EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2012
EMA/428915/2012
Patient Health Protection

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

GVP Module VII – Periodic safety update report

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

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

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

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16/Apr/2012

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

Comments from:

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

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

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

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1. General comments

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

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')*
General comment		Comment: IBD versus EU HBD. In some parts of the module is mentioned IBD, but a list with EU reference dates will be published by EMA. Proposed change (if any): It would be better to have a list with IBD in order to harmonize worldwide.
General comment		Comment: In ICH-E2C(R2) the name for PSUR has been changed to PBRER (Periodic Benefit-Risk Evaluation Report). Proposed change (if any): As ICH-E2C(R2), the PSUR name could be changed for PBRER in order to avoid confusion. Or at least, it should be mentioned that PSUR is equivalent to PBRER.
General comment		Comment: Please confirm what to do for the authorisation renewal? The last PSUR will be submitted and some reports should be included to cover the period from the last DLP. Proposed change (if any): Please, give some instructions on what to do when a period is not covered by the last PSUR.
250-255		Comment: For purely nationally authorised medicinal products: CCDS and CCSI may not exist. Is it possible to use as reference document the authorised SmPC? Proposed change (if any): If it is possible to use the SmPC as reference document, it could be mentioned in this section.
1010-1011		Comment: The training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities. It is very difficult to comply it because the new format will be valid from Jul2012.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1118-1119		Comment: To be in line with E2C(R2), add the following statement: "Where the PSURs are no longer required to be submitted, it is expected that MAH's will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the benefit-risk profile or the labelling of the product" Proposed change (if any): Add the previous text.
1782-1784		Comment: Any estimated date for electronic submission of PSUR?

Please add more rows if needed.

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18 April 2012

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

Comments from:

Name of organisation or individual
AESGP

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We appreciate that most non-prescription medicines may fall under the routine PSUR exemptions (i.e. well-established medicines, traditional herbal medicinal products, registered homeopathic medicines) and it is important that such exemptions apply to both existing and new marketing authorisation and registrations. Generally, it is positive to see the benefits reflected in the PSUR however the benefit-risk evaluation is rather extensive and makes the PSUR closer to a continuous renewal. Also given that the PRAC will mostly focus on pharmacovigilance, we wonder whether this is appropriate to have such an extensive section on benefit in the PSUR… The requirements are very detailed compared to the current PSUR and the number of sections has grown from 11 to 19 which seems contrary to the objective of the new pharmacovigilance legislation to rationalise the system. We fear that the new format may prove difficult for small companies. There are a number of redundancies with the RMP and cross-reference should be authorised to minimise unnecessary workload. In particular the following sections are of concerns: • the mandated provision of case narratives 'where relevant to the scientific analysis of a signal or safety concern'. This appears to be completely contrary to the intent of the new report and seems to be reintroducing the 'old PSUR' approach as compared to the focus on summaries of information and scientific benefit-risk evaluation. • 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 requirement without caveat to provide a qualitative and quantitative analysis of actual use as well as how this may differ from indicated use appears to be mandating drug utilisation studies or other quantitative measures on all products when this is not necessarily warranted particularly for old and well established products.

Stakeholder number *(To be completed by the Agency)*	General comment
	Final version of Module VII will be published very shortly before it comes into effect. MAHs will most likely not be able to adapt their processes to the new requirements in GVP in such a short timeframe. This is further hindered by the fact that in many sections of Module VII reference is made to the ICH-E2C(R2) which will become available as final version approximately 6 months after the final version of the final version of GVP (December 2012). Transition period needed - A realistic timeframe for providing PSUR according to the new requirements would be 6 months after finalization of ICH-E2C(R2).

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')*
233-247		Comment: This section only discusses products with one active substance. We understand this is addressed in the IM but it should be good to refer to it in the GVP module as well or cross refer to the section of the IM.
244-245		Comment: The mandated requirement for cases narratives relevant to the scientific analysis is an additional requirement to ICH E2C and the quote is now not in line with the IM which states that: *"Detailed listings of individual cases, including case narratives, may not be included routinely, but shall be provided in the relevant risk evaluation section of the periodic safety update report where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section."* We understand that, in line with the principle of the legislation, PSURs should focus on summaries of information as opposed to routine inclusion of individual case narratives. If the intent of this additional wording is that only important cases driving the analysis would be included e.g. an index case or those involving a positive re-challenge, then this should be stated more clearly. As the wording currently stands though, it could be open to interpretation by Competent Authorities who may consider that all case reports contributing to a signal or safety concern should be included. In addition, from an MAH perspective there is concern that, in an inspection situation, they may be required to justify why some narratives were included and others were not and so will err on the side of caution and include everything. This could amount to tens or even hundreds of narratives, particularly in PSURs covering a period of time greater than one year which is clearly not in keeping with the intent and purpose of the PSUR. Proposed change: Case narratives are not routinely included in PSURs but ~~must~~ should be provided in the relevant risk evaluation section when they make an important contribution ~~must be provided~~ ~~where relevant~~ to the scientific analysis of a signal or safety concern or are integral to the benefit risk assessment ~~in the relevant risk evaluation section.~~ Every case narrative contributing to a disproportionality score, signal or safety concern should not be provided, only those which are considered critical to the assessment e.g. an index case or where there has been a clear positive rechallenge(s)
261-262		Comment: We note that different requirements for the CCDS/CCSI provided as an appendix to the PSUR have been introduced compared to the ICH E2C Step 2 guideline. The ICH guideline states that a *"tracked changes version of the reference document should be included (as an attachment that identifies changes over the*

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		reporting interval". The PSUR GVP module, on the other hand states that "*The CCDS/CCSI should be dated, version controlled and it should state the version of the coding dictionary used"* We consider that provision of a track change version provides clearer advice to MAHs and will make it easier for review by the PSUR Assessor. In addition, submission of multiple track change versions of the CCDS/CCSI instead of one only as requested in ICH E2C (R2) must be allowed for in situations when the CCDS/CCSI was updated more than once in the report interval (i.e. from version 10 to 11 and once more from version 11 to 12). Otherwise the MAH would need to create one "artificial" track-change version from multiple individual track change versions to encompass all changes in one document. This would be quite impractical. Proposed change [the first sentence is taken from ICH E2C (R2) step2]: A tracked changes version of the reference document should be included (as an attachment) that identifies changes over the reporting interval. When more than one update of the reference document had been conducted during the report interval, separate track change versions may be included.
263-265 434- 436 and 1581- 1588		The marketing authorisation holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorised product information. These meaningful differences should be included in the PSUR regional appendix (see VII.B.5.20). And The marketing authorisation should also provide information of any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI in the regional appendix, see VII.B.5.20. And The marketing authorisation holder should include in this section the meaningful differences between the CCSI and their proposals for the summary of product characteristics (SmPC). When the marketing authorisation holder considers that changes to the SmPC are required in line with the provisions established in Article 16(2) of Regulation (EC) No 726/2004 and Article 23(2) of Directive 2001/83/EC, the proposed amendments to the SmPC should be submitted with the PSUR provided these changes are in relation to the new safety information regarding the new interval covered. If not directly

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		related to the new safety information, the amendments should not be delayed. It is the obligation of the marketing authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a marketing authorisation. The proposed SmPC and package leaflet should be included as an appendix to the PSUR. Comment: For MAHs with multiple national procedures for a medicinal product (DCP, MRP), the inclusion of each proposed local product labelling (in the local language?) and current variation status will create a large administrative burden. Highlighting meaningful differences as requested in the first text above appears of value to maintain oversight on non-compliance with the CCSI for both regulators and companies, whilst a detailed representation at the member state level as requested in the second text may exceed the scope of what should be in an EU document. In terms of general company process, the evaluation of CCDS vs. National SmPC is conducted at the Local Affiliate. This would mean an additional step for Global Safety to request, receive and collate these Local Affiliate evaluations + associated documentation prior to finalising the PSUR Regional appendix and distributing the PSUR back to Local Affiliates for submission. Before the PSUR repository is established, such information should be within the NCA specific cover letter. It is also beyond the scope of the more detailed presentation of the European procedure which is outlined in the third quoted text above. Proposed change: The second text presented above should be rephrased as follows: The marketing authorisation should also provide information on meaningful differences and – where applicable – proposed amendments of the SmPC ~~of any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI~~ in the regional appendix, see VII.B.5.20.
320		Comment: The only information that should be provided in the section "Reference Information" is information about the version of the coding dictionary used. Therefore, the title of the section is misleading. It also implies a link to section 4 with the header "Changes to Reference Safety Information". Proposed change: Change header name from "Reference Information" to "Coding Dictionary Information".
321-322		Comment: The two headers 6.2 and 6.3 do not follow the same logic, because 6.2 includes what has to be presented (SAEs) in the ST, whilst 6.3 does not include such information. For clarity, section 6.3 should reflect that adverse reactions are to be presented.

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		Proposed change: Change header name of 6.3 to read "Cumulative and Interval Summary Tabulations of Adverse Reactions from Post-marketing Data Sources".
339		When writing PSUR sections 16.2 and 16.3 clear distinction needs to be made regarding which signals/new risks go into which of these two sections. The text makes clear that 16.2 is exclusively intended for presentation of each closed signal *individually*. Opposed to that section 16.3 should include an evaluation of *all* risks (not just these completed during the interval) in the light of new information. Therefore, this section is likely to present summarising information opposed to individual presentations of single signals. Unfortunately the header name of section 16.2 does not reflect the expectation of presenting closed signals from the interval. In addition, use of the term "evaluation" in both section headers for 16.2 and 16.3 adds to the level of uncertainty. Proposal: Change header name of 16.2 from "Signal Evaluation" to "Closed Signals".
438-442		Comment: This section refers to an "*accurate estimate"* which is an oxymoron and not reflected in E2C for that very reason. In addition the remainder of the paragraph can be interpreted as requiring drug utilisation studies on all products regardless of whether or not this is warranted. The apparent need to conduct such studies in all products during the lifecycle also seems inconsistent with the risk proportionality principle and is not in line with E2C(R2) requirements. Proposed change: PSURs shall provide an ~~accurate~~ estimation of the population exposed to the medicinal product including all available data relating to the volume of sales and volume of prescriptions. Where data available to the MAH allow the analyses to be made, ~~T~~this estimation of exposure should be accompanied by both a qualitative and quantitative analysis of actual use including how it may differ from indicated use ~~based on all data available to the marketing authorisation holder including~~. Sources of information for the analyses should include the results of observational (e.g. registries) or drug utilisation studies when these have been conducted.
516		Comment: Include post-marketing data in the scope of this section, as discussed later in the section. Proposed change: The objective of this PSUR section is to present clinical and post-marketing safety data

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		through summary tabulations of
603-607		Comment: The subsection B.5.7.4. "Other therapeutic use of medicinal product" is located under the main section B.5.7 clinical trials, but does not refer to clinical trial information. At present the GVP text in this subsection reads as follows: "*This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D [10] (e.g. expanded access programmes, compassionate use programmes, particular patient use and other organised data collection).*" Proposed change: The subsection B.5.7.4. should be placed under section B.5.8 "Non-interventional studies" instead of B.5.7 "clinical trials".
611-613		Comment: This sentence is slightly confusing in that a "product" cannot be authorised or developed as a component of a fixed combination product. Proposed change: The term product in the following sentence should be replace by "active substance": "If the ~~product~~ active substance that is the subject of the PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy."
728- 732		Comment and proposed change: Add important to the bullet points • Important interactions with other medicinal products; • important identified medication error where no adverse events occurred, or near misses of medication errors • Important interactions with foods and other substances; • important occupational exposure;

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		• important pharmacological class effects.
776-779		The introductory text in sub-section VII.B.5.16.4 reads as if *every* important risk that has been identified in the time period since the IBD needs to be presented *individually* including all assessment elements presented in lines 780 through 795. This understanding arises also because – opposed to ICH E2C (R2) - the GVP uses the term "should" instead of "may" in line 779. It is understood that the elements listed are similar but not equal to the elements in section 1.5.2 of the present RMP template. At present ICH E2C (R2) in Appendix D does not consider this a module to be shared between PBRER/PSUR and RMP. Based on the above understanding, sub-section VII.B.5.16.4 might become excessively long. Obviously a risk-based approach should be taken, and the extent of information to be provided will depend on whether every important identified risk from the beginning of time has to be presented in its full characterisation, or whether such risks which may have been removed from the RMP over time may be presented in a very concise manner. The GVP module text should foresee such options. Proposed change: please reword as follows: This sub-section will characterise important identified risks and important potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe important missing information. The level of detail to be portrayed for each identified risk should be greater for more recent risks compared to those which are acknowledged for many years and adequately established in the CCDS/CCSI since then. In addition the text in line 779 should read as in ICH E2C (R2) and use the term "may":Where applicable, taking into account the data source, risk data ~~should~~ may include the following:
791		Comment: Define the "sentinel" adverse reaction in the definition annex.
820-821		Comment: This text likely refers to results of local evaluations confined to one or more EEA member states and which may therefore be of limited relevance for the international PSUR document. This may be made slightly clearer. Proposed change: we propose rewording as follows

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		Results of evaluations that became available during the reporting interval and refer to individual member states only should be provided in the regional appendix (see VII.B.5.20.), to comply with national or regional requirements.
939		Comment and proposed change: In addition, as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the…
946		Comment: Does this refer to the Reference Safety Information? Proposed change: 1. Reference Safety Information
1003		Comment: The 'person responsible for the Pharmacovigilance system' – is this the QPPV? Please clarify. Proposed change: The person responsible for the local pharmacovigilance system.
1163		Proposed change: Marketing authorisation holders shall submit PSURs immediately upon request (within 90 days) from a competent…
1226 - 1227 & 1633 -1635		Comment: MAH shall *continuously* check the European medicines web-portal for any relevant updates... And then; It is the responsibility of the MAH to check *regularly* the list of EU reference dates and frequency of submission published in the European medicines web-portal... Proposed change (if any): Marketing authorisation holders shall ~~continuously~~ check regularly the European medicines web-portal for any relevant updates..
1232-1233		Comment: We understand this refers to proposed variations to amend the PSUR submission schedule. Because the schedule has already been agreed through the EU URD list, amendment of the MAH's authorization thereto represents a formality and should be managed with the least possible administrative effort in the interest of both MAHs and authorities.

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		Proposed change: Where appropriate, marketing authorisation holders shall submit a variation if they cannot implement the new information in their respective PSUR reporting system within these six months. ~~the relevant variation within these six months in order to reflect the new information in their marketing authorizations.~~
1555		Comments: Presentation of the renewal date is requested in sub-section "EU marketing authorisation status" that is part of the PSUR EU regional appendix. That sentence can be misread due to the use of the term "subsequent" in two ways: • either to refer to the first ever renewal (not the most recent one if multiple) • or to require a renewal date to be provided in any case. We trust that only outstanding renewals should appear in the list. This is because all past renewals are of no relevance for the PSUR assessment procedure. Disclaimer: Just in case the above assumption is inaccurate, the following needs consideration: For products that historically had (or products which in future might have) more than one renewal date, guidance is needed as to which renewal date should be presented in the regional appendix. For practical reasons the latest renewal date appears more meaningful than historical earlier renewal dates, as it is the one to most likely trigger regulatory decisions (if any). Proposed change: This information should contain the following: • dates of marketing authorisation and ~~subsequent~~ outstanding renewals
1581-1587		Comment: The intent of the sentence on line 1585 is not clear. Changes directly related to new safety information might be more relevant and hence require more timely variations compared to non-safety changes. The sentence should therefore be rephrased. Proposed change: If not directly related to the new safety information, the amendments of the SmPC may ~~should not~~ be delayed.
1588		Comment: This could lead to quite extensive and unnecessary workload. We propose rephrasing.

