A track change version of the proposed reference product information ~~SmPCs and package leaflets~~ based on the assessment and conclusions of the PSUR should be provided.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25-Jun-13

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
F. Hoffmann-La Roche Ltd

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

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment: The Guideline on Good Pharmacovigilance Practices does not make the same distinction between "authorized" and "approved" made by the ICH Guidelines E2C (R2) on PBRERs (see footnote on page 6 of that document). Consistency regarding this point affects several areas of text and headings. Recommend that clear, consistent instructions be provided regarding this terminology.

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')*
754		Comment: Please define ‘particular patient use’. Proposed change (if any):
719-723, 840-844, 1101-1114		Comment: Please clarify what information on ‘lack of efficacy’ should be included in section 7, 13, and 17, respectively. Proposed change (if any):
1597 and 1654 (process maps)		Comment: Figure VII.6 and Figure VII.7. PSUR assessment procedure for a single centrally authorised medicinal product and for "EU single assessment" is shown. Proposed change (if any): Please amend the process flow for CAP products (Line 1597) to match that of a NAP (Line 1654) when subsequent PRAC recommendation is reached. If no variation, suspension of the marketing authorisation is recommended the PRAC recommendation is sent to MAH and the procedure will be closed. Visualization of the process flow for CAP products needs to be updated accordingly in line with the NAP process flow.
1597-1755		Comment: Allow possibility for discussion within the process on controversial points. Proposed change (if any): MAH recommends considering the possibility allowing discussion between MAH, Rapporteurs (PRAC Rapporteur/CHMP Rapporteur, RMS or NAP) on controversial points (e.g. clock stop).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 consider the clock stop approach would be in line with the Type II variation procedure and would allow all key stakeholders to have sufficient time to submit high quality data considering all possible aspects have a thorough review and reach a consensus on a high quality wording for the label.
1629		Comment: Circulation of updated PRAC assessment report Proposed change (if any): The guidance should include dissemination of the updated PRAC assessment report to the MAH. Otherwise the MAH has no means to know if he/she shall proactively ask or not for a PRAC Oral explanation in case major disagreements remain after the first comments phase.
1630-1632, 1701-1703		Comments: Contact and Time Point for the Oral Explanation to be clarified Time point for the request of an oral explanation by MAH should be specified. Clarification on the contact point(s) for request on an oral explanation in case of CAP products, MRP and NAP (i.e PRAC contact, project leader (PTL), RMS, NCA). Proposed change (if any): Clarification please

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd

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When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
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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')*
534		Comment: Text deviates from text provided in ICH E2C (R2): 'significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated.'
2168-2171		Comment: Table heading and column heading deviate from text provided in ICH E2C (R2). Footnote is not in ICH E2C (R2) and is unnecessary Proposed change (if any): **Table VII.8.** Numbers of adverse reactions by preferred term from post-Marketing sources SOC MedDRA PT | Spontaneous, including regulatory authority and literature | Non-interventional post-marketing study and reports from other solicited sources ** Serious | Non-serious | Total Spontaneous | Serious Interval | Cumulative | Interval | Cumulative | Cumulative | Interval | Cumulative <SOC 1> <PT> ~~* Non-interventional post-authorisation studies, reports from other solicited sources and spontaneous ICSRs (i.e., 2169 reports from healthcare professionals, consumers, competent authorities (worldwide), and scientific literature)~~ ** This does not include interventional clinical trials.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
Janet Taylor Consultancy Ltd

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It would be helpful to have further ‘best practice’ guidance from Regulators on those Sections where MAHs may not be meeting their expectations.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
309 and 336-339		Comment: Please confirm if a list of all authorised indications in all ICH regions is required if the PSUR is only due to be submitted in one ICH region. Proposed change (if any):
781-789		Comment: This introduction does not include 'medication errors' although there is a subsection. Proposed change (if any):
790		Comment: Should this be 'Other clinical trials **and sources'**? Proposed change (if any):
718		Comment: Please clarify section Proposed change (if any):
1098-1100		Comment: Please can further clarification be provided using examples e.g. recently approved products, older products of the type of information expected and volume of information required (e.g. is it necessary to re-present data in the MA application). Further clarification would be helpful. Proposed change (if any):
1118-21		Comment: Further guidance is requested on what level of detail is expected (see also comment on 1098-