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		Proposed change: The proposed new text parts for the SmPC(s) and package leaflet(s) should be ~~included~~ summarized into one document and included as an appendix to the PSUR.
1769-1773		Comment: This sentence may be read in such way that PSURs have to be submitted on all active substances even if they are not on the EU reference date list. This may not be the intent of the text (the intent may be to indicate that in case a PSUR is needed, submit to all competent authorities). However, this should be clarified. Submission of PSUR for all active substances is not in the spirit of the key concept of the whole New Legislation which – among others – aimed to both simplify and therewith strengthening Pharmacovigilance by focus on a risk-balanced approach. The reference to DIR Art 2(7) does not appear entirely correct, as this refers to Directive 2010/84, not Directive 2001/83 as amended as all other references to the DIR. For 2001/83 reference to Transitional provision number 7 would need to be made; alternatively the reference might read DIR 2010/84 Art 2(7). Proposal: "Until the Agency can ensure the functionalities agreed for the repository, marketing authorization holders under the obligation to submit PSURs *shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised* *1769 [DIR 20410/84 Art 2(7)]. This requirement to submit PSURs holds* irrespectively of whether the medicinal product is authorised in one Member State only or more than one Member State and irrespective of whether the active substance or combination of active substances is on the EU reference date list ~~shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised1769 [DIR Art 2(7)]~~.
149		Comment: add "be" into the sentence Proposed change: normally be specified in the request,
156		Comment: Remove extra s from PSUR Proposed change: PSUR reporting should therefore be

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166		Comment: add "the" before basis Proposed change: State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active
235		Comment: Add the word "safety" before information and change "on" to "covering" before all Proposed change: containing the same active substance with safety information covering all the authorised indications, route of…
253		Comment: Remove the comma after "both" not required Proposed change: should be used as the reference for both, the benefit and the risk sections of the PSUR. The core safety
406		Comment: Add "for safety reasons" to the end of the sentence Proposed change: marketing authorisation application for safety reasons;
418- 419		Comment: Add "for safety reasons" to the end of the sentences Proposed change: failure to obtain a marketing authorisation renewal for safety reasons; withdrawal or suspension of a marketing authorisation for safety reasons ;
634		Comment: Change "is" to "are", as the sentence discusses the plural "sources" Proposed change: medicinal product from other clinical trial/study sources that are accessible11 by the marketing
644		Comment: Change the order of this sentence slightly Proposed change: This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal

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		product.
646		Comment: add "of" after "aware" Proposed change: the medicinal product that the marketing authorisation holder became aware of during the reporting
815		Comment: Change "has" to "have" Proposed change: important identified risks that have become available during the reporting interval should be
1048		Comment: Remove extra s from PSURs Proposed change: Optimisation of the management of PSURs and PSUR assessments within the EU:
1087		Comment: addition of "is" Proposed change: Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU
1230		Comment: Add an "s" to PSUR Proposed change: Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six
1247		Comment: Change to "an EU" Proposed change: list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from
1334		Comment: change "hold" to held" Proposed change : whether or not held by the same marketing authorisation holder and for which the frequency and dates
1344		Comment: Change "has" to "have" Proposed change: have been granted in accordance with the centralised procedure;

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1376		Comment: Change "from" to "of" Proposed change: and to the Member States concerned [DIR Art 107e(2)], within 60 days of the start of the
1409		Comment: Change "from" to "of" Proposed change: meeting following the PRAC adoption. Within 30 days of receipt, the CHMP shall consider the PRAC
1645		Comment: Add an "s" to the first risk Proposed change: authorisation holder should maintain on file a specification of important identified risks, important
1696		Comment: Remove "s" from program Proposed change: consistent, sustainable and efficient records management program and it has been developed in
1714		Comment: Change "on" to "of" Proposed change : information in cases of non-compliance and take appropriate regulatory actions as required.
1716		Comment: Change to "an " EU Proposed change: only one Member State and containing an active substance for which an EU reference date and
1724		Comment: Remove the "s" from communication Proposed change : communication across the EU regulatory network and the actions to be taken regarding the variation,
1735		Comment: Add a full stop at the end of the sentence Proposed change: EudraVigilance database or other data used to support the PSUR assessment.
All throughout the document		Consistently use either benefit-risk or risk-benefit, not a mixture of both throughout the document

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		Clarify the differences between annexes and appendices and exactly what information should be found in each

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18 APRIL 2012

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Comments from:

Name of organisation or individual
ALEXION Europe SAS

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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
	Alexion recognises the high level quality and completeness of this module as compared to what was in Volume9A. It will be of great support for PV systems management and continuous improvement.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 323		Comment: this sentence refers to the summaries of significant findings from clinical trials. However, the PSUR does not include a specific section with regard to significant findings from post-marketing data. Please clarify whether post-marketing data should only be included in the section 15 (Overview of signals: new, ongoing, or closed.). Proposed change (if any):
Lines 276-278		Comment: Please clarify whether the summaries of significant safety and efficacy information should be presented separately for 1) marketing experience, 2) clinical trials and studies, 3) other sources Proposed change (if any):
Line 327		7.4 "other therapeutic use": does such a section correspond to the section where information obtained from off label use shall be discussed?
Line 323 and 276		The terminology should be harmonised between "summary of safety findings" and "summaries of significant safety information"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

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

Comments from:

Name of organisation or individual
AstraZeneca

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	AstraZeneca welcomes the opportunity to provide feedback to GVP Module VII – Periodic safety update report (EMA/816292/2011) AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to those. Additionally, AstraZeneca would like to provide further comments which follows below as general and specific comments. The Guideline needs to be amended to clarify how it is to be applied for Centrally Approved products, respectively; MRP/DCP/NP approved products when there are differences. It is unclear if the new Guideline will replace current PSUR Work sharing procedures for MRP/DCP/NP approved? Clarity needs to be added to recognise when and where there are differences in the requirements due to different approval procedures. It is acknowledged that there will be information presented in a PSUR that may also be in a DSUR and/or RMP. There is concern that the same information may be assessed in different ways, possibly resulting in divergent outcomes. It would be preferable to make cross-reference rather than duplicate information. If the same information is presented in multiple documents, cross-reference could be used to put into context and to inform assessor that it is being used elsewhere. Suggest using "benefit-risk" throughout rather than "risk-benefit"

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')*
144		**Comment:** ICH is more clear regarding PSURs covering interval of 12 months **Proposed change (if any):** 'Within 70 calendar days of the data lock point for PSURs covering intervals up to *and including* 12 months'
162-163		**Comment:** Waiver for routine PSUR submission for well-established use medicinal products. Who, when and by whom is it decided what is classed as a "well-established use" medicinal product? If this is covered by the definition is as per line #1121 then suggest the definition is moved up to line #162/3 **Proposed change (if any):** Well-established use medicinal products *(authorised under DIR Art 10a)*
164-165		**Comment:** "For such products, PSURs shall be submitted where there is a condition in the Marketing Authorisation or where requested by a Competent Authority in a Member State..." **Proposed change (if any):** Condition of the MAA is mentioned a few times in this guideline and it needs to be clear what is in scope of "conditions".
171-178		**Comment:** Is this different to the current work sharing procedure? Will a new procedure override the current WS? **Proposed change (if any):** Guideline should clarify if current work sharing procedure continues until details of single assessment procedure are implemented
226		**Comment:** Suggest clarification of the sentence to help setting expectations on what needs to be presented, including timing, content and coming actions. **Proposed change (if any):** Summarising any risk minimisation actions that may have been taken or ~~are planned~~ *implemented during the reporting interval, as well as risk minimisation activities that have been agreed to be implemented during the following safety reporting period*
234-243		**Comment:** During the EU synchronisation, MAHs proposed some cases where products were written together or separately. In some cases this aligned timelines though reports were still separate. If the new legislation takes these further and put products together into one report, this may make some reports very large as they will encompass so many products (eg the budesonides).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): It would be beneficial if MAHs had a route to discuss the issue of separate PSURs for these products that are already established. .....in the event of formulations for entirely different indications.... please add "or in the event of co-licensing agreements where both parties are only able to produce separate PSURs"
234-243		**Comment:** If there is co-licensing agreement, is it expected that one PSUR produced to cover both parties, or each provide their own? **Proposed change (if any):** Please clarify if one PSUR should be produced to cover both parties, or each provides their own.
244-245		**Comment:** Additional pharmacovigilance data, in particular, in relation to requests from competent authorities should be included in the PSUR – what is meant by 'additional pharmacovigilance data'? **Proposed change (if any):** It should be clarified what is meant by 'additional pharmacovigilance data'?
263-265		**Comment:** .....highlight meaningful differences between the CCSI and their proposals for the local safety authorized safety information. For CAP products this is something we effectively do already. For national/MRP products, many are assessed via work sharing so we propose a CSP. Will that process remain if these products are included? Alternative would seem to be all MCs preparing separate comparison which was deemed ineffective when work sharing was introduced For NAPs, there may be different SmPCs and though core information will be the same, any revisions would be presented within texts that may differ. **Proposed change (if any):** It seems logical to use the principle of CSP for this purpose
287-296		**Comment:** See 'General' comment - could it be considered sufficient to allow the PSUR to cross-refer to the DSURs for the clinical trial sections OR to have alternative ways of avoiding overlapping/duplicated information? Also it may be the case that a 6 month PSUR is being written with same DLP as DSUR covering a 12 month period. What is the value to presenting data from the shorter interval if the same end point (in time) is considered? (Also applies to section VII.B.5.7) **Proposed change (if any):** It should be sufficient that in the PSUR to cross-refer to the DSURs for the clinical trial sections.
353		**Comment:** For products already approved and having a PSUR scheme already, it is suggested that existing PSUR numbers

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		are allowed to be kept and new PSURs are numbered sequentially from this. Recognising that some PSURs submitted in EU will also be submitted elsewhere, and that additional PSURs may need to be submitted at different intervals elsewhere, is numbering necessary? Should it be EU specific numbering on a separate title page? **Proposed change (if any):** No numbering should be used and reporting period should be used for identification.
353		**Comment:** Will it be acceptable to refer to the report as Periodic Benefit Risk Evaluation Report, in line with the ICH guidance and with recognition that this report may be submitted in other markets/regions? **Proposed change (if any):** It should be acceptable to use the term PBRER for reference in line with ICH
350 - 354		**Comment:** Where a product is nationally approved with a different MAH in each territory, should a separate title page be submitted for each, or a representative MAH nominated? **Proposed change (if any):** Please clarify if a separate title page should be submitted for each, or a representative MAH be nominated.
354		**Comment:** PSUR title page - "The title page shall also contain the signature" – question the reasoning/validity of this approach, given that many reports/companies provide sign-off through a separate signature sheet (including the signature on the title page does not add anything). **Proposed change (if any):** PSUR may include separate signature page(s) but the signature should not be included on title page
382 and also 533		**Comment:** .....any information that has not been included in the PSUR. **Proposed change (if any):** Please clarify, by use of examples, what could be an acceptable omission.
378-382		**Comment:** The introduction should contain the following information - followed by bulleted list **Proposed change (if any):** Suggest to include an additional point for rationale for submission of multiple PSURs if this is the case (as in ICH)
383		**Comment:** The information (lists etc) required in this section (VII.B.5.1) appears to be duplicative of the previous section (VII.B.5.2). **Proposed change (if any):** Suggest to remove requirement for duplicative information

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
383-386		**Comment:** VII.B.5.2. PSUR section "Worldwide marketing approval status" – This section ends with the phrase "…if applicable". Believe that all of this must be applicable (and therefore this wording is superfluous) given that PSURs relate to marketed products. **Proposed change (if any):** Suggest to delete "...if applicable".
419		**Comment:** Withdrawal of a particular license does not necessarily relate to safety reasons. In most instances, withdrawal is due to commercial reasons, where possible and alternative treatments are available. **Proposed change (if any):** It should be clarified/confirmed it is only safety related withdrawals that are supposed to be provided within the PSUR.
427		**Comment:** "This PSUR section should list any significant changes made to the ~~reference safety information~~ within the reporting interval." **Proposed change (if any):** "This PSUR section should list any significant changes made to the *CCSI* within the reporting interval."
434-436		**Comment:** ....."information on any final and ongoing changes to the national/local authorised products information".....It is a very different impact if this relates to CP or nationally approved products. See also comment for 263-265 **Proposed change (if any):** ~~The marketing authorisation holder should also provide information on any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI in the regional appendix~~ The final and ongoing safety related changes to national product information should be reflected within the proposed Core Safety Profile which should be updated since completion of the previous PSUR work sharing assessment
473-505		**Comment:** It is recognised (line 477) it is difficult to obtain and validate patient exposure data from marketing experience. Nevertheless, the draft guideline demands exposure estimation on even more detailed level, i.e. patient exposure by sex, age, and also for special populations. These new demands are considered even more difficult for MAH to fulfil as access to such detailed and robust information is limited. Collation of this type of detailed information is also potentially sensitive in the light of personal data protection. Furthermore, national registries will vary in quality and quantity. The registries usefulness outside their local setting and health care system must be carefully considered before pan-European conclusions are made based on such local data. In addition, observational studies are not routinely performed for all marketed products. **Proposed change (if any):** Any detailed exposure data will only be presented, when available and if drug utilisation or observational studies have been carried out during the reporting period.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
561-568		**Comment:** This sub-section indicates that cumulative and interval non-serious adverse reactions from non-interventional studies should be presented and indicates that an example of summary tabulation can be found in the ICH-E2C (R2) guideline, Appendix B, table 7. The sample table in the Step 2 ICH-E2C (R2) guideline, Appendix B, table 7 contains a footnote indicating that non-serious ADRs from non-interventional post-authorisation safety studies (PASS) only should be tabulated here. Is the intent to discount non-serious non-interventional ADRs from other post marketing sources, or should the wording be strengthened to indicate that non-serious ADRs collected from PM Study sources (including PASS) should be presented here? **Proposed change (if any):** There is a discrepancy to ICH that needs to be clarified.
609		**Comment:** "unless otherwise specified by national or regional regulatory..." National specific requests should be avoided and the guidance should, when adhered to, fulfil all EU member States requirements. **Proposed change (if any):** This guidance s per definition a regional regulatory/EU guidance and not a global document why the first part of the sentence shall be removed. Reference to Regional requirements in other part of this guidance also needs to be re-considered, (e.g. 954-955)
657		**Comment:** "medication error where no AE occurred or "near misses". Unclear why medication errors not having safety implications are of interest. The term "near misses" may not be commonly understood. **Proposed change (if any):** Clarify why there is a need to report medication errors that do not have a safety implication. Please re-word to avoid using a term that may not be consistently recognised.
700		**Comment:** ..... PSUR section "Overview of signals: new, ongoing, or closed" Line 700 states "should consist of a tabulation of signals that are ongoing and closed during…" **Proposed change (if any):** Add "new" to the text.
709		**Comment:** Suggest provide clarity that this section presents information relating to what's known at start of reporting interval. This is covered later in lines 714-715 but is less clear than in section VII.B.5.17.1 **Proposed change (if any):** The purpose of this PSUR sub-section is to provide a baseline summary of important safety concerns *as identified at the beginning of the reporting interval*, against which new information and evaluations within the PSUR can be made.
780		**Comment:** There should be consistency in how frequency is presented in PSUR compared to how it is presented in SmPC, e.g. .taking actual figures from CT database if one exists, which will not cover all marketed exposure? This section will cause