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		1110). For example is it expected to re-justify the authorised indication for a recently authorised product and re-present data from the original dossier? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (Rev 1) (EMA/816292/2011)

Comments from:

Name of organisation or individual
Merck Sharp & Dohme (MSD)

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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')*
308-309		Comment: It is recommended that the reference label should be the companies CCDS and not authorised indications per individual countries. Proposed change (if any): "….the reference product information document should list all ~~authorised~~ indications ~~in ICH countries[3] or regions~~ *that are defined in the CCDS*."
464-465		Comment: The IBD should refer to the first MA granted to **any company in any country** in the world. However it is unclear how this information could be obtained as it might not readily be available to the company (if the product is not included in the EU RD list). Proposed change (if any): Remove "to any company" or explain how to obtain the information.
528		Comment: It is unclear why a failure to apply for a marketing authorisation renewal is a safety issue. Perhaps there is just no further commercial interest by the company? We recommend adding safety reasons for clarity. Proposed change (if any): "failure to obtain or apply for a marketing authorization renewal *for safety reasons*;
531		Comment: "Suspension of supply by the marketing authorisation holder". We recommend adding a clarification that this relates to suspension for safety reasons. Proposed change (if any): "suspension of supply *for safety reasons* by the marketing authorisation holder

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
598		Comment: Routine presentation of exposure by various breakdowns is not feasible as the Company has found that most databases used (e.g. IMS) do not have this information. Proposed change (if any): In addition, the data should be ~~routinely~~ presented by sex, age, indication, dose, formulation and region, ~~where applicable~~ *when available*.
621-628		Comment: While the Company may become aware of off label use resulting in AEs reported in the PSUR, off label use is not endorsed in any way by the Company. Proposed change (if any): *It is recognized that Marketing Authorization Holders do not endorse off label use of their products. However, ~~i~~if* known, the marketing authorisation holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. If quantitative.....the PSUR (e.g. authorised indication, contraindications).
619-620; 784; 797-802		Comment: Description of patterns of use is required here (overdose, abuse, misuse, etc). However it is unclear whether this should be linked to section VII.B.5.9 for AE information. There is only a subsection dedicated to medication errors. Proposed change (if any): Clarify the use of the new template with regards to medication error, overdose, abuse, etc.
719-723		Comment: Considering the presence in the PSUR of a standard section titled “Lack of efficacy in controlled clinical trials,” it is curious to find a requirement to discuss selected evidence of lack of efficacy in controlled clinical trials in this section, and other evidence of lack of efficacy in controlled clinical trials in a different section of the PSUR. The instruction to separate such discussions by whether the product is intended to treat

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"serious or life-threatening illness" or "non-life-threatening diseases" is also somewhat ambiguous, as a product intended to treat a serious but non-life-threatening condition could fall under either category. Proposed change (if any): Suggest that all information about clinically important evidence of lack of efficacy in controlled clinical trials be included in section 13 "Lack of efficacy in controlled clinical trials," irrespective of the therapeutic indication of the product of interest.
771-772		Comment: The parenthetical cross-reference "(see VII.B.5.7 for the information that should be included in the listing)" would be more relevant to the following paragraph, instead of to the paragraph to which it has been appended. Proposed change (if any): Relocate the parenthetical cross-reference to the end of the **second** paragraph in this section (section VII.B.5.8), immediately following the sentence, "The marketing authorisation holder should include an appendix listing marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval."
839		Comment: This section refers to summary of information obtained from other MAHs. We recommend that information should be included in this section if the other MAH independently writes the PSUR and sends a courtesy copy. If MAHs were sharing ICSRs and having a global database assigned, it should be stated that only one PSUR would be expected. Proposed change (if any):
910–913		Comment: This instruction to place reviews of a "topic (not considered a signal)" in the PSUR section titled "Overview of signals" creates potential for confusion and misinterpretation. Each signal that is included in 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')*
		PSUR has undergone a careful signal validation process to determine that there is sufficient evidence for a potential association to justify further analysis. Section 15 “Overview of signals” documents the results of this validation process. If “topics not considered signals” are also placed in this section, the distinction between these topics and the true, validated signals becomes blurred. Proposed change (if any): Suggest that “topics not considered signals” be placed elsewhere in the PSUR, for example, in PSUR Section 9 “Information for other clinical trials and sources,” where the guidance already has placed the reviews of other safety topics such as overdose, abuse, off-label use and medication error.
938		Comment: “this section can be **either the same** as, or **derived from** the safety specification summary”. We suggest clarification which amendments are intended and to clarify what would be the trigger for the amendments. Proposed change (if any): To clarify the expectations of the new wording.
1867-1873		Comment: • Confirm that for CP products the proposed product information should be provided twice, once in EU Appendix and then in section 1.3.1 of eCTD. • Detail the process to follow for national products and whether the proposed product information should only be included in the EU Appendix. Proposed change (if any):