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		a lot of work and we'll need some good guidance on how to manage this for older products if they're included in the scope **Proposed change (if any):** Suggest adding that the CCSI is to be used as reference for frequency. Should the MAH consider that the frequency have changed since previous safety reporting period, the MAH will have updated the CCDS/CCSI with this information (and it will be shown in the marked up highlighted version of the CCDS that is requested as an Appendix.)
824, 831		**Comment:** If this sub-section is for baseline information how can it include changes? If this refers to changes during the reporting interval, will they not be presented in sub-section 5.17.2? **Proposed change (if any):** 5.17.1 should be used for baseline information and 5.17.2 should be used for changed.
882		**Comment:** Does 'as used in clinical practice' mean just approved use or cover recognised off-label use (as per lines 507-514) **Proposed change (if any):** Please clarify if off-label use is included in the definition "as used in clinical practice".
951		**Comment:** Line 951: VII.B.5.20. Appendices to the PSUR – "5. Signals evaluation, when applicable" – unclear why this appendix has been introduced here as it is not mentioned in the ICH E2C (R2) draft. **Proposed change (if any):** Please clarify the discrepancy to ICH.
953-955		**Comment:** "The information included in this appendix should be used to comply with national or regional requirements." National specific requests should be avoided and not encouraged by this guidance. The guidance should, fulfil all EU member States requirements and there should be nothing requested beyond this. **Proposed change (if any):** "The information included in this appendix should be used to comply with EU requirements, when submitted to EU Member States.
1019		**Comment:** This flow chart includes nationally approved products – assume this includes MRP/DCP? Not sure if these products are in scope from the outset, though. The flow chart mentions CAP and NAP right at the end of the process, after EC decision. Unclear how this flowchart relates to the process outlined at #1336-38 **Proposed change (if any):** Please clarify which parts of flow chart applies to CP, respectively, MRP/DCP and NP approved products, or make two separate flow charts.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1022-33		**Comment:** In line with the EFPIA comment for section VII.C.3.2 regarding the possibility to take international harmonisation into account, Article 107c (6) stipulates that MAH shall be allowed to submit a request to CHMP to achieve international harmonisation. **Proposed change (if any):** It would be beneficial to reflect that possibility also in section VII.C.2 'Standard Submission Schedule of PSURs'.
1051		**Comment:** What type of variation shall be submitted if there is a need to vary submission frequency to comply with the published list? After PSUR WS there was an issue over whether it was Type II or Type Ib. **Proposed change (if any):** Please clarify on the variation category as well as type.
1330		**Comment:** Is the EU Single assessment a replacement for the existing work sharing procedure and national assessment of products on the current synchronisation list? As this will be delayed until after 2012 do the current assessment procedures remain in place? **Proposed change (if any):** Please clarify the procedures for assessment of products that are included on the List of Union Reference dates, but which are approved through MRP/DCP and purely national routes.
1553-1554		**Comment:** Marketing authorisation holders should provide a detailed description of the marketing status for all Member States where marketing authorisation(s) have been granted. This information should contain the following…… **Proposed change (if any):** Please add: "where available" to read: This information should contain the following *where available.*
1569-1573		**Comment:** VII.C.5.2. PSUR EU regional appendix, sub-section "EU marketing 1550 authorisation status" – The paragraph which starts "Typically, indications, populations (e.g. children versus adults)…" would appear to apply worldwide, not just to EU Member States. **Proposed change (if any):** Suggest that this guidance will be provided in Section VII.B.5.2. (PSUR section "Worldwide marketing approval status") as it is generally applicable– where there are important differences they should be highlighted.
1580 & 1588		**Comment:** Which SmPC needs to be added, is it clear and comparable to what we currently do? For products authorised through work sharing will this be the CSP? Should the appendix be the CSP or actual SmPC/leaflet? If the latter, will QRD document be acceptable where there is a harmonised text? What is the expectation for NAPs – it is impractical to include numerous SmPCs if the product has been assessed via work sharing **Proposed change (if any):** The marketing authorisation holder should include in this section the meaningful differences

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		between the CCSI and their proposals for the summary of product characteristics (SmPC) *or Core Safety Profile* The proposed SmPC and package leaflet, or Core Safety Profile should be included as an appendix to the PSUR.
1799		**Comment:** As it seems the Single assessment will not be implemented yet, can clarity be provided on the impact on MRP/DCP/NAP products? Will the reports still be required in new format and with new submission timelines, but assessed under existing procedures? Or will the existing style PSUR be acceptable until the guideline and new EU single assessment procedure are implemented? **Proposed change (if any):** Please clarify what will be required during the period until Single assessment is implemented.
1808		**Comment:** As it seems the Single assessment will not be implemented yet, can clarity be provided on the impact on MRP/DCP/NAP products? Will the reports still be required in new format and with new submission timelines, but assessed under existing procedures? Or will the existing style PSUR be acceptable until the guideline and new EU single assessment procedure are implemented? **Proposed change (if any):** Please clarify what will be required during the period until Single assessment is implemented.

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The omission of line listings gives rise to the principal question whether conclusions drawn from PSURs by the MAH can be properly assessed and judged by NCAs/PRAC without knowledge of the quality of the source data (=individual case reports) ?

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')*
144 - 150		Comment: MAHs should submitted PSURs within 70 calendar days, respectively 90 calender days of the data lock point - What are the consequences if the MAH fails to submit the PSUR in due time ? Proposed change (if any):
155 - 161		Comment: The modular approach (PSUR, RMP, DSUR) will probably be available for new marketing authorizations only. Proposed change (if any):
1283-1286		Comment: Will the listings of individual cases retrieved from Eudravigilance database include the case narratives? Please specifiy what "other relevant data" created by the Agency will be made available to the PRAC Rapporteur (e.g. PV inspection reports, Reports of inspections of clinical studies?) Proposed change (if any):

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Based on my own review, I think this is a substantial change to the old PSUR. There's significant overlap between the RMP and Signal Detection modules. The data presentation looks very similar to the E2F DSUR document. The requirement for Line Listing in section six is removed and overall focus is a greater emphasis on benefit-risk assessment and in depth data analysis. So the challenge for companies would be to find organisational structures to provide benefit-risk position per product. Data collection will also be quite challenging as significant cross-functional collaboration is required to pull clinical and post-marketing info.

2. Specific comments on text

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

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Bayer HealthCare

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

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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')*
487-490		Comment: The overall/global estimation of patient exposure will routinely be estimated from the sales figures for a respective product, using pre-defined algorithms to calculate number of patients/ patient-days/ etc. A routine presentation by sex, age, indication, (dose) is not possible based on sales estimates. To obtain this level of detail, drug utilisation studies are needed to determine patient characteristics, prescription patterns etc. Proposed change: Move requirement for post-marketing exposure by patient (age, sex, indication, dose) subgroups to sub-section 3. Pattern of use of the Medicinal Product

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Issue: single assessment of periodic safety update reports Background: A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and frequency of periodic safety update reports has been established. The single assessment shall be conducted by either of the following: (a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004; or (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. comment: It is necessary that the RRAC PSUR Rapporteur or RMS has to be appointed at a reasonable time point **before** start of the PSUR-assessment procedure. The GVP module should elaborate in what way this will take place and can be ensured. Or will it be sufficient to refer to URD list once it is adopted by the PRAC since in the URD list suggestions for the Rapporteur/RMS are contained?

Stakeholder number *(To be completed by the Agency)*	General comment
	Issue: Post CHMP opinion – CAP MRP NAP background: *a*. Post CHMP opinion - Centrally authorised products Where the CHMP opinion states that the terms of the marketing authorisation(s) needs to be varied, the marketing authorisation holder(s) of centrally authorised products should **provide the translations of the product information in all EU official languages**, in accordance with the translation timetable adopted by the CHMP. comment: It could be helpful if the same applies in principle for the single assessment not including centrally authorised product leading to a CMDh position. The MAH of the originator product could provide translations of the product information in EU official languages of those countries there the active ingredient is authorized according to an authorized time table. **Issue: Assessment timetable** It is noted that the timetable for the assessment is addressed in the Directive. However, only 15 days are provided to prepare an updated AR. Against the background of the general high workload of all NCAs it seems nearly impossible to include and assess all comments from MAHs and MSs within 15 days. It is strongly recommended to extend this timeline or to implement the possibility of a clock stop.

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 260-262		Comment on: "Principles for the preparation of PSURs" Proposed change (if any): In case of different indications and routes of administration especially in cases of systemic versus topical application the data should be always presented in separate sections within the body of the PSUR (and not "when relevant").
Line 576 and Lines 621-624		Comment on: "Cumulative summary tabulations of serious adverse events from clinical trials" "The tabulations should include blinded and unblinded clinical trial data." In blinded studies it is unclear if the investigational drug, placebo and/or the active comparator(s) have caused the ADR. Besides there is currently a discrepancy to PSUR sub-section "Ongoing clinical trials". In this subsection it is mentioned that the MAH should summarise clinically important information from ongoing clinical trials e.g. as a result of unblinding of subjects with adverse events. Here only unblinded data are requested. Proposed change (if any): Only unblinded studies should be included in section "Cumulative summary tabulations of serious adverse events from clinical trials".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

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

Comments from:

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

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

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
	From the generics' perspective the current situation is relatively clear in as much as three-yearly PSURs are the default situation save in exceptional circumstances. The new guideline for PSURs introduces an element of uncertainty with regard to the requirements for PSURs for generic products, especially as the list of Union reference dates is not yet available.
	Will the Core Safety Profile as it is currently understood continue to be included as part of the PSUR FAR?
	Include definitions of efficacy and effectiveness.
	"By way of derogation, generics, well-established use, homeopathic and traditional herbal medicinal products are exempted from submitting PSURs except in the following circumstances:" - informed consent and hybrid can sometimes generally be considered a generic product, but the regulatory routes have forced them into another category, will the need for a PSUR also be exempt in these circumstances.

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')*
164-165		Comment: "condition of the marketing authorisation" needs to be clarified, i.e. whether details of proposals for PSURs included in close-out letters/FARs form part of MA conditions. Proposed change (if any):
165-167		Comment: "… when (PSUR) requested … due to lack of PSURs for an active substance" This could cause issue with respect to predictability and resources when planning/scheduling PSURs. Proposed change (if any):
302-308		Comment: What is a Periodic Benefit Risk Evaluation Report (PBRER)? What are the differences to a PSUR? A definition/ clarification is needed. Will (generic) companies be required to prepare and submit PBRERs to the agencies in addition to PSURs? Proposed change (if any):
352		Comment: Is the PSUR title page now part of the main PSUR document or separate as is the current PSUR cover sheet? Proposed change (if any):
356		Comment: Please clarify whose signature should be contained on the title page. Author, EU QPPV or Local QPPV?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
487-488		Comment: For generics, how can the data be presented in this way? Proposed change (if any):
562		Comment: What is the definition of 'IBD' in this context? Which date applies for generics? Is it the date of MA grant? Proposed change (if any):
709		Comment: It seems that the sections 'Summary of Safety Concerns', 'Evaluation of risk and new information', and 'Characterisation of risks' contain similar information and it seems difficult to not repeat the information as mentioned in line 760 ("should not summarize or repeat information already presented"). Proposed change (if any):
1019-1021		Comment: Needs explanation. No mention of FAR in the process. Proposed change (if any):
1050-1053		Comment: This implies that a variation is required when a substance is included on the list whereas before, generics could move directly to align with EU DLPs without the need for a variation. Proposed change (if any):
1081		Comment: Will this always be annual or three-yearly or are other periodicities envisaged?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
1087		Comment: Typo: “Where specificity *is* deemed necessary……” Proposed change (if any):
1095		Comment: What exactly does “lack of PSURs” mean? Time period or safety data on generic products, etc? How will the ‘lack’ of PSURs be assessed? Clarification is needed. Proposed change (if any):
1120-1123		Comment: Where a product has been approved under Article 10.c, Informed consent, and the reference product was approved under Article 10.1, generic, no PSUR should be required unless requested in the EURD list. Proposed change (if any):
1120 - 1123		As per the recommendations of the CMD(h) (http://www.hma.eu/210.html) applications for marketing authorisation for products for local use should be submitted according to Article 10(3) of Directive 2001/83/EC, since bioequivalence cannot be demonstrated. However, some locally applied products are a copy of the reference product so they are essentially a generic of the reference product. Proposed change (if any):
1122		Comment: From when does this (“generics exempted from submitting PSURs”) take effect for generic products already authorised before July 2012, i.e. will it be applied retrospectively? 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')*
1124		Comment: "Condition" needs to be clarified. How will conditions be communicated in future or where will they be indicated? Will there be a standard approach by the authorities (i.e. part of MA documents or close-out letters or FARs)? This line mentions that a PSUR needs to be submitted for generic/ well-established medicinal products if the MA provides for the submission of PSURs as a condition. For most of the generic/well-established medicinal products automatically a 3-yearly PSUR cycle was applied with the grant of a MA which is mentioned within the MA. It needs to be clarified that this case is not because of 'concerns relating to pharmacovigilance data' as mentioned in line 166 and therefore the submission of a PSUR is NOT required. Proposed change (if any):
1137-1138		Comment: Will information be made publicly available in advance on products which are under consideration for ad-hoc PSURs? Proposed change (if any):
1163		Comment: What does "immediately" mean in this context (i.e. what timeframe for preparation is envisaged, how will DLPs be decided)? Proposed change (if any):
1202		Comment: If an MAH requests a change to the EU reference list will this need to be justified? This could be used as a barrier of entry by branded companies. 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')*
1230-1231		Comment: "…changes to dates and frequencies… take effect six months …". Surely the effective date depends on the new DLP versus DLP a company is currently working to? This provision will introduce an element of unpredictability into scheduling PSURs which is an issue from a resource and planning point of view. Proposed change (if any):
1230 - 1231		Comment: When will the initial list take affect? Will this be six-months from the first publication of the list? Or can MAHs "take advantage" and start going by the submission list immediately? Proposed change (if any):
1232		Comment: What type of variation is envisaged to cover this change? IA/IB? Implementation of future date is not possible if IA. Cost issues. Proposed change (if any):
1588		Comment: Package leaflets in the past were not required to be included in appendices to PSURs – only SmPCs - why is PL now required at PSUR assessment stage? Proposed change (if any):
1644-1646		Comment: Does this section place specific obligations on generic/well-established use products if they are exempt from full RMPs? 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')*
1775		Comment: Previously, PSURs for generic products not authorised through the centralised procedure did not have to be submitted to the Agency. Proposed change (if any):
1782		Comment: What is the timeline for availability of the structured electronic format “ePSUR”? Proposed change (if any):

`Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.
	As the different GVP modules should replace Volume 9A information is missing regarding PSUR obligations in the context of renewal procedures (e.g. section 6.2.4.b Submission of Periodic Safety Update Reports for Renewal of Marketing Authorisations). Particularly interesting in this context is the information on Addendum and Bridging Reports.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 162 – 167 and Line 1123		**Comment**: For many medicinal products with well-established medicinal use a PSUR period of 3 years was applied for with the registration. Usually this PSUR period was accepted by the authorities and is mentioned in the registration. It should be agreed with the authorities that these cases do not fulfil the condition mentioned in line 163 as in these cases there was no concern related to pharmacovigilance.
Line 302 - 308		**Comment**: What is the difference between PSUR and PBRER? Definition / differentiation is needed.
Line 630		**Comment:** PSUR section “Information for other clinical trials and Sources”. The word “for” should be replaced by the word “from”.
Line 709 ff		**Comment**: It appears to be difficult to differentiate the content of the chapter “Summary of safety concerns” from the contents of the chapter “Evaluation of risks and new information” (lines 753 ff) and “Characterisation of risks” (lines 773 ff) without repetitions.
Line 737		**Comment:** Clarification is needed where these signals should be discussed: in section 16.2, 16.3 or in both sections (because the “discussion of the signals” is mentioned in this section (16.2) but on the other hand 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')*
		discussion should be included in section 16.3).
Line742		**Comment:** Clarification is needed which section is meant by “can be included in the PSUR body”. Does it mean 16.2?
Line 918 ff		**Comment**: It is not clear how the methology of a benefit-risk evaluation could be explained/established. Clarification is needed.
Line 1115		**Comment**: In Chapter VII.C.3.3.2 explanations on the submission of PSURs for homeopathic medicinal products are given and circumstances are mentioned when PSURs have to be submitted. In this context it must be noted that the PSUR is a document intended to provide an evaluation of the risk-benefit balance of a medicinal product. However, according to Directive 2001/83/EC Art. 14 for homoeopathic medicinal products no specific indications are allowed on the labelling or any other information. That means that these products have per definition no indication/benefit. How should an evaluation of a risk-benefit be carried out if there is no benefit? The section VII.B.5.17 would therefore not be suitable for homoeopathic medicinal products. Furthermore, for hardly any homoeopathic medicinal product a study or a clinical trial is available. In summary, module VII seems not to be appropriate for homoeopathic medicinal products. The requirement to submit a PSUR for homoeopathic medicinal products should be deleted completely or the content for such a PSUR should be tailored to the nature of the products.