Please add more rows if needed.

14 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
Mundipharma Research GmbH & Co.KG

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We understand that the last page of the current version of GVP module VII (therein rightly termed „template for cover page for PSUR submission") has been taken out of the revised version of module VII to become an extra Annex II. Within that Annex II, the header now reads "Cover page of Periodic Safety Update Report (PSUR)". In our opinion this is quite misleading for some parties – we learnt from discussion with other companies that some believe this template should reflect the first page of the actual PSUR/PBRER document. We quite strongly believe that the long list of *European* product data would not belong onto the first page of the PSUR itself as this represents a document for *global* use, but rather into the accompanying cover letter as used for submissions in the EEA. Proposal: The template header should be renamed to reflect that it reflects the template for the cover letter accompanying the submission of the PSUR document (it is not intended to be used as the first page of the actual PSUR).

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
lines 1867 through 1873		**GVP text:**: A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed product information should also be submitted to Module 1.3.1 of the Electronic Common Technical Document (eCTD). All the SmPCs and packages leaflets covered by the PSUR should be reviewed to ensure that they reflect the appropriate information accordingly to the cumulative data included and analysed in the PSUR. **Comment:** We would like to request clarification on these sentences. Where multiple SmPC/PLs exist for a given medicinal product (e.g. multiple national licences and different formulations) how will this be accomplished? Will it be acceptable for the MAH(s) to submit a summary of the proposed changes to a given SmPC/PL section? We understand that the statement in line 1871 refers to the need to review all SmPCs of the products covered by the PSUR independently of the PSUR submission and that there is no expectation to submit all SmPCs together with the PSUR. **Proposal:** The proposed new text parts for implementation into the local EU SmPC(s) and package leaflet(s) by variation should be summarised into one document and included as an appendix to the PSUR.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25th June 2013

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1)'

Comments from:

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

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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)
	Novartis welcomes the opportunity to comment on the revised GVP modules VII – Periodic Safety Update Report.
	Currently Novartis has had experience with PSUR assessment of centrally authorized products (CAP) only. Therefore, all our comments relate to our experience so far.
	Novartis notes that certain elements of this GVP are yet to be implemented (PSUR repository, single assessment) and would welcome some transparency on when these will be implemented, and on whether any GVP update triggered by this implementation will be circulated for consultation prior to implementation.

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')*
58 and 780		**Comment:** Novartis proposes that the title "Information for other clinical trials and sources" is changed to "Information from other clinical trial and sources".
153 -223		**Comment:** Novartis proposes that a reference is made to the *Guideline on good pharmacovigilance practices (GVP): Product-or population-specific considerations I: Vaccines for prophylaxis against infectious diseases* in the introduction of the GVP module VII as this product-specific guideline contains information on special considerations for vaccine PSURs.
186-187		**Comment**: In order to ensure completeness of the introduction Novartis proposes modification of the wording and specifying that all the pertinent and available data sources have to be reviewed by the MAHs that they should integrate evidence from the different available data sources. Proposed change (if any): The PSUR should focus on summary information **from all pertinent and available data sources, resulting in** scientific safety assessment and integrated benefit-risk evaluation.
239-241, 1630-1631		**Comment:** While lines 239-241 clearly indicate that the "PSUR should not be used to provide initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted", there is no clear guidance in the GVP on the extent of the changes to product information (PI) a PSUR procedure may trigger. It would be helpful to have an indication of the scope of changes a PSUR may acceptably trigger and of the scope of changes when a separate variation should be filed. While it is clear that a PSUR procedure can change SmPC 4.8 or 4.4, lines 1630-1631 imply that changes to SmPC 4.1, 4.2 and 4.3 are also possible, but it is not clear if the procedure could also trigger changes to SmPC 5.1 or 5.2.
261-263		**Comment:** This paragraph suggests that the benefit-risk (B/R) profile of the product should be based on all authorised indications. However, this contradicts somewhat the principle outlined later in the document (lines 1153-1156) that explains that B/R is different for each indication, as the unmet medical need and analysis of the condition are indication-dependent. Therefore, Novartis proposes that the requirements on B/R evaluation across the GVP module are aligned.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
306 - 318		**Comment**: The revised GVP module suggests that the reference product information for the PSUR should include authorized indications in all ICH countries. Novartis would like to point out that the Global Core Data Sheet (CDS) which is attached to the PSURs represents the company position and the indications that are supported globally. If there is a difference in the indications from the CDS, this is typically due to local requests from the HA and there may be limited data to support those thus justifying their non-inclusion in the CDS. Having these indications listed in a global document (such as a PSUR) could be seen as encouraging the use of the product in these indications in other countries. Therefore, Novartis believes that it is appropriate that the PSUR includes only information on the indications that are supported by the global CDS. Hence, we propose that the text related to providing information on the authorized indications in all the ICH countries is removed from the GVP module VII.
367 and 378		**Comment:** Novartis suggests to harmonize the wording and use the following term "data sources" **Proposed change (if any):** • "The PSUR shall be based on all available data sources and shall focus on …" • "Examples of data sources of efficacy, effectiveness and …"
398 - 399		**Comment:** Not all data sources are free from systematic biases, so in cases where the Marketing Authorisation Holder (MAH) is using less conventional data sources, such as claims databases, it will be important to understand whether it will be necessary to describe the limitations of these data sources. If this is expected, it should be also defined where in the PSUR this information should be provided.
597 - 598		**Comment:** It has been clarified that the data on sex, age, indication etc. should be provided routinely; however, at the end of the sentence there is also a statement "where applicable". The current text as it stands could be perceived as confusing. Therefore, Novartis proposes modification of the text. **Proposed change (if any): "**An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, ~~where applicable~~ **when available**."
717-718		**Comment:** In the revised GVP module it is suggested that findings from clinical trials not sponsored by the MAH should also be described in the PSUR. Based on the current statement, it is unclear what is meant by clinical trials "not sponsored by the MAH". It will be essential for the MAHs to have clarity on whether this