<Date of submission>

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
	None provided.

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')*
244-245		**Comment:** Case narratives must be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR. **Suggested language:** Within a signal evaluation, narratives should only be shown for the compelling cases satisfying specific criteria, as specified in context in the evaluation (e.g., index cases). Other reports contributing numbers should be presented as aggregate numbers, for instance for estimating reporting rates.
267-269		**Comment:** "PSUR shall contain cumulative data starting from the granting of the marketing authorisation, though with the focus on new information emerging in the period since the data lock point of the last PSUR. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment. **Suggested language:** The PSUR shall contain cumulative data starting from the granting of the **first** marketing authorisation….
690		**Comment:** Identification and evaluation of safety signals. **Suggested additional language**: The scope of the review for signal evaluation should be broad, knowing that the conclusions might not apply to approved indications.
1160-1163		**Comment:** Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a Member State [DIR Art 107c (2)]. This is in conflict with timelines for ad hoc requests for PSURs described in lines 146 – 148. **Suggested Language change:** Marketing authorisation holders shall submit PSURs within 90 days of receiving a request from a competent authority in a Member State when a timeline for submission has not been specified in the formal request.

<Date of submission>

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

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PSUR Module (GVP VII) is aligned with ICH E2C(R2) Step 2 guideline (Periodic Benefit Risk Evaluation Report) which has not yet been replaced with the current PSUR guideline. There are regions and countries where submission of PSUR is required by local regulations. If this PSUR Module (GVP VII) becomes effective in July 2012, a MAH who is submitting a PSUR to both EU and other countries should prepare both PBRER style report and current PSUR for the same active ingredient. To avoid this duplicated work, we would like to request to postpone the effective date for PSUR Module in EU until ICH E2C(R2) guideline is finalized (i.e. expected in the end of 2012). Or, at least, accept classic PSURs for certain period after effective date.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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1. General comments

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

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
DAIICHI SANKYO Japan

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This is a request related EU GVP module 7. As **ICH E2C(R2)** is step 2 at this moment, for Non-EU health authorities, it may be difficult to receive the new PSUR before ICH E2C(R2) is implemented. Therefore, we propose a transitional period where both, an old PSUR or a new PSUR, would be accepted.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 261-263		Comment: To further improve the usefulness of this section, we suggest that the description of the differences between the CCSI and the product information are accompanied by a description of the consequences on the PSUR conclusion. This would help the decision of whether to amend the local SmPC. Currently, Volume 9A section 6.3.5 includes a text which we suggest to re-include. Proposed change (if any): Sentences 261-263 should be replaced by the following: The marketing authorisation holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorised product information, **preferably as a comparative overview. For each meaningful difference, the MAH should argue why or why not regulatory actions should be initiated. This overview** should be included in PSUR regional appendix (see VII.B.5.20.).
Lines 447-470		Comment: The list is quite exhaustive. Still, data for fixed combination products are worth to include. Proposed change (if any): Addition of: Exposure from studies of fixed combinations including the medicinal product.
Lines 488		Comment: In analogy with the above, we suggest to include brief data for fixed combination products. Proposed change (if any): Addition of "Exposure data for fixed combination product should be included."
Lines 505 - 508		Comment: The following changes are suggested.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the interpretation of safety data, ~~provide~~ a brief description **should be provided** thereof. Such patterns may include, in particular, off-label use (e.g. an anti-epileptic drug used off-label for neuropathic pain and/or prophylaxis of migraine headaches). **If relevant and applicable, an exposure estimate should be provided.**
Line522		Comment: Listedness in the summary tabulations is a valuable tool for the regulators to detect ADRs which might need inclusion in the CCDS and/or SmPC. We support the inclusion of listedness in the summary tabulations as a complementary risk analysis tool to the section "Signal and risk evaluation" performed by the MAH in the PSUR. Proposed change (if any): Listedness should be shown in the summary tabulation(s). The reference document should be specified by the MAH and appended to the PSUR (eg. the CCDS). This should not increase the number of summary tabulations included in the PSUR; listed and unlisted ADRs should be shown in the same table(s)
Line 646-7		Comment: The following changes are suggested for clarification Proposed change (if any): Literature searches for PSURs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects **and other products containing the same active substance**.
Line 657		Comment: To improve clarity, we suggest to add the word "other" in the sentence. Proposed change (if any): If relevant and applicable, information on **other** active substances of the same class should be considered.
Li ne 752 b		Comment: In the last bulletpoint information regarding information sent to the authorities could be included. Proposed change (if any): Conclusion, including **whether the signal been reported to the Authority and ongoing, previous or proposed actions on the signal.**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
line 574 and line 623.		Comment: It is proposed that not only sponsored trials but also trials where the MAH is contributing significantly to the trial planning and/or conduct e.g. where the MAH is providing monitoring resources or having subsequent ownership of data is listed in the appendix. Proposed change (if any): Text to be added according to the comment

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Drug Safety Solutions Limited

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	If in a PBRER we don't do line listings, and start non-serious submissions from July 2012, then the Authorities will not receive the non-serious cases that occur during period up to July 2012 that would normally be submitted in the next PSUR due after July. For example, for a 3 year PSUR due August 2012 – they won't get 2 years 11 months worth of non-serious cases? Proposal – next PSUR after July 2012 should have special appendix of just the non-serious cases up to July 2012 in a line listing.

2. Specific comments on text

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

Please add more rows if needed.

<18 April 2012>

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

Comments from:

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

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
	EFPIA appreciates the extent to which the draft PSUR GVP module has utilised the Step 2 ICH E2C (R2) guideline in order to promote international harmonisation and hence avoid unnecessary duplication and burden on industry. Whilst some deviation from ICH E2C is expected and understandable due to the constraints of the PV Legislation, there are nevertheless six main areas of concern where either additional requirements have been introduced or where EU specific provisions have been included that do not support international harmonisation : • the mandated provision of case narratives 'where relevant to the scientific analysis of a signal or safety concern' This appears to be completely contrary to the intent of the new report and seems to be reintroducing the 'old PSUR' approach as compared to the focus on summaries of information and scientific benefit-risk evaluation. Furthermore, inclusion of narratives in the main body of the report will effectively impose individual case narratives on the other ICH regions when this was not required. • 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 requirement without caveat to provide a qualitative and quantitative analysis of actual use as well as how this may differ from indicated use appears to be mandating drug utilisation studies or other quantitative measures on all products when this is not necessarily warranted particularly for old and well established products. • Although section*VII.B.2.* ***Principles for the evaluation of the benefit-risk balance within PSURs*** clearly refers to conducting an integrated benefit-risk analysis for authorised indications based on the cumulative information available since the international birth date (IBD), subsequent sections of the module then appear to contradict use of the IBD by stipulating use of the EU reference dates, namely, the date of the first authorisation in EU. As the legislation makes provision for changes to the Union dates in order to promote international harmonisation and global companies are already preparing PSURs based on the IBD, EFPIA urge that the IBD is used to prepare the List in order to avoid the burden of frequent variation requests. For products already subject to the work-share scheme, EFPIA recommend that the dates already in

Stakeholder number *(To be completed by the Agency)*	General comment
	place for these products are used as they are already harmonised across Europe • EFPIA fully understands the constraints on the nomenclature of this report imposed by the new legislation. (i.e. a periodic safety update report) Nevertheless, the name of the future PSUR has been changed to Periodic Benefit-Risk Evaluation Report (PBRER) per the ICH E2C guideline, predominantly as the old "PSUR" terminology is no longer an accurate descriptor of the report required under EU legislation or the ICH guideline which is consistent with EU legislative requirements. In practice this will cause considerable confusion and lack of harmonisation at an international level as companies operating across multiple regions struggle to know what to call the report when developing international templates etc. In the interests of international harmonisation, therefore, EFPIA urge that a statement is inserted in Module VII to clarify that the terms PSUR and PBRER should be considered equivalent. If this is not possible then, EFPIA recommend that clarification is provided in the definitions Annex as well as in a Q&A. • Module VII is silent on the role of the future PSUR/PBRER in the renewal process after July 2012 when the report was formerly an integral part of the renewal process. The lack of any mention or guidance on this point in Module VII has led to many questions amongst EFPIA company members. It is understood from the draft Guideline on the Processing of Renewals in the Centralised procedure released for consultation on 23 March 2012 that formal PSURs as such will no longer required to be submitted with a renewal application after July 2012. Nevertheless the content and format of the proposed Clinical Overview accompanying the renewal application bears a striking resemblance to that of Module VII (and even refers to Module VII with respect to writing the Clinical Overview) but with no provision for any similar transition period. According to the EU Commission Q&A on transitional arrangements published in February 2012, the renewal dossier for the worst case for a national product with a marketing authorisation expiring after 21 April 2013 has to be implemented by 21 July 2012 instead of the "current" submission by 21 October 2012. This implies that the process for compiling the Clinical Overview (in the future PSUR format) in the renewal package would have to be initiated by July 2012 and cover the period from approval or last renewal .This seems to equate to an "ad hoc" PSUR/PBRER report per the ICH E2C (R2() guidelines and EU legislation, but since the submission of the renewal does not fall into the currently stated category for such reports, it is EFPIAs position that a further category be considered for the ad PBRER/PSUR, namely, where, for renewal of licence purposes, provision of an ad PBRER/PSUR cover the period since approval or last renewal may be required. • The arguments given already for implementation of the new PSUR format apply equally to the content of the proposed future Clinical Overview so a similar 6 month transition is requested. In addition, EFPIA recommend that, for the sake of clarity, cross reference is made to the renewal guideline in module VII and a statement to the effect that whilst PSURs as

Stakeholder number *(To be completed by the Agency)*	General comment
	such are no longer required with a renewal procedure, the content of the Clinical Overview is the same as sections xxxx/yyyy/etc of the future PSUR per Module VII of the GVP guidelines . Further details on the interface between future renewals and the content and format of the proposed Clinical Overview and whether or not this should be treated as an ad hoc PBRER/PSUR ideally should be addressed in Module VII. If this is not feasible, a Q & A should be provided . As it possible that our interpretation of the areas of concern highlighted above are not in line with the underlying intent, EFPIA have proposed some additional wording in the detailed comments section below which we consider to be more in keeping with the intent, provide clarity and be less open to interpretation and ambiguity A number of areas have been identified by EFPIA as requiring further clarification but we considered that these were best place in a future Q&A so will provide these separately. **Transitional Arrangements** A final area of concern relates to the transition period that will be allowed to implement what will be a fundamentally different periodic report to that currently being written. In order to move to the future PSUR format, companies will need to make extensive changes in existing processes, re-programme database outputs and validate computer system changes, write new SOPs, create new templates and train multiple staff, many of whom will be outside the main pharmacovigilance department. Another factor to take into consideration is that many companies utilise a software package from external vendors for the production of a PSUR. As such the MAH is not able to make changes to the software but has to rely on the vendor of the commercial system. These changes would need to be implemented first at the level of the software creator and then implemented by the MAH Similar considerations were also needed for implementation of the Developmental Safety Update Report, a far less comprehensive report than the future PSUR. For the DSUR, a year from publication of the final Step 4 ICH E2F document was provided to implement the process. EFPIA recognises that the constraints of the legislation are unlikely to allow a similar transitional period for the PSUR but given the sheer extent of changes needed to implement, EFPIA propose that the new PSUR format applies to all reports whose data lock points occur after January 2013.This equates to a 6 month transitional period and has the advantage that it should coincide with Step 4 of ICH E2C (R2) and facilitate international harmonisation i.e. it will minimise the likelihood of divergent requirements among ICH regions.
	Transitional Arrangements

Stakeholder number *(To be completed by the Agency)*	General comment
	A final area of concern relates to the transition period that will be allowed to implement what will be a fundamentally different periodic report to that currently being written. In order to move to the future PSUR format, companies will need to make extensive changes in existing processes, re-programme database outputs and validate computer system changes, write new SOPs, create new templates and train multiple staff, many of whom will be outside the main pharmacovigilance department. Similar considerations were also needed for implementation of the Developmental Safety Update Report, a far less comprehensive report than the future PSUR. For the DSUR, a year from publication of the final Step 4 ICH E2F document. EFPIA recognises that the constraints of the legislation are unlikely to allow a similar transitional period for the PSUR but given the sheer extent of changes needed to implement, propose that the new PSUR format applies to all reports regardless of approval path whose data lock points occur after January 2013.This equates to a 6 month transitional period and has the advantage that it should coincide with Step 4 of ICH E2C (R2) and facilitate international harmonisation.

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')*
171-175		Comment: Article 107e seems to have been misinterpreted in this paragraph. A single assessment of PSURs is also to be performed for medicinal products authorised in more than one Member State - the single assessment is not restricted to different medicinal products for which a Union reference date and PSUR frequency have been set. Proposed change (if any): In order to increase the shared use of resources between competent authorities in Member States, a single assessment of PSURs shall be performed in the EU for **medicinal products authorised in more than one Member State and for** different medicinal products containing the same active substance or the same combination of active substances ~~**authorised in more than one Member State**~~ for which a Union reference date and frequency of submission of PSURs has been established [DIR Art 107e].
244 - 245		Comment: The mandated requirement for cases narratives relevant to the scientific analysis is an additional requirement to ICH E2C. EFPIA understands that, in line with the principle of the legislation, PSURs should focus on summaries of information as opposed to routine inclusion of individual case narratives. If the intent of this additional wording is that only important cases driving the analysis would be included e.g. an index case or those involving a positive rechallenge, then this should be stated more clearly. As the wording currently stands though, it could be open to interpretation by Competent Authorities who may consider that **all** case reports contributing to a signal or safety concern should be included. In addition, from an MAH perspective there is concern that, in an inspection situation, they may be required to justify why some narratives were included and others were not and so will err on the side of caution and include everything. This could amount to tens or even hundreds of narratives, particularly in PSURs covering a period of time greater than one year which is clearly not in keeping with the intent and purpose of the PSUR. Proposed change: Detailed listings of individual case including case narratives shall not be routinely included

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		in PSURs but ~~must~~ may be provided in the relevant risk evaluation section when they are integral ~~must be provided~~ ~~where relevant~~ to the scientific analysis of a signal or safety concern (IM 34 (5)) It is expected that such cases will be integral to the benefit risk assessment ~~in the relevant risk evaluation section.~~ As a guidance to what is considered relevant, every case narrative contributing to a disproportionality score, signal or safety concern should not be provided, only those which are considered critical to the assessment e.g. an index case or where there has been a clear positive rechallenge(s)
246-247		Comment: This requirement is in addition to ICH E2C and is a concern as it appears to perpetuate "the old PSUR" concept with continued reliance on extensive analyses of spontaneous data . With some exceptions, the utility of spontaneous data should be to generate safety signals, not evaluate them, so it is important that any additional requests for analyses by competent authorities be confined to those where they will make a contribution to the overall benefit risk assessment. The scientific validity for specifically requesting analyses of non serious cases is highly questionable. Proposed Change : Additional ~~pharmacovigilance data~~ scientific analyses, in particular in relation to requests from competent authorities should be included in the PSUR. Such requests will generally be made via the Assessment Report of the previously submitted PSUR or on an ad hoc basis if a safety concern arises and will be confined to those. ~~This~~ ~~may include~~ analyses ~~of cases classified as non serious~~ which are likely to make a meaningful contribution to the overall benefit risk assessment.
Line 247		Comment ; ICH E2C (R2) guideline on PBRER (section 2.7.3) states, that the Summary Bridging Reports and Addendum Reports, introduced in ICH E2C(R1), should no longer be submitted. It is EFPIAs understanding that Summary Bridging Reports and Addendum reports will no longer be acceptable in Europe either so consider that Module VII should make this point clear. Proposed change: add the following (per ICH E2C(R2) "Each PSUR should be a stand-alone document: the format and table of contents of all reports should be as described in this GVP module. Regardless of the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		duration of the interval covered, each report should include interval data for the period covered, as well as cumulative data. Summary Bridging Reports and Addendum Reports, introduced in ICH Guideline E2C(R1), should no longer be submitted."
250-255		Comment: The sentence *"The latest CCDS in effect at the end of the reporting interval* ***should*** *be used as the reference for both, the benefit and the risk sections of the PSUR"* would oblige MAHs to create a CCDS for each product, even for purely local ones, whose Reference Information can be the approved SmPC . Proposed change: Replace the above sentence with *"The latest CCDS or the latest SPC in effect at the end of the reporting interval should be used as the reference for both, the benefit and the risk sections of the PSUR"*
259-262		Comment: EFPIA notes that different requirements for the CCDS/CCSI provided as an appendix to the PSUR have been introduced compared to the ICH E2C Step 2 guideline. The ICH guideline states that a *"tracked changes version of the reference document should be included (as an attachment that identifies changes over the reporting interval".* The PSUR GVP module, on the other hand states that "*The CCDS/CCSI should be dated, version controlled and it should state the version of the coding dictionary used"* EFPIA consider that provision of a track change version provides clearer advice to MAHs and will make it easier for review by the PSUR Assessor. The purpose of providing the version of the coding dictionary and how this information will be used in a scientific review of benefit risk is unclear, particularly given that the primary purpose of the PSUR in the future is as a scientific evaluation document and not a compliance tool. In addition, we propose that it would be clearer to request that a copy of the Reference Document "in effect at the end of the reporting period" be appended to the PSUR, rather than the "current" version: if the Reference Document was revised after the data lock point, "current" may be interpreted as that later version; the revised wording would also be consistent with lines 252-253. Furthermore, for a PSUR spanning a number of years (e.g. a "for cause" PSUR) there will be multiple versions of MedDRA used and therefore this will impose an unnecessary bureaucratic burden for the MAH to have to check back exactly what MedDRA version was in place when a particular adverse effect was added to the Reference document or even a new , contraindication or warning and precaution added. This takes into account