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		term is referring to those trials conducted by the contractual partners or for all clinical trials that are not sponsored by the MAH. Additionally, specific guidance on where in the GVP module the information on clinical trials "not sponsored by the MAH" should be provided is necessary.
719-723, 840-844		**Comment:** Currently there is no definition of the terms drug used to treat life threatening disease, drug used to treat non-life threatening disease, and drug used to treat serious illness in the context of the GVP module. Therefore, Novartis suggest that more clarity on what parameters should be used to determine if a drug is used to treat a life-threatening versus a non-life threatening illness as well as a serious illness is provided.
750-754		**Comment**: Sub-section 7.4 is intended to capture clinically-important safety info from clinical trials (CTs) conducted in other therapeutic uses (as per the section title). However, further on in the text it is mentioned that the section is intended to capture "other programmes conducted by the MAH that follow a specific protocol, with solicited reporting" (i.e. compassionate use, expanded access, etc.). Therefore, Novartis suggest that the title is changed to reflect the requirements of the section. **Proposed change (if any):** "Other Specific therapeutic uses of the medicinal product"
781-787		**Comment:** Novartis acknowledges that there is a cross-reference between sub-section 5.9 and GVP Module VI-Management and reporting of adverse reactions to medicinal products. However, Novartis believes that alignment of the text between the two modules would bring further clarity. Therefore, Novartis proposes that the following information from module VI is also reflected in sub-section 5.9: 1) "reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable" and 2) "reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be reported, but should be discussed in periodic safety update reports as applicable."
781-787, 796-802		**Comment:** In the introduction of sub-section 5.9, there is a mismatch between the introductory paragraph of the sections and the sub-sections titles. In the introduction it is described that information obtained from other sources outside of a study environment with examples including overdose, abuse, misuse, off-label use, etc. should be listed in this section. However, later on in this section, there is a sub-section on other clinical trials and on medication error. Novartis proposes that the term medication error is included in 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')*
		introductory paragraph of this section. Additionally, clarification is needed on where in this section information on misuse, abuse and off-label use should be provided.
807-808		**Comment:** It is mentioned that the findings from the non-clinical data should be discussed in the "relevant evaluation sections of the PSUR". Novartis suggests that clarification is provided on the specific evaluation sections of the PSUR where findings from the non-clinical data should be provided.
829 -839		**Comment:** Novartis acknowledges that this section will not be routinely used for all the products but only in the cases where there are separate PSURs for fixed-dose combination products or products with multiple formulations and/or indications where multiple PSURs are available. Therefore, we suggest that the title of this section is changed to "other periodic safety update reports with the same active substance".
893 -903, 2172-2177		**Comment:** Currently there is a discrepancy in the text describing what is to be included into the signal tabulation (line 893-903) and table VII.9 and in the appendix (line 2172-2177). The following information is not mentioned in the Appendix "a brief description of the signal" and "plans for further evaluation" as part of the example signal tabulation. Novartis requests clarification on whether these two pieces of information are required in the tabulation.
910-913		**Comment:** In certain cases the MAHs are historically monitoring topics based on HA requests which are not related to signals or on-going risks. For these topics the current level of review may be more in depth than expected in section Sections 15 and 16. Guidance on where this information should be provided in the PSUR will be appreciated.
912-913		**Comment:** In order to align with line 963-964, Novartis would suggest wording modification as described below. **Proposed change (if any):** If the specific topic becomes a signal, it should be included in the signal tabulation. **If, additionally, this signal is closed, it should still be included in the signal tabulation** and discussed in sub-section 16.2 ("Signal evaluation").
914		**Comment:** Currently there is no location where the general methodology/approaches taken for the risk evaluation and risk characterisation are provided, in particular the type of analyses conducted in each data sources and their objective. Therefore, Novartis would like to request clarification in which section/subsection general methodology/approaches used for risk evaluation (Sub-section 16.3) and characterisation (Sub-section 16.4) can be described by the MAH.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
992		**Comment**: Currently the guidance does not provide examples of analytical approaches. Therefore, giving specific examples of potential analytical approaches (such as Bradford-Hill criteria application for establishing the plausibility of a causal relationship between the drug and a type of event) can be helpful for the MAH.
1082–1084		**Comment**: The GVP module suggests that results of evaluations which refer to the individual regions should be provided in the regional appendix. It is also specified that these results should be provided only "when required for reporting in the PSUR". Novartis would appreciate clarification and specific examples on regional evaluations that would be required for PSUR reporting.
1209		**Comment:** In certain cases the MAHs may need to provide additional appendices to support Section 16 data. Therefore, it would be important for the MAH to have explicit guidance on whether additional appendices can be added (i.e. response to requests from other health authorities).
1298-1305		**Comment:** Novartis believes that the PSUR procedure – general process can be further improved. Novartis would like to raise a concern that in the current process both the MAH and the PRAC Members in the Member States (MSs) comment at the same time on the PSUR Preliminary Assessment Report (PrAR). As a result, the MAH has no chance to see the comments from the MSs and to provide feedback on those. This leads to late involvement of the MAH in discussion on potential changes to the product information (PI) and requests from PRAC to submit final labelling text in very short timeframe (e.g. one or two days, or even less). We believe that the quick review and finalisation of new text for the product information can lead to misinterpretation of the data and/or misleading labelling text which in our opinion is not in the interest of public health. Therefore, we recommend the following improvements of the current process. • First, we propose that the 30-day review period is clearly separated into a period for commenting by MSs followed by a period for commenting by MAHs. MSs could provide their comments on the PrAR in a shorter period of time (e.g. 15 days) and their comments could then be shared with the MAHs, giving the MAH 15 days to address any concerns that may have come out of the MS review. • Secondly, for centralized products the point of contact for the MAH is the PTL. Therefore, ensuring good communication between the PRAC secretariat and the PTL **prior to and during** the PRAC meeting is the best way of warning the MAH of any upcoming discussion that may impact the PI. This will improve the current procedure and the preparedness of the MAH.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		• Lastly, another round of comments (incl. MAH) and final agreement on the labelling text can be integrated in the 30-day period allowed between the PRAC recommendation being received by the CHMP and the CHMP issuing its opinion (as described in graph p. 49). We believe that by utilizing the suggestions above the PSUR review process will be optimized and the outcome of the review will be of a higher quality and will better contribute to patient safety.
1597-1598		**Comment:** Overall Novartis would like to recommend clarification in the term "variation" used in the revised GVP module. We understand that amendments to the SmPC, PL and labelling as a result of the PSUR assessment should be implemented without a subsequent variation procedure for centralised products (CP) and through the appropriate variation procedure for the national, MRP and DCP registered products. However, in table VII.6 the term "variation" is used as a possible PRAC recommendation to CHMP for centralized product. We suggest that this term is changed in order to avoid confusion with the regulatory procedure of submitting a variation. Alternative terms that could be used for the CP are PRAC recommendation for an "update" or a "change" of the Annexes.
1831-1846		**Comment:** Novartis has noted that in the new Pharmacovigilance legislation MAH comments on the RMP preliminary assessment report are not envisioned. In certain cases there have been exceptions to the process and the MAH has been allowed to respond to questions related to the RMP as a part of the comments sent with the PSUR PrAR. Novartis believes that giving the company position on the RMP feedback as a part of the PSUR PrAR comments is valuable for all the stakeholders. Therefore, we suggest that this process is clearly reflected in the GVP module VII and GVP module V.
1867-1870		**Comment:** The revised GVP module VII suggests that a tracked change version of the SmPC and the PL based on the conclusion of the PSUR for CP should be submitted to module 1.3.1 of the eCTD. Novartis believes that in order to streamline the process it would make better sense to submit an eCTD closing sequence to update module 1.3.1 once the PSUR procedure is finalized.
1874-1878		**Comment**: Novartis proposes that further clarity needs to be provided regarding submission of amendments to the PI that are not related to information presented in the PSUR. We believe that if new efficacy or safety data emerges during the time of the PSUR preparation it will make sense that this information is provided and assessed during the PSUR procedure rather than by submitting a parallel variation. In case a safety signal is

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		emerging during the preparation of the PSUR a parallel variation can be filed however a mechanism of cross reference should be in place to avoid “double review”. This would ensure that the assessors are looking at the most up-to-date risk-benefit profile of the product.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
Reckitt Benckiser Brands 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')*
Lines 306-316 AND Line 327		Comment: The CCDS currently used by Reckitt Benckiser does not list all indications for the active(s). A separate document will need to be appended to the PSUR as required, but what would be the extent of the indications as this varies from country to country. We propose to provide this information by brand, i.e Brand 1, Brand 2, Brand 3, or is this to be provided by country/indications/strength? Proposed change (if any): N/A
Lines 357-359		Comment: Clarification is requested on what would constitute a 'final' change. We consider that once a proposed change is finalised it becomes approved and therefore part of the authorised product information and as such ceases to be a change. We therefore propose to remove the word final from the text. Proposed change (if any): If stipulated by applicable regional requirements, the marketing authorisation holder should provide, in the regional appendix, information on any ~~final,~~ ongoing and proposed changes to the national or local authorised product information (see VII.C.5.).
Lines 1203-1208		Comment: Although we agree that the MAH should draw conclusion in the PSUR regarding a general need for updating specific sections in the SmPC, based on the evaluation of cumulative safety data and the risk-benefit analysis, we do not consider that any specific proposals should be made in the PSUR regarding amendment of the package leaflet. Should the need arise for the SmPC to be updated then the package leaflet would get reviewed by the MAH and relevant proposed amendments will be carried out via a variation. Particularly, for national licences the