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		too that in the Reference Document statement would be conveyed in the most medically meaningful way to aid the prescriber as opposed to strict adherence to MedDRA terminology which was not designed for labelling purposes. Finally , as highlighted previously, the local SPC may be used e.g. for purely nationally authorised products so EFPIA considered that the term Reference Document should be used Proposed Changes: The marketing authorisation holder should provide a copy of all ~~current~~ versions of the Reference Document in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) referred in the PSUR as an appendix to the PSUR. The Reference Document should be dated, and provided as a track changes version that identifies changes made over the reporting period. ~~version controlled and it should state the version of the coding dictionary used.~~
263		Comment: The reference to the regional appendix includes an analysis of the meaningful differences between CCSI and local authorized product information. It should be clarified that it is not systematic for products with national approvals in the EEA to include all local SmPC with an analysis of the difference with CCSI. Furthermore, "meaningful differences" need to be further defined. Proposed change: The marketing authorization holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorized product information, i.e. differences in indications, safety profile, warning, and precautions. These differences should be included in PSUR regional appendices, to be provided only if there are specific issues in one member state.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
267		Comment: In the interests of clarity and consistency with ICH E2C, it is important to specify that the marketing authorisation refers to the IBD. The sentence has also omitted the E2C wording in relation to the Development International Birth Date (DIBD). It is important to reinstate this as the cumulative CT information and tabulations relate to the DIBD and not the IBD Proposed Change : ~~A~~ PSURs shall contain cumulative data starting from the granting of the marketing authorisation <u>(IBD) or DIBD</u> though with a focus....
349		Comment: Although it is similar in the ICH E2C (R2) proposal, the terminology ”analysis evaluation” seems to be including duplicative concepts . *Proposed Change :* We suggest this sub-heading to simply read “18.2. Benefit-risk Analysis” or “18.2. Benefit-risk Evaluation”
369 - 370		Comment: *significant changes to the labelling* [ICH E2C(R2)] is replaced by *significant changes to the investigator brochure and post-authorisation product information.* EFPIA considers that for both the ICH E2C (R2) guideline and this GVP module use of the word labelling may be confusing , particularly as post authorisation product information will be very specific to a region or country so the question then becomes “ which product information”? In the interests of clarity, international harmonisation as well as consistency with the title of section 5.4 of the PSUR (**Changes to the Reference Safety Information),** EFPIA propose

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		that the term "Reference Safety Information" is used. This recommendation also takes into account the provision in section 5.4 that any final and ongoing changes to the national /local authorised product information based on the most recent version of the CCSI will be included in an EU specific appendix. In addition , any significant amendments to labelling outside the EU would be summarised in section 5.3 (Actions Taken for Safety Reasons) , Proposed change: actions taken and proposed for safety reasons including significant changes to the Reference Safety Information ~~investigator brochure and post-authorisation product information~~ or other risk minimisation activities;
378		Comment: In the introduction section of the PSUR, EFPIA notes the addition of the sequential number of the report to IBD and reporting period when this had been removed from the ICH guideline as the sequential numbers were likely to vary between the regions when reporting intervals were different. However the sequential number is already included in the title page so when the reporting intervals are the same across one or more regions, it would enable the same introductory section to be used internationally if the need for repeating the PSUR number in the Introduction section was removed Proposed Change : IBD and reporting interval ~~and sequential number of the report;~~
379 and 385		Comment: As there may be significant variations in indications outside the EU, it should be specified what authorised indication(s) need to be stated, namely EU only or worldwide. The scope of indications will clearly be of high importance for the benefit/risk analysis. Proposed change: indications "listed in the CCDS when available, otherwise major authorised indications worldwide".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
After 382		Comment: The final bullet point in the introduction section of the PBRER (ICH E2C (R2), namely "*rationale for submission of multiple PBRERs (PSURs)* has been omitted from the GVP module. It is understood that in Europe multiple PSURs will be discouraged unless justifiable on legitimate scientific grounds so, in those circumstances, it would be anticipated that the competent authorities and PRAC Rapporteur would wish to know the rationale. This would in any case be provided to the other ICH regions in accordance with the E2C format. If only permitted to compile a single PSUR in Europe, it seems highly unlikely that an MAH operating in other regions would wish to create more work by compiling multiple documents for other countries. Proposed Change : Add a final bullet point to section 5.1: • rationale for submission of multiple PSURs, if applicable
400-425		Comment : This section is identical to the DSUR section 3. A distinction is made between investigational drugs and marketed drugs. This is confusing since the PSURs apply to authorised medicinal products and not to investigational drugs. In addition, an authorised medicinal product can be under investigation whether marketed or not. Proposed changes: Line 400: Actions related to investigational ~~drugs~~ uses Line 417: Actions related to ~~marketed drugs~~ marketing experience
438-442		Comment: This section refers to an "*accurate estimate*" which is an oxymoron and not reflected in E2C for that very reason. In addition the remainder of the paragraph can be interpreted as requiring drug utilisation studies on all products regardless of whether or not this is warranted. The apparent need to conduct such studies in all products during the lifecycle also seems inconsistent with the risk proportionality principle as well as being in addition to what has been agreed in the ICH E2C Step2 guideline. In addition, for vaccines, it will be difficult to estimate the exposure and the use, the volume of sales is known but the administration for the public

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		vaccination campaign is under the responsibility of national programs for immunization. Outside Europe, in developing countries these campaigns can be organized by NGO through donations of vaccine doses and the MAH is not always involved. EFPIA considers that this is not the intent of this wording but simply how it can be interpreted based on the wording as it stands Proposed change : PSURs shall provide an ~~accurate~~ estimation of the population exposed to the medicinal product including all available data relating to the volume of sales and volume of prescriptions. Where data available to the MAH allow the analyses to be made, ~~T~~this estimation of exposure should be accompanied by both a qualitative and quantitative analysis of actual use including how it may differ from indicated use ~~based on all data available to the marketing authorisation holder including~~. Sources of information for the analyses should include the results of observational (e.g. registries) or drug utilisation studies when these have been conducted.
450 - 451		Comment: EFPIA assume that the intent of this section is to provide subject exposure from clinical trials sponsored by the MAH as a denominator for the Cumulative Table of SAEs presented in section VII.B.5.6.2 which is focused on SAEs reported in the MAH's clinical trials (line 529-530). Therefore to align these sections we propose that is clarified that the scope of the cumulative clinical trial exposure to be presented here is for MAH's Clinical Trials only. Please see also next comment. Proposed Change: This section of the PSUR should contain the following information on the patients studied in clinical trials sponsored by the MAH
452-453		**Comment:** The MAH should only be expected to provide numbers of subjects from trials that they have sponsored. It would be extremely difficult for the MAH to provide numbers of patients from trials not sponsored by themselves, e.g., investigator-initiated studies. **Proposed change:** Revise to read: "*cumulative numbers of subjects from ongoing and completed clinical trials* ***sponsored by 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')*
		***MAH** exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD."*
487-488		Comment:"The data should be routinely presented by sex, age,…" EFPIA are concerned that, whilst there are ways to estimate total exposure based on sales volumes, it will be impossible for all products to reliably break down these data further and present them by sex and age and to provide estimates without conducting specific studies. Such studies would require to track patient information and to access patient information which seems unduly burdensome from a data privacy perspective if required systematically. It should also be noted that exposure data are frequently calculated from externally owned data sets which simply do not contain these parameters. Proposed change: remove these additional estimates: "The data should be routinely presented by ~~sex, age,~~ indication, …"
513-514		Comment: The CCDS may not be an appropriate basis to determine what could constitute an off-label use, since companies may not always list all registered indications of a product in the CCDS. Proposed change (if any): 'For purposes of identifying which patterns of use are off-label, the marketing authorisation holder should include all authorised indications e.g. as included in the CCDS.
536		Comment One of the sentences in the section on Cumulative Summary Tabulations of SAEs from Clinical Trials" in both ICH E2C and ICH E2D is missing, namely "*data can be integrated across the programme.* As this is helpful advice and as this section, as well as the tabulation will be common modules with the DSUR , EFPIA recommend that the original ICH E2C wording is retained 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')*
		Data can be integrated across the programme. Alternatively, ~~W~~ when useful and feasible, data can be presented by trial, indication, route of administration or other variables.
564		Comment: In listing the data sources of reports used to generate the summary tabulations from post-marketing sources, the wording " *reports...from regulatory authorities*" in ICH E2C (R2) has been replaced by " *competent authorities"* in the GVP PSUR module. Whilst understandable in a European context, this change is likely to have the unintended consequence that, as "competent authority" is a term only applicable to the European regulatory authorities, it could be interpreted as restricting reports to those originating from Europe as opposed to all regulatory authorities worldwide. Proposed change : These adverse reactions are derived from non-interventional studies, and spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, and ~~competent~~ regulatory authorities.
570 - 571		Comment; EFPIA note that a phrase has been retained that was removed from the ICH E2C guideline as it was a non-sequitur i.e. a statement that does not follow logically from that which preceded it. Proposed change : As described in ICH-E2D guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter, ~~although certain reports may need further evaluation (e.g. reports of hepatotoxicity).~~
574-585		Comment: Section VII.B.5.7 is entitled "**Summaries of significant findings from clinical trials in the reporting interval",** so appears to refer to findings from all interventional clinical trials. However, the first paragraph requires the inclusion in an appendix of *"sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the reporting interval" (i.e., those qualifying as a Post Authorisation Safety Study) Therefore, clarification is needed on the data to be included in this section (i.e. from all clinical trials or from just interventional PASS Proposed changes: <u>This section of the PSUR should provide summaries of significant findings from all the marketing authorisation holder`s interventional clinical trials. In addition</u>, t~~The~~ marketing authorisation holder should include as an appendix a listing of the MAH sponsored interventional trials with the primary aim of…….
589-592 673-678		Comment: EFPIA appreciate that these sections reflect ICH E2F but note that Section 5.13 refers to lack of efficacy findings while Section 5.7 of the PSUR should present a summary of clinically important efficacy finding. As a result these sections would appear to leave open a large potential for overlap. It is also noted that additional wording to that in E2F has been added to section 5.7, namely "*When relevant to the benefit-risk evaluation, clinical trials demonstrating lack of efficacy for products not intended for treatment of life-threatening diseases in the approved indications should also be summarised in this section".* As section 5.13 refers to clinically important efficacy information, we assume that these findings referred to in section 5.13 could be summarised in the earlier section to minimise confusion and bring the sections back in line with E2F Proposed change (if any): In section 5.13: Line 589 .....clinically important <u>or relevant to the benefit risk evaluation</u> guideline..... Lines 676-678: delete ~~*When relevant to the benefit-risk evaluation, clinical trials demonstrating lack of efficacy for products not intended for treatment of life-threatening diseases in the approved indications should also be summarised in this section".*~~
650 - 658		Comment: EFPIA note that wording in the Literature section of the PBRER which was removed by the ICH E2C Expert Working group has been retained in the PSUR GVP guideline. The wording as it is currently written is very prescriptive, may not be feasible and/or applicable to all products and appears to be inconsistent with proportionality principles. Please also see next comment in relation to the proposed changes to medication error

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		Proposed Changes : The special types of safety information that should be reviewed where applicable ~~included,~~ but which may not be found by a search constructed specifically to identify individual cases, include: • pregnancy outcomes (including termination) with no adverse outcomes; • use in paediatric populations; • compassionate supply, named patient use; • lack of efficacy; • asymptomatic overdose, abuse or misuse ▪ medication error ~~where no adverse events occurred, or "near misses";~~ • important non-clinical safety results.
657 and 729		Comment: the inclusion of *'identified medication error where no adverse events occurred, or near misses of medication errors'* would seem to imply the need for a specific analysis of those medication errors that did not have any consequences for the patient. EFPIA considers that from a clinical and patient safety perspective, any analysis of medication errors should include those resulting in adverse events in order to estimate the relevance of the error. Analysis of medication errors without associated events or even near misses will rarely yield any important information upon which the MAH could act over and above analysis of errors with clinical sequelae. This is also an additional requirement to what was agreed in ICH E2C and EFPIA consider that the E2C wording should be reinstated in both the lines referenced Proposed change: identified medication error ~~where no adverse event occurred, or near misses of medication errors~~
716 & 722		Comment: Section 16.1 of the PSUR has been identified as a common module with Part II module SVIII and

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		both are titled "Summary of Safety Concerns". Therefore reference to " summaries" in lines 716 and 712 is confusing and ambiguous. Proposed Change : 716: The summary ies should represent the best available knowledge of the product..... 722: ….should be equal to the summary ies provided in the version of the safety specification current at the beginning of the PSUR reporting interval.
724 – 726		Comment: This paragraph assumes that all authorised indications are always listed in a CCDS. However, this may not be common practice for all companies and/or all types of products. Proposed change (if any): 'This sub-section of the PSUR summarises baseline information on both efficacy and effectiveness of the medicinal product as of the beginning of the reporting interval. This information should relate to authorised indication(s) of the medicinal product, e.g, listed in the CCDS.'
829-830		Comment: As noted before not all necessarily have a CCDS for all their products. and it is not a regulatory requirement to do so. In addition whilst CCDSs may contain the licensed indications globally they do not (per CIOMS II/V guidelines) usually contain benefit information Proposed change: When there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, the summary should be succinct, essentially the content of the CCDS
735-754		Comment: EFPIA note that the Signal Section 5.16 and subsection 5.1.6.2 refer to " signal" where Module IX refers to validated signal. EFPIA appreciate that " validated signal " is specific to the EU signal management process but it would be helpful to provide to clarify that the term signal used in Module VII is equivalent to a validated signal in Module IX. This would avoid confusion and provde the neeed link between the two modues

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		Proposed change : add a footnote to page 20 to the effect that " for the purposes of the PSUR , use of the term signal is the same as " valid signal" described in GVP Module IX
1006		Comment: This line refers to staff being trained "*according to the applicable guidelines"* when it is unclear what guidelines are being referred to. If the " applicable guidelines " refer to ICH E2C and/or the PSUR GVP module, it would be helpful to add this in parenthesis Proposed change : ....and trained according to the applicable guidelines (e.g.ICH E2C (R2) and this GVP PSUR module)
1019-1021 Figure VII.1 1275-1329 1330-1521		Comment: On review of the procedure for assessment of PSURs for a "single centrally authorised medicinal product only" we can see the initial review is longer than currently (60 rather than 30 days) and the assessment will need to go to PRAC and CHMP. Whilst we welcome the introduction of the MAH being able to comment on the preliminary assessment report, we are concerned that the longer procedure may mean that for a PSUR on a 6 month review cycle, that the procedure may end after the next PSUR data lock point which will give little time to implement the recommendations from the review before the next PSUR is due for submission. We have a similar concern for "Assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance" where the outcome of the assessment by the Rapporteur is reviewed by member states, then has to go to PRAC, and then to CHMP or CMD(h). Measures/allowances will need to be put in place to prevent unfavourable feedback from reviewers in cases where the MAH may not have had sufficient time to incorporate new requests to the PSUR. Proposed change (if any): If time between end of a PSUR assessment and the next PSUR data lock point does not allow enough time to implement the recommendations of the assessment, that these activities can be include in the subsequent PSUR.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1065-1072		Comment: For the reasons already highlighted in the general comments section, EFPIA is concerned that no provision has been made to take the International Birth Date into account in assigning the Union reference dates although this is a clear recommendation of ICH E2C in the interests of international harmonisation . EFPIA appreciates that the Directive Article 107c (5) stipulates use of the EU birth date. However, there are also a number of references to use of the IBD in the module , therefore it is contradictory and confusing that this has not been included as an option in section C.3.2 Proposed change : The Union reference date of medicinal products containing the same active substance or the same combination of active substances shall be [DIR Art 107c(5)]: • the date of the first marketing authorisation in the EU….. • if the date of first marketing authorisation cannot be ascertained, the earliest of the known dates of the marketing authorisations…… In the interests of international harmonisation, due consideration will be made to utilisation of the international birth date or reference dates already assigned under the work share scheme in the determination of the Union Reference dates for the list.
1148-1150 (Fig.VII.3), 1205-1206 (Fig.VII.4) And 1232-1233		Comment: The MAH is required to submit a variation to the MA to update the PSUR frequency in line with the list of EU reference dates. Such a variation should only be necessary when a product is first included in the list of reference dates, to simply include a statement in the MA that the PSUR frequency will be in line with the list. To require the submission and assessment of subsequent variations whenever the list is updated would be a waste of time and resources. Proposed change (if any): Amend the wording in these sections to "Where appropriate, marketing authorisation holders shall submit the relevant variation to include a statement that PSUR submission frequency will be in accordance with the list of EU reference dates, within 6 months of the inclusion of the product in that list"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1263-1267 1296-1300 1370-1374		COMMENT: As highlighted in the General Comments section, EFPIA consider that an analysis of spontaneous non serious cases only to be of dubious scientific validity as these would have already been analysed by the MAH should a signal have been generated in the time period. Any additional analysis requested should be on the basis that it will be relevant to the overall benefit risk evaluation of the product. Proposed change (applicable to all references cited): Listings of individual case safety reports may be requested in the context of the PSUR assessment procedure where these are relevant to the benefit risk assessment ~~for~~ e.g. adverse reactions of special interest and should be provided by the marketing authorisation holder within an established timeframe to be included in the request. This may be accompanied by a request for additional analysis (es) of data where these will contribute to the overall assessment of benefit risk. ~~cases classified as non-serious.~~
1311-1313		COMMENT: It is unclear why the marketing authorisation holder does not receive the updated assessment report. This would be important information to share that would aid the marketing authorisation holder in engaging in collaborative interactions with the PRAC. Proposed change: Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG 1311 Art 28(3)] using the template available in Annex III, within 15 days (i.e. by Day 105). The updated assessment report is made available to the members of the PRAC and the marketing authorisation holder
1323–1324		There are several statements similar to "*Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC.*" The PRAC should resolve divergent issues within the PRAC in order to provide clear, unified requests and comments to MAHs. **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')*
		Add wording to line 1324 to read: "*Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC [REG Art 28(3)].* ***However, The PRAC will resolve divergent issues prior to issuing an Assessment Report or making requests in order to provide clear, unambiguous communications to MAHs***."
1577-1588		Comment: In Section VII.5.3 it says MAHs need to make a comparison between the CCSI and their proposals for the SmPC, and that the proposed SmPC and package leaflet should be included as an Appendix to the PSUR. However, it does not say how this information should be provided when the active substance is subject to a mixture of national and MR/DCP licences. Proposal: For products authorised via a mixture of national and MR/DCP, we propose that MAHs should submit a proposed Core Safety Profile in place of the proposed SmPC, as is requested under the current EU PSUR worksharing procedure. Clarification is required on what should be submitted for the package leaflet, as this is not currently provided in the EU PSUR worksharing procedure.
1550-1576		The EU regional appendix requiring EU marketing authorisation status (VII.C.5.2) has detailed requirements which EFPIA consider to be unnecessary duplication of information that MAHs are required to submit to the EMA via EudraVigilance (Article 57). This information can change frequently, so the information in EudraVigilance will be more up-to-date than that in a PSUR. In addition, some of the information required in the new format may not be available for PSURs for products that have been authorised for a number of years, Proposal: It would be preferable to allow MAH to refer to information included in EudraVigilance. If this section remains, amend the first paragraph as follows: "Marketing authorisation holders should provide a detailed description of the marketing status for all Member States where marketing authorisation(s) have been granted. This information should contain the following, where available:"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1757-1759		Comment: The reference to DIR Art 106a seems inappropriate, as it concerns public announcements on "pharmacovigilance concerns" (emphasis added): the information to be released regarding PSURs and their assessment will not always be associated with "concerns". The requirement for the Agency and NCAs to remove personal information or commercially confidential data is applicable to the release of any documents to the public. Proposed change (if any): Any personal or confidential data **shall be deleted from the documents to be** made public by the Agency or the competent authorities in Member States ~~**as referred to in paragraphs 2 and 3 of Article 106a of Directive 2001/83/EC shall be deleted**~~ unless considered necessary in terms of protection of the public health ~~**[DIR Art 106a(4)]**~~.
1806-1808		Comment: **Transitional Arrangements for PSURs for national/MR/DCP products.** In this section it states that the EU single assessment procedures detailed in VII.C.4.2.2, VII.C4.2.3 and VII.C.4.2.4 will be delayed until funds are available. We request that additional information is added to the Transitional Arrangements Q&A document to inform MAHs on the interim arrangements. Proposal: Clarify the following points • Will current HMA PSUR work sharing arrangements continue as previously agreed and presumably to agreed EU harmonised dates? • Does the Agency have a target date for implementation for single EU assessment procedure? • Will the previously agreed EU HBD and submission cycle (or interval dates going forward) remain and continue to previously agreed dates as posted to HMA website?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		• When will list of Union reference dates be published and will MAH have access to the prior to implementation? • How will products that do not require PSURs be determined and how will this be communicated to MAHs?
		The following comments are of an editorial nature only
253		**Remove the comma after both as not required.**
582-583		"Over view on Signals: New, Ongoing and Close" should read " Overview of Signals : New , Ongoing and Closed)
609		Comment: the phrase "Unless otherwise specified by national or regional regulatory requirements,....." seems to be carried over from the ICH E2C Step 2 guideline but not relevant for the GVP module. It is also confusing in a purely European context. Proposed change : ~~Unless otherwise specified by national or regional regulatory requirements, t~~ The following options can be used to present data from combination therapies :
669		Correction (highlighted in bold): "…the marketing authorisation **holder** should summarise…"
700		Comment: The sentence "*This section should consist of a tabulation of signals ongoing and closed during the reporting interval.* appears to have omitted the concept of new signals (per ICH E2C). Proposed change : This section should consist of a tabulation of signals new, ongoing and closed during the reporting interval.
715		"public heath" should read "public health".
1019 - 1021		Comment: **Figure VII.1.** PSUR procedure - general process still includes provision for 60/75 /90 days between PSUR creation by the MAH and submission. The proposals are for 70 and 90 day submission from the DLP Proposed Changes : Change 60/75/90 days to 70/90 days

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		Throughout this module and the other GVP modules, the terms “benefit-risk” and “risk-benefit” have been used. It would be preferable to use one term consistently – the preferred terminology is “benefit-risk”.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
EGA – European Generic Medicines Association

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Since in general the requirement for writing PSURs for generics is waived, the complexity and impossibilities of PSURs for generic products are not taken into account. In some sections of the below commented document we will describe what should be exempted for generics. For products for well-established use and generics there is usually a variety of indications and dosage schedules present in all different SPCs – therefore generic companies do not have a CCDS, but work with a CCSI. The PSUR should not be considered as a document to discuss the correct indications and posology – so a thorough review and reassessment of that should not be expected. PSUR is not the place where all the local SmPCs, PILs and changes made to them should be appended.
	From July 2012, PSUR submission not applicable to generics, unless specified in the MA or requested. However, it is not clear in the GVP module VII if this statement will apply also for renewal process for these products (i.e., no need to submit a PSUR for the renewal) or if a PSUR will be still required within the renewal package. This should be clarified in the GVP.
	Other general comments: - Transitional period not specified - Is new PSUR template applicable to PSUR with DLP after 21/7/2012 or to PSURs to be submitted after 21/7/2012? - Not clear, if in generic PSURs for active substances not listed in URD, submission of variation to PSUR cycle/submission is required - ICH guideline on PBRER (section 2.7.3) states, that the Summary Bridging Reports and Addendum Reports, introduced in ICH E2C(R1), should no longer be submitted. We have not found any comment in GVP module VII. - ICH guideline states, that when the MAH needs to prepare PBRERs covering different intervals for different regulatory authorities, overlapping periods could be introduced. Again, no comment found in GVP module VII. - The integration of DSURs and PSURs in a single template/document encompassing both pre- and post-authorization data should be foreseen. To implement PSUR's there should be a template available which is a format that is also usable outside

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 146		Comment: Considering all the new analysis and requirements to be covered in the PSUR, lot of cross-departmental inputs, PSUR submission deadline should be longer than 70 days (for PSURs up to 1 year). Proposed change: Change to at least 3 months.
Lines 157-161		Comment: Regarding modular approach of the PSUR - it is still not efficient to repeat and maintain the same information in 2 documents. Furthermore, only a link to the RMP is needed when available. Proposed change: Instead of copying sections from the RMP, it should be sufficient just to make a reference to the RMP, when available.
Line 165		Comment: Term “condition” in the marketing authorisation is too broad and may be understood as any statement in approval decision. According to present legislation a decision on PSUR submission cycle has been included as a rule in every EU procedure (MRP, DCP, and CP); in most cases it was not based on any safety issue. To avoid unnecessary workload and costs in relation to existing marketing authorisations of generic, WEU, traditional use, and homeopathic products, the term “condition” should be limited to conditions, which are really relevant. Proposed change (if any): For generic products PSURs shall be submitted where there is a condition in the marketing authorisation due to a safety ~~or efficacy~~ issue or.....
Lines 165-167		Comment: If there is a request for a generic PSUR on basis of concerns relating to pharmacovigilance data there should be a possibility to provide only relevant parts/data instead of whole PSUR, if appropriate, in order to reduce workload with both MAHs and authorities.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): We suggest to add the following: In case of concerns relating to pharmacovigilance data and if agreed by competent authority in a member state, PSUR content may be limited to include only those parts or data, which are relevant for evaluation of the safety concern.
Lines 220 - 223		Comment: it is not really clear what the starting point for the cumulative data is. It should not be necessary to include the definition of IBD or DIBD here. Also, this should take into account that not all MAH who need to write PSURs have a comprehensive database (e.g. MAHs for Generics). Proposed change (if any): Conducting an integrated benefit-risk analysis for authorised indications based on the cumulative information available i.e. since the international birth date (IBD), or the date of the first marketing authorisation for the MAH in any country in the world or the development international birth date (DIBD) or the date of first authorisation for the conduct of an interventional clinical trial sponsored by the MAH in any country.
Lines 220-221, 821		Comment: A difference between terms efficacy and effectiveness is not clear. Proposed change (if any): Clear definitions should be provided so that the terms will be understood by stakeholders in the same way. The EGA proposes to include these definitions in Annex I
Lines 222-225		Comment: DIBD is not relevant for generic, WEU and traditional use products due to very limited or not existing preauthorisation clinical studies. Proposed change (if any): Risk-benefit analysis of generic, WEU and traditional use products should be conducted since IBD.
Lines 231		Comment: PSUR conclusion should primarily indicate whether any actions or changes are needed to the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		CCDS/CCSI, and not to the approved SmPC(s). Relevance for the individual SmPCs should be discussed separately related to the procedure. Proposed change: Replace "summary of product characteristics" with "CCDS/CCSI".
Lines 252 - 254		"The latest CCDS in effect at the end…..sections of the PSUR" Since generic companies do in general not have a CCDS, also the CCSI should be mentioned as possible reference document. For summary tables from clinical trials it should be considered to use the IB as a reference for safety information. When the marketing authorisation is approved in only one member state, the MAH may not have a CCSI/CCDS. In that case, the SPC should be considered rather than the CCDS/CCSI. Change to: "The latest CCDS *or CCSI or SPC in* effect at the end…..sections of the PSUR" "for summaries from clinical trials the IB can be used as reference.
Lines 261 - 262		The ICH guideline states that a *"tracked changes version of the reference document should be included (as an attachment that identifies changes over the reporting interval".* The PSUR GVP module, on the other hand states that "*The CCDS/CCSI should be dated, version controlled and it should state the version of the coding dictionary used"* The purpose of providing the version of the coding dictionary and how this information will be used in a scientific review of benefit risk is unclear, particularly given that the primary purpose of the PSUR in the future is as a scientific evaluation document and not a compliance tool. Furthermore, for a PSUR spanning a number of years (e.g. a "for cause" PSUR) there will be multiple versions of MedDRA used and therefore this will impose an unnecessary bureaucratic burden for the MAH to have to check back exactly what MedDRA version was in place when a particular adverse effect was added to the CCSI or even a new, contraindication or warning and precaution added. This takes into account too that in the CCSI statement would be conveyed in the most

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		medically meaningful way to aid the prescriber as opposed to strict adherence to MedDRA terminology which was not designed for labelling purposes. Proposed Changes: "The CCDS/CCSI should be dated and~~,~~ version controlled. ~~and it should state the version of the coding dictionary used~~"
Lines 263, 432, 434		Comment: The reference to the regional appendix includes an analysis of the meaningful differences between CCSI and local authorized product information. Does it mean that for a product with a national approval all local SmPC should be included and analyzed? Many products have been approved through in several European countries with national procedure. Proposed change (if any): the regional appendix should be added only if there are specific issues in one member state. Definition of word "meaningful" should be described in detail.
Lines 285-286		Comment: Terms co-marketing and co-distribution are not defined. Proposed change (if any): Clear definitions should be provided so that the terms will be understood by stakeholders in the same way.
Lines 288-289		Comment: Some clinical studies, e.g. bioequivalence studies are usually may not be relevant. Proposed change (if any): We propose that the text is changed: - ongoing clinical trials and other studies that the MAH or its representative is conducting or has completed during the reporting period, if applicable for evaluation of benefit/risk ratio.
Line 302		Comment: The guidelines don't allow simplified format of PSUR although in some cases such approach is

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		rationale. Proposed change (if any): An option for a simplified format of PSUR, if agreed with the authorities, should be foreseen.
Lines 353, 378		Comment: In some companies PSURs are numbered in a non-sequential way - such as based on the active substance internal number and/or data lock point Proposed change (if any): remove the word "sequentially"
Lines 354-355		Comment: A large generic company may have many different MAHs for the same product, it is impossible to name them all on the title page. Proposed change (if any): MAHs should be indicated in the registration status of the PSUR, not on the title page.
Lines 369 - 370		Comment: *significant changes to the labelling* [ICH E2C(R2)] is replaced by *significant changes to the investigator brochure and post-authorisation product information.* It is considered that for both the ICH E2C (R2) guideline and this GVP module use of the word labelling may be confusing, particularly as post authorisation product information will be very specific to a region or country so the question then becomes “which product information”? In the interests of clarity, international harmonisation as well as consistency with the title of section 5.4 of the PSUR (**Changes to the Reference Safety Information),** we propose that the term “Reference Safety Information” is used. This recommendation also takes into account the provision in section 5.4 that any final and ongoing changes to the national /local authorised product information based on the most recent version of the CCSI will be included in an EU specific appendix. In addition , any significant amendments to labelling outside the EU would be summarised in section 5.3 (Actions Taken for Safety Reasons) ,