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		package leaflet is usually amended by the relevant local affiliates in their own language based on the proposed SmPC. As such, we do not consider that any specific proposals should be made in the PSUR regarding the package leaflet. Proposed change (if any): Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved summary of product characteristics (SmPC) for the product(s) for which the PSUR is submitted [IR Art 34(5)]. The regional appendix should include proposals for product information (SmPC only ~~and package leaflet~~) together with information on ongoing changes when applicable.
Lines 1268		Comment: Reckitt Benckiser is an OTC drug company and does not develop new drugs. A risk/benefit analysis is provided as part of the PSUR. Will there be detailed guidelines on assessing a risk/benefit analysis? Proposed change (if any): N/A
Line 1269		Comment: PSURs would not be the appropriate forum in which to submit adequate proposals for the update to local product information. A company will submit variations if any updates to the local product information is needed. We are therefore proposing to remove this sentence in its entirety. Proposed change (if any): ~~Failure to provide adequate proposals for the local authorised product information~~

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Lines 1864-1866		Comment: See above, as per our comment for lines 1203-1208. In addition, we consider that is sufficient for the MAH to provide within the PSUR a general recommendation to update specific sections of the SmPC without the need for the specific wording to be dictated in the PSUR. Proposed change (if any): In this sub-section, the marketing authorisation holder should provide the proposals for product information (SmPC ~~and package leaflet~~only) based on the above mentioned evaluation. It is sufficient for the proposal to include recommendations for updating specific sections of the SmPC, without indicating the exact proposed wording. These should be based on all EU authorised indications.
Lines 1867-1870		Comment: We consider that the PSUR is not the correct forum for submitting or proposing the actual tracked changes that need to happen in the SmPC and indeed the package leaflet. Although we agree that a general recommendation to update specific sections of the SmPC may need to be made as a result of the benefit-risk analysis, we do not consider that a tracked version of the SmPC and package leaflet needs to be provided. We maintain that it is sufficient to provide a commitment to update the product information as required, without the need to propose specific wording within the PSUR. Considering the strict timelines for PSUR submission and the cross functional reviews that would be required in order to agree a proposed product information we believe that this requirement would complicate the process, stretch the timelines and as result increase the likelihood that errors are made. In addition, we request clarification as to the actual sequence of events should we be required to provide a tracked proposed SmPC and package leaflet with the PSUR. Specifically, would we need to wait for comments on the proposed product information prior to submitting the updates? Furthermore, what would happen should the authorities not agree with our recommendations and proposal? We believe that tracked proposed SmPCs and package leaflets should only be submitted with a variation and not with the PSUR. We therefore propose to remove the complete section Lines 1867-1870, inclusive.

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		Proposed change (if any): ~~A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed product information should also be submitted to Module 1.3.1 of the Electronic Common Technical Document (eCTD).~~
Lines 1871-1873		Comment: See above, as per our comment for lines 1203-1208. Proposed change (if any): All the SmPCs ~~and packages leaflets~~ covered by the PSUR should be reviewed to ensure that they reflect the appropriate information accordingly to the cumulative data included and analysed in the PSUR.

Please add more rows if needed.

2013.06.21

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

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

2. Specific comments on text

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297-299		Comment: "Partner" referred to in verses 297-299 should be further defined. The text suggests that data provided by a partner normally need not be analysed in the PSURs. For better clarification "partners" are recommended to be defined as other MAHs having their own pharmacovigilance obligations and preparing their own PSURs – in such case additional inclusion of meaningful information from Partner is justified. Please see our proposals in green. Proposed change (if any): When data received ~~at~~ *by* the marketing authorisation holder from a partner *company, having its own pharmacovigilance obligations (e.g. different MAH of medicinal product with the same active substance, another MAH from CMS/RMS participating in Mutual Recognition or Decentralised Procedure) and preparing its own PSURs,* might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorisation holder's product information, these data should be included and discussed in the PSUR.
327-329		Comment: Does it mean that more than one document for a particular product can be used as RSI? It should be further specified. Please see our proposals in green. Proposed change (if any): When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR. *In such situations, MAH can use more than one document as reference safety information.*
331-335		Comment: It should be specified whether SmPC could be in (a) national language or (b) in English. Please see our