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: actions taken and proposed for safety reasons including significant changes to the Reference Safety Information ~~investigator brochure and post-authorisation product information~~ or other risk minimisation activities;
Line 379		Authorised indication(s): EU or worldwide? They are of highest importance for the benefit/risk analysis: - Although the GVP is a EU document, the document is meant to be implemented worldwide according to ICH, then leading to a worldwide range of indications (not only EU indications). How to list these indications (written summary, table?)
After 382		Comment: The final bullet point in the introduction section of the PBRER (ICH E2C (R2), namely "*rationale for submission of multiple PBRERs (PSURs)* has been omitted from the GVP module. It is understood that in Europe multiple PSURs will be discouraged unless justifiable on legitimate scientific grounds so, in those circumstances, it would be anticipated that the competent authorities and PRAC Rapporteur would wish to know the rationale. This would in any case be provided to the other ICH regions in accordance with the E2C format. If only permitted to compile a single PSUR in Europe, it seems highly unlikely that an MAH operating in other regions would wish to create more work by compiling multiple documents for other countries. Proposed Change : Add a final bullet point to section 5.1: • rationale for submission of multiple PSURs, if applicable
Lines 385-386		Comment: What does it mean "where authorised, if applicable"? Do we need to list all countries where the product is authorised or not? Proposed change: Clarify if we need to indicate where the product is authorised, or not.
Lines 387-399		Comment: It is not clear if actions for safety reasons should be described in relation to active substance or to

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		relevant products of the MAH; similarly it is not clearly defined whether to include information from countries where the MAH is holding its MAs or worldwide. Proposed change (if any): To include clarification of the requirements.
Lines 400 - 425		This section is identical to the DSUR section 3. A distinction is made between investigational drugs and marketed drugs. This is confusing since the PSURs apply to authorised medicinal products and not to investigational drugs. In addition, an authorised medicinal product can be under investigation whether marketed or not. Proposed changes: Line 400: Actions related to investigational ~~drugs~~ uses Line 417: Actions related to ~~marketed drugs~~ marketing experience
Lines 422-423		Comment: in the phrase "safety related changes in labelling documents that could affect the development programme" - it is unclear why is the development programme mentioned here when those changes concern actions related to already marketed drugs? Proposed change (if any): remove this requirement from the section "marketed products" because it concerns products under development, and not marketed products.
Lines 434-436		Comment: PSUR is not the place where changes made to the local SmPCs should be reported. This is done locally, in local language. Proposed change: Remove the requirement to report changes made to local SmPCs in the PSUR (regional appendix).
Lines 438-442		Comment: Often it is not possible to accurate estimate a volume of prescriptions or the nature of the population

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		exposed. Proposed change (if any): It should be recognised that a volume of prescriptions or the nature of the population exposed may not be obtainable.
Line 475		"When possible, separate estimations should be provided for cumulative exposure (since the IBD) and interval exposure (since the DLP of the previous PSUR)" For generic companies which grow through acquisitions the cumulative sales going back to first sales is not combined and therefore not available. The phrase "when possible" will be interpreted that it should in fact be available, which for the general safety profile of the product is not needed. The sentence should be rephrased to indicate that most important are the sales of the PSUR period and less important is the sales since IBD. Proposed change to: "Interval exposure since the DLP of the previous PSUR should be provided. When readily available and considered relevant when there is only one MAH in the EU, separate estimations could be provided for cumulative exposure (since the IBD)
Lines 487-488		Comment: If patient exposure is derived from sales data, the data on indication, sex and age are sometimes not available. Proposed change (if any): Add "where such information is available" for data on sex, age and indication
Line 514		Comment: Some companies maintain and attach CCSI but not CCDS to the PSUR. For MA that only covers one Member state, the CCSI may not be available. In this cases, please consider the SPC rather than CCDS.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Add the option to attach SPC or CCSI if CCDS is not available.
Line 519 – 521		This paragraph states that the seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to the ICSR. This does not take into account that ICSRs may contain serious and non-serious events/reactions. If non-serious reactions are categorised as serious because they are part of an event episode that included a serious event, incorrect conclusions might result from the presentation of data in summary tables in this way.
Lines 566-567		Comment: Automatic generation of a single table where interval and cumulative data are presented side by side may not be possible since many of current databases are not yet upgraded to be in-line with the new requirement. Manual compilation of a table does not comply with quality requirements; especially not for big volume of data the risk for mistakes can be substantial. Proposed change (if any): There should be a long enough transitional period to allow for appropriate upgrade of safety databases; during transitional period it should be allowed to present interval and cumulative data in separate tables.
Lines 611-616		Comment: Please specify or give examples of what "important safety findings" for a combinational product should be included in the single-substance PSUR and vice versa. Proposed change: see above
Lines 625 - 629		This paragraph states that any MAH sponsored non-interventional study with the aim of measuring the effectiveness of risk management measures which was completed or ongoing during the reporting interval (i.e. post-authorisation safety studies). For the scenario where one of the risk management measures is controlled distribution, there may be studies which do not involve patients or the drug use, but look at compliance with operational measures (for example what happens at the pharmacy level). It would be very helpful if it could be

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		specified whether this type of study should or should not be included in the relevant appendices.
Lines 630-631		Comment: For PASS studies conducted locally as a local requirement the progress/final study reports are available in the local language only? Proposed addition: "Progress or final study reports…. Appendix in the PSUR. *If the report is in local language a summary in English is sufficient*"
Line 669		Correction (highlighted in bold): "…the marketing authorisation **holder** should summarise…"
Line 823		What is the difference between 'efficacy' and 'effectiveness' in this context? Could definitions be included in Annex 1?
Line 830		It is not clear what is meant with 'the summary should be succinct, essentially the content of the CCDS'. As the CCDS should be appended, could the MAH in this scenario refer to the CCDS?
Line 844		Comment: It is unclear if the new information on efficacy and effectiveness, as mentioned in this section, refers to MAH's own data, or MAH is expected to search the literature. Proposed change: Clarify the scope of new information.
Line 888		Comment: Some of the data requested in this section are overlapping with the data in subsection "Important baseline efficacy and effectiveness information". It would be clearer to present them together. Proposed change (if any): The data from this section should be added to the section on "Important baseline

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		efficacy and effectiveness information", and the section "Benefit-risk context-medical need and important alternatives" should be deleted.
Lines 948-949		Comment: cumulative and interval summary tabulation; see comment to lines 566-567 Proposed change (if any): a single or separate tabulations of cumulative and interval ADRs should be allowed
Line 963		The term “clinical study report” has a different meaning, i.e. the CSR as a write-up of the clinical study. It would be better to change the sentence to: “…are ~~case~~ management of **individual** spontaneous and clinical study **case** reports,”
Lines 956 – 1001 / 1631 - 1663		Comment: Sections VII.C.6.1 and VII.B.6 both guide on quality systems with regard PSURs at the level of the MAH. Having this topic divided in two sections is confusing for the MAHs and may easily result in overlooking of one part. Proposed change (if any): We suggest that both sections are put together at the end of the guide.
Line 1000		Comment: The agreement should specifically detail the options to audit the PSUR preparation process.
Lines 1050, 1106, 1232		Comment: The URD list to be published as well as the DIR and the REG determining the periodicity changes are all parts of the legislation and as such legally binding documents. The intentions of the new legislation are amongst better protection of the patients, simplification, reduction of duplication, and reduction of bureaucracy. Submitting variations to move to either no PSURs (for generics) or other dates (from the URD list) is not only a waste of time, money and resources at the site of the MAH, but even more of the MS and the agency spending community money on useless administration instead of the real health care topics.

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		The only reason given by the agency until now is that there is a “legal requirement” – since the documents as drafted now do have a legal basis there should be a way to solve this.
Line 1079		Comment: It would be useful to also add in the URD list the name of the company that is responsible to write a PSUR for a particular substance. Proposed change: see above
Lines 1083-1086, 1218-1219, 1226-1227		Comment: no possibility of active remainder for changes in the URD list is mentioned Proposed change (if any): A technical tool should be implemented to allow a possibility for automatic information in case of new documents or changed documents on web sites with URD list and other important safety information
Lines 1111, 1155		Comment: Often in generic companies one PSUR is prepared for the group of MAHs and not for individual MAH. Proposed change (if any): add: one marketing authorisation holder or a group of MAHs
Line 1124		Comment: see comment for line 165 regarding the term “condition”
Lines 1146-1149		Comment: Figure VII.3. Variation to a MA is required to follow the URD list in each case when there is condition to MA to submit PSUR, even if such “condition” has nothing with any safety issue but simply follows current valid recommendation, e.g., 3-yearly PSUR submission based on worksharing. Such position does not improve public health nor reduce administrative burden and we find it extremely bureaucratic, leading to unnecessary workload and costs for both, MAHs and authorities. Before placing a substance to the URD list, to define an appropriate PSUR submission schedule, any safety concern is taking into account, therefore any further assessments from

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		national authorities are redundant. Proposed change (if any): Any time/costs burden due to unnecessary variation procedures should be avoided. A simple notification by the MAH to national regulatory authorities with a list of MAs planned to follow an URD defined PSUR submission schedule should suffice to inform authorities in all cases where PSUR submission schedule has been defined based on usual legislative requirements and devoid of any safety issue affecting this schedule (which could be confirmed with a statement by the MAH). MAH should only apply for a variation in case that there was a condition in the MA raised by a safety issue, which influenced the PSUR submission schedule.
Lines 1152-1157		Comment: in case that the MAH only holds MA to the combination product, neither of suggested option is appropriate Proposed change (if any): An option for a stand-alone PSUR without cross-references to the single substance PSUR should be available
Lines 1158-1161		Comment: It is not rational, neither efficient, to always have to contact and agree with the competent authorities upfront whether we shall write a stand-alone PSUR for a combinational product, or we shall cover it in the same PSUR for the single substance product. Proposed change: Leave the option for MAH to choose the preferred way, without the need to agree with authorities.
Line 1163		Comment: the minimum deadline (after the request from the competent authority) for ad hoc PSUR submission should be defined. 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')*
		"shall submit PSURs "immediately" with a mutually agreed deadline, taking into account the amount of data and analysis necessary for PSUR preparation.
Lines 1164 - 1166		Comment: "To facilitate the EU assessment….. the competent authorities in the MS may make use of the list of EU reference dates……" To eliminate and facilitate requests as much as possible "may" should be replaced by "should" unless justified. Proposed "To facilitate the EU assessment….. the competent authorities in the MS ~~may~~ should make use of the list of EU reference dates……"
Line 1226		Comment: The agencies webportal should enable pushmail in order to make sure MAHs will receive essential information important for the safety of their products. Proposed change "*The agency shall facilitate pushmail so* MAH shall *be notified* ~~continuously check the European medicines portal~~ for any relevant updates…"
Lines 1254-1258		Comment: see comment to lines 1442-1445
Lines 1276-1279, 1330-1339		Comment: From Figure VIII.5 it is evident that PSUR assessment procedure will take at least 135 days. Taking into account 70 days for compilation of PSUR, the ARs may not be released before the DLP of the next (eventually) 6-monthly PSUR. In case that PSUR submission cycle follows the dates on URD list, it is too late to publish the next 6-monthly PSUR DLP after the AR is released. Proposed change (if any): It should be taken into account that in case of need for another 6-monthly PSUR, 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')*
		next DLP is published before final AR.
Lines 1421-1423 Lines 1442-1445		Comment: the guidelines state that the MAH(s) of CAPs should provide the translations of the product information in all EU official languages. It is not clear if this is also required from the MAHs of the generic CAPs. As simultaneous translations of the same text by several MAHs will undoubtedly result in several versions of national text therefore it is crucial that only one version of national translation is in place to avoid unnecessary time spent on assessment and LoDs to variations. Proposed change (if any): We suggest that translations of the texts are only provided by the innovator.
Lines 1461-1464		Comment: There is no guidance of who will provide translations of the varied texts in case, where no CAP exists. As simultaneous translations of the same text by several MAHs will undoubtedly result in several versions of national texts therefore it is crucial that only one version of national translation is in place to avoid unnecessary time spent on assessment and LoDs to variations. Proposed change (if any): To assure timely and smooth implementation of identical national texts in SmPC s and PILs of the innovator and all generic products, we suggest that the text, which should be implemented, is published in all EU languages by the authorities for both, the SmPC and PIL after approval of national text versions of the originator.
Lines 1424-1428, 1481-1484		Comment: CMD position will include an annex indicating the new safety warnings, if applicable. Proposed change (if any): The annex indicating the new safety warnings should include texts for SmPC and PIL in all relevant EU languages. See also comment to lines 1442-1445.
Line 1538		Comment: It is good to have such a table to allow for a direct comparison between common sections of the PSUR and RMP. However, the PSUR modules that are interchangeable with RMP modules could have the same

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		title/name to make it easier to recognize parts of report that are interchangeable. Proposed change (if any): Please change names to the PSUR/DSUR and/or RMP titles/sections to make them more similar and easier to cross-reference.
Line 1559		Comment: only cases of lack of MA due to efficacy or safety are relevant Proposed change (if any): the requirement should be limited to reasons regarding efficacy or safety
Lines 1562-1564		Comment: The exact data about cessation of launch may not be available. It is not clear what kind of data is expected; even the date of last shipment may be difficult to obtain, especially in cases of co-marketing. Data may not be obtainable per MA number. Proposed change (if any): Should be clarified. Information about cessation of launch should not be strictly required. Instead, only a presence of the product on the market should be required.
Lines 1565-1567		Comment: revocation, suspension and withdrawals are only relevant if due to safety/efficacy reasons Proposed change (if any): the requirement should be limited to reasons regarding efficacy or safety
Line 1576		Comment: Different dosage forms and formulations of products containing same active substance in one country may be authorised at different times. A presentation of MAs in chronological order will lack clarity of MA status per country Proposed change (if any): We suggest MAs should be arranged per country
Line 1588		For national approved medicinal products, the SmPCs and PLs are different from one country to another one. In this context, it is not possible to provide a proposed harmonised Product Information as an appendix to the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		PSUR. The EU Labeling sections impacted by the CCSI update should be included as an appendix of the PSUR as already suggested lines 1579-1580. Proposed Changes: ~~The proposed SmPC and package leaflet should be included as an appendix to the PSUR.~~
Lines 1605-1610		Comment: Not many details may be obtainable from ongoing safety studies (eg. outcome is usually evaluated after conclusion of study, exact number of included patients could not always be exactly determined -especially in large multicentre studies it changes on daily basis and information derive at different times). Proposed change (if any): We suggest that only basic information on study progress (summary on milestones, problems etc.) should be required.
Lines 1661 - 1664		Comment: This means at a given life-cycle of 30 years of a product, PSURs including sales figures etc should be kept up for 40 years? A PSUR includes cumulative data which are interesting during the life cycle of a PSUR. But PSURs older than two 3-years periods are out-dated and might have only historical value. PSURs are no real source documents. Proposed change (if any): PSURs should be kept only for 6 years max.
Lines 1715-1719		Comment: For products which are not included in the URD list, how will a MAH know if this is due to the fact that no PSURs are needed for this substance, or if this is due to the fact that it is purely nationally authorized product registered only in one member state, so such products are not considered in the EU single assessment project? Proposed change (if any): Include in the URD list also substances for which no PSURs are needed at all, and mark them appropriately in the list. This would be more transparent.
Lines 1769-1776		Comment: In transitional period it is required to submit PSURs to all relevant MSs + to EMA (if according to

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		URD). As this represents some additional work for the MAHs, this may be a minor issue under condition that for no submissions (to EMA and to national authorities), e-CTD PSUR is required. Proposed change (if any): It should be specified that e-CTD PSURs will not be required after implementation of new legislation - not even in transitional period.
Lies 1806-1808		Comment: it is stated that single assessments will be delayed until funds are available. Proposed change (if any): Single assessments are transferred from worksharing or national assessments therefore a way should be found to transfer also the funds, which are currently available for national and worksharing procedures as these will not be needed anymore.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

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

Comments from:

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

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: There is evident potential for inconsistency between the new ICH E2C guideline and this Module VII as a result of the differing timelines for the introduction of the Module and the revised ICH guideline. This could have significant adverse impact for Marketing Authorisation Holders marketing the same products globally.
	Recommendation regarding Comment 1: The mandatory implementation of the revised periodic safety update report format should be delayed until the final ICH E2C guideline becomes available.
	Comment 2: The Module appears to require significant duplication both within the periodic safety update report itself and with the risk management plan (e.g. identified and suspected risks and their characterisation).
	Recommendation regarding Comment 2: Review the guidance so as to minimise duplication.
	Comment 3: There is insufficient practical guidance with regard to the transitional six month period (draft Implementing Regulation, Article 39), in particular as to periodic safety update reports due to be submitted immediately after July 2012.
	Recommendation regarding Comment 3: Specific guidance should be issued prior to July 2012 as to what will be acceptable by way of submission from Marketing Authorisation Holders whose periodic safety update reports are due during the specified period immediately after July 2012.