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		proposals in green. Proposed change (if any): When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one country or region, or for established/generics products on the market for many years), the marketing authorisation holder should clearly specify the reference information being used. This may comprise national or regional product information such as the EU summary of product characteristics (SmPC). *(a) Such reference information may be in a national language.* *Or* *(b) Such reference information should be in English.*
336-339		Comment: This is a little bit confusing. Please see our proposals in green Proposed change (if any): Where the reference information *(CCDS)* for the authorised indications is a separate document to the reference safety information (the *CCSI* core safety information contained within the reference product information), the version in effect at the end of the reporting interval should *also* be included *within the* ~~*as an*~~ appendix *no. 1* to the PSUR (see VII.B.5.20.).
464 – 465 and further		Comment: Please consider the redefining of the IBD. According to the definition it is the date of the first MA for any product containing the active substance granted to ANY company in any country in the world. It is not possible to define IBD for MAHs not being originator, there is no place where the IBD can be found. But first of all it is required to provide sales data or adverse reactions reports cumulatively since the IBD – it is not possible for generics companies to have such data if the IBD is defined as above. Moreover even if IBD is calculated as the date of the MA of the originator, sales and adverse reactions data from IBD are known to generic companies the addition of MAH data to the originator data has no sense. Each company has at its disposal only data from its own first MA in the world not MA of any company in the

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		world. Proposed change (if any): (…) the date of the first marketing authorisation for any product containing the active substance granted to ~~*any*~~ *the interested* company *preparing PSUR* in any country in the world (…)
561-562		Comment: Please define “old products”. Does it mean that when such detailed data are not available or when it is not possible to receive them, the product might be considered as an “old product”?
598		Comment: Addition of “where applicable” is not clear, as data may be applicable but not available. Since such data are available in very rare cases it should remain as previously “where available”. Proposed change (if any): An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where ~~*applicable*~~ *available*.
717 - 718		Comment: The sentence suggests that MAH should describe all trials not sponsored by MAH. Proposed change (if any): *If available for MAH* findings from clinical trials not sponsored by the marketing authorisation holder should be described in the relevant sections of the PSUR.
783- 785		Comment: Does the available information on reports of use beyond that recommended in the RSI means off label use? which is normally described in point 5 estimated exposure and use patterns? Proposed change (if any): For example, this would include available information on reports of asymptomatic overdose, abuse, use

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		beyond that recommended in the reference product information *(e.g off-label use)*, or use in special populations
856-858		Comment: It is not clear which period is meant: period covered by PSUR or period after DLP and PSUR preparation. Proposed change (if any): Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during ~~*this*~~ *period between DLP and PSUR preparation*, should also be included in this section of the PSUR (see VII.B.4.), where feasible.
863		VII.B.*5*.21 should be instead of VII.B.21
948 - 949		Comment: It is not clear what risk should be considered and where the data should be taken from.
986-987 1021-1022		Comment: Please specify the exact number of an appendix.
1066		Proposed change (if any): risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products);~~ *and*~~
1203 - 1208		Comment: Should the proposals for changes include package leaflet also? Is it not enough to propose changes in the SmPC as it is now and changes to package leaflet and labelling will be submitted with variation?
1210		Comment: If any of the appendixes is not available should the numbering of appendixes be changed or numbers should remain?

Please add more rows if needed.

30 July 2013

Submission of comments on GVP Module VII – Periodic safety update report (EMA/816292/2011)

Comments from:

Name of organisation or individual
UEMS-D/V

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1. General comments

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

No comments – well done

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)*
		Comment: no Proposed change (if any):	
		Comment: no Proposed change (if any):	
		Comment: no Proposed change (if any):	

Please add more rows if needed.