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 4: The Module does not address what is required in respect of periodic safety update reports/evaluation of data in periodic safety update reports in relation to the renewal of marketing authorisations pursuant to Article 24.2 of Directive 2001/83/EU as amended by 2010/84/EU.
	Recommendation regarding Comment 4: Clarify what aspects of periodic safety update reports submitted need to be addressed and in what format upon renewal.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 162 – 167 and Line 1123		**Comment**: For many medicinal products with well-established medicinal use a PSUR period of 3 years was applied for with the registration. Usually this PSUR period was accepted by the authorities and is mentioned in the marketing authorization. It should be agreed with the authorities that these cases do not fulfill the condition mentioned in line 163 as in these cases there was no concern related to pharmacovigilance.
Line 244-245		**Comment:** Case narratives must be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR. **Suggested language:** Within a signal evaluation, narratives should only be shown for the compelling cases satisfying specific criteria, as specified in context in the evaluation (e.g., index cases). Other reports contributing numbers should be presented as aggregate numbers, for instance for estimating reporting rates.
Line 267-269		**Comment:** PSUR shall contain cumulative data starting from the granting of the marketing authorization, though with the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		focus on new information emerging in the period since the data lock point of the last PSUR. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment. **Suggested language:** The PSUR shall contain cumulative data starting from the granting of the **first** marketing authorization….
Line 302 - 308		**Comment**: What is the difference between PSUR and PBRER? Definition / differentiation is needed.
Line 690		**Comment:** Identification and evaluation of safety signals. **Suggested additional language**: The scope of the review for signal evaluation should be broad, knowing that the conclusions might not apply to approved indications.
Line 709 ff		**Comment**: It appears to be difficult to differentiate between the content of the chapter "Summary of safety concerns" and the content of the chapters "Evaluation of risks and new information" (lines 753 ff) and "Characterisation of risks" (lines 773 ff) without repetitions.
Line 737		**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')*
		Clarification is needed where these signals should be discussed: in section 16.2, 16.3 or in both sections (because the "discussion of the signals" is mentioned in this section (16.2) but on the other hand this discussion should be included in section 16.3).
Line742		**Comment:** Clarification is needed which section is meant by "can be included in the PSUR body". Does it mean 16.2?
Line 918 ff		**Comment**: It is not clear how the methodology of a benefit-risk evaluation could be explained/established. Clarification is needed.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 1115		**Comment**: In Chapter VII.C.3.3.2 explanations on the submission of PSURs for homeopathic medicinal products are given and circumstances are mentioned when PSURs have to be submitted. In this context it must be noted that the PSUR is a document intended to provide an evaluation of the risk-benefit balance of a medicinal product. However, according to Art. 14 of Directive 2001/83/EC for homoeopathic medicinal products no specific indications are allowed on the labeling or any other information. That means that these products have per definition no indication/benefit. How should an evaluation of a risk-benefit be carried out if there is no benefit? The section VII.B.5.17 would therefore not be suitable for homoeopathic medicinal products. Furthermore, for hardly any homoeopathic medicinal product a study or a clinical trial is available. In summary, module VII seems not to be appropriate for homoeopathic medicinal products. The requirement to submit a PSUR for homoeopathic medicinal products should be deleted completely or the content for such a PSUR should be tailored to the nature of the products.
Line 1160-1163		**Comment:** Marketing authorization holders shall submit PSURs immediately upon request from a competent authority in a

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Member State [DIR Art 107c (2)]. This is in conflict with timelines for ad hoc requests for PSURs described in lines 146 – 148. **Suggested Language change:** Marketing authorization holders shall submit PSURs within 90 days of receiving a request from a competent authority in a Member State when a timeline for submission has not been specified in the formal request.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
EuropaBio

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the first wave of draft GVP modules. EuropaBio's mission is to promote an innovative and dynamic biotechnology based industry in Europe. EuropaBio, has 62 corporate and 7 associate members operating worldwide, 2 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises. EuropaBio broadly supports the comments provided by EFPIA, the European Federation of Pharmaceutical Industries and Associations, and would like to provide some additional general comments of specific importance to its members. Our comments focus on important aspects related to the expected business impact for small and medium-sized enterprises, as well as to advanced therapy medicinal products. EuropaBio welcomes the alignment with existing ATMP-specific guidance (e.g. guideline on safety and efficacy follow-up – Risk management of ATMPs – EMEA/149995/2008), which brings a certain level of stability in the legal framework for companies operating in the field. We would like to highlight that specifically for SMEs adequate transitional periods and proportionate implementation of the significant system changes are necessary while avoiding unnecessary administrative burden.
Module II PSMF – Transition from the DDPS	We strongly welcome the introduction of the PSMF independent from a specific marketing authorisation and we recommend a simple and pragmatic transition process for products with existing DDPS. As a PSMF is required for any new MAA and for all renewals due after the implementation date, we believe that many MAHs would have an interest in moving to PSMF for all authorised products at once to avoid maintaining both a PSMF and a DDPS in parallel as well as reducing the number of variations to be submitted.

Stakeholder number *(To be completed by the Agency)*	General comment
	The change-over is currently proposed to occur for each product including a DDPS via a Type IB Variation. In order to reduce administrative burden for Industry and Regulators, we recommend using a Type IB worksharing procedure per group of MAHs sharing the same PSMF and including a list of all affected products authorised in the EEA regardless of their specific registration route covering one Type IB fee. We strongly encourage the national competent authorities to immediately implement the outcome of the worksharing procedure into all national authorisations without any further national process. This will ensure a consistent and pragmatic phasing in of the new PSMF across EEA without unnecessary administrative burden. The management of changes to the PSMF should completely be delinked from the Variation regulation and any specific MAAs. The summary of the PSMF covering location and contact details of the EU QPPV person should solely be managed through notification of required updates to the EVMPD and not trigger any variation process.
Module II PSMF – Co-licensing/Co-marketing scope	The scope of description and documentation of co-licensing and co-marketing arrangements in the PSMF is unclear. However, the expectations for inspections need to be explicit. Within the current Volume 9A it has until now been applicable to arrangements within the EEA. Please clarify that the scope is being limited to commercial arrangements applicable to markets within the European Economic Area.
Module V RMP – ATMP section	Duration of exposure to the medicinal product may be a challenging subject to describe for ATMPs, as the kinetics of cells and genes are different as compared to classical molecules. E.g. Manipulated cells can be used in a single administration to initiate a biological repair process. It is however unknown what proportion of these cells will actually become an intrinsic component of the repair tissue and for how long these cells will be retained. Please specify how exposure duration should be calculated and how relevant is this parameter is in such case.
Module V RMP vs Module VII PSUR - document structure and interchangeable modules	The scope and purpose of PSUR and RMP are not always clear, because of the focus and the overlap in some modules of both documents. Although the PSUR is considered to be mainly used for post-authorisation information reporting, it is also expected to capture pre-market experience. This applies vice versa to the RMP where post-authorisation data are reported. We propose to clarify and simplify both document purposes and structures. The RMP should focus on the pre-authorisation strategy including the binding commitments for post-authorisation development, while the PSUR should focus on the post-authorisation phase reporting the results or the development activity and monitoring of the adverse events. Emerging post-

Stakeholder number *(To be completed by the Agency)*	General comment
	authorisation data should not require updating of both documents, but rather require only one document update. A specific section for risks associated with a Medical Device is necessary for the use of Drug Delivery Systems and better linkage with the Risk Management Systems of such devices that follow different methodologies. For the sake of clarity, we propose that all post-authorisation studies, whether they are PASS or PAES, are included into one Annex to the RMP. Both study types usually include safety parameters and may not easily be distinguishable. The significant expansion of the RMP content and the administrative burden of producing an updated RMP document should be taken into account by the Regulators. We discourage establishing a practice of "routine" updates to an RMP in the absence of any new information that materially affects the product's benefit-risk balance and, consequently, the absence of any need for modifications to the pharmacovigilance and risk minimisation activities.
Module V RMP – comprehensive review process including local inputs	A comprehensive process to include additional national risk minimisation activities or drug utilisation studies within the RMP needs to be thought through in detail as multiple ongoing parallel discussions in the post-authorisation phase might unnecessarily slow down market access for innovative products and can prove to be especially challenging for SMEs. The PRAC is responsible for assessing the overall RMP and as such involves representatives from all Member States. We recommend that this process should ensure that any specific local requirements are included during the PRAC assessment process. In addition, drug utilisation studies to be recorded within the RMP should be strictly limited to the EEA region.
Module V RMP and Module VII PSUR – submission schedule for updates and document life-cycle management	The schedule for submissions of RMP updates is not well defined, and may differ from the schedule for submission of PSURs. The data intervals under review may therefore differ between the 2 documents, limiting the "interchangeability" of the overlapping content. A clear co-ordination and document life-cycle management process needs to be established for both documents to maximise their value and avoid any confusion or redundancy. To ensure consistency, the same rapporteur should be utilised for the assessment of PSURs and RMPs as well as any product related PASS. The assessment process for PSURs may last beyond 6 months. This will pose challenges for products requiring very short PSUR submission cycles and taking into account the data lock points and adequate time to analyse and prepare the following PSURs. We strongly welcome the new proposal that any changes recommended as a consequence of a PSUR review are implemented into

Stakeholder number *(To be completed by the Agency)*	General comment
	the product information without any subsequent variation submissions.
Module VI ICSR - webmonitoring	In support of a proportionate implementation of the new requirements, we propose that the monitoring of ICSRs from websites should be focused on company-sponsored sites. Active screening of non-sponsored websites for adverse reactions is a resource consuming and challenging task, especially for SMEs. In addition, the scientific validity of such sources is often not quantifiable. The added value of such reports over scientific publications is questioned in relation to the additional effort required to capture, analyse and assess the information from blogs, forums, etc.
Module VI ICSR – Validation of reports	Under the new requirements patient or consumer reports should be handled as spontaneous reports irrespective of any subsequent 'medical conformation'. The only requirement for a reporter to be considered identifiable is the availability of contact details in order to confirm or follow-up the case. We are concerned that a MAH or Regulatory Agency may not be able to distinguish genuine, authentic adverse reactions reported by a patient/consumer from fake reports that may have been submitted under a fake email address (identifiable reporter with contact details). Some clarification regarding the confirmation of the existence of a reporter needs to be established.
Transitional periods	As a general rule, new processes or templates should become mandatory for use 6 months after they have been finalised to allow companies adapting their internal processes and documents. Changes involving adaptations to IT systems should be phased in with at least 18 month transitional periods as significant re-programming, validation and company investment are required for their implementation.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases

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

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

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1. General comments

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

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')*
246-247		Comment: The definition of non-serious cases excludes some adverse reactions that although being non-serious can have an important and negative impact on patients' life. Seriousness of the adverse reaction and severity are different characteristics, nevertheless patients and their organisations are interested to learn more on the severity of adverse drug reactions, serious or not. For example, grade II headache, grade I nausea, grade II itching at injection point etc., when repeated every day, after every intake, sometimes life-long, may have a negative effect on the patients' ability to comply and thus diminishing the treatment 'effectiveness. Therefore, the analysis of cases classified as non-serious but still severe by the patients is desired. Proposed change: Additional pharmacovigilance data, in particular, in relation to requests from competent authorities should be included in the PSUR. This should~~may~~ include analysis of cases classified as non-serious particularly when patients report these reactions as being severe.
287-296		Comment: Information collected from compassionate use programmes is not listed here, but only in section *VII.B.5.7.4. PSUR sub-section "Other therapeutic use of medicinal product".* It would be important to highlight compassionate use programmes as a source of data in the summary, to emphasize the utility of such programmes. Proposed change (if any): summaries of information from clinical trials and studies: – ongoing clinical trials and other studies that the marketing authorisation holder or its representative is conducting or has completed during the reporting period (Phases I - IV); – therapeutic use of an investigational medicinal product (e.g. compassionate use programmes);

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		– observational or epidemiological studies; – drug utilisation studies; – non-clinical studies (toxicological and in vitro studies); – clinical trials conducted by a co-development or co-marketing partner; – clinical trials with results indicating lack of efficacy that could have a direct impact on the benefit-risk assessment;
311-351		Comment: We would like to be involved in the selection of PSUR content to be made public. From the table of content presented here, we can already propose that the following becomes public, as a summary, or in details: 2. Worldwide Marketing Approval Status (in details) 5. Estimated exposure and use patterns (in details) 6. Data in summary tabulations (summarised) 7. Summaries of significant findings from clinical trials in the reporting interval (summarised) 8. Finding from non-interventional studies (summarised) 9. information from other clinical trials and sources (summarised) 10. Non-clinical data (summarised) 11. Literature (summarised) 12. Other periodic reports (summarised) 13. Lack of efficacy in controlled clinical trials (in details) 14. Late-breaking information (in details) 15. Overview of signals: new, ongoing, or closed (summarised) 16. Signal and risk evaluation (summarised) 17. Benefit evaluation (summarised) 18. Integrated benefit-risk analysis for authorised indications (summarised) 19. Conclusions and actions (summarised or in details, case by case)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
387-425		Comment: This section does not explain the description of actions taken due to product defect that may expose patients to a potential or identified risk.
455-456		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: More detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age and , sex~~, and racial group~~ for the entire development programme);
483		Comment: The measures of drug sale should consider the % of drug sold on the European market to a distributer/exporter which is then exported outside the EU (thus not consumed by patients in the EU), and/or drug sold outside the EU to an importer and consumed by patients living in the EU
493-505		Comment: Descendants of patients treated with advanced therapies e.g. gene therapy and who are followed-up can constitute a special population to be reported in the PSUR
505		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: Delete line 505
730		Comment: In addition to food, interaction to alcohol and/or illicit/recreational drugs should also be reported Proposed change: interactions with foods and other substances, including nutritional supplements, alcohol and/or

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		illicit/recreational products;
789		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: relevant co-morbidity, disease severity, genetic polymorphism~~, racial and/or ethnic origin~~), dose;
793		Proposed change: Reversibility, rechallenge;
843		Comment: See general comment on the use of "race" and "ethnicity' in the agency activities. Proposed change: important subgroups, (e.g. age, sex, ~~ethnicity~~, disease severity, or genetic polymorphism).
903-905		Comment: For rare diseases, the context is extremely important to explain the availability or absence of data. In addition to disease/indication prevalence, difficulties to diagnose cases and then to treat patients can explain quantitative information or lack of information. Proposed change: Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness; rare condition).
1739-1748		Comment: We would like to be involved in the definition of the type of PSUR information that will go public in the final assessment conclusions.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 17th, 2012

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

Comments from:

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

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EVM is in agreement with general comments of EFPIA
	The concept of "same active substance" cannot be applied for biological products in general and to vaccines. A combined paediatric vaccine cannot be analysed with another vaccine containing the same valences. PSUR should be specific to one vaccine and don't mix data reported with other vaccines containing the same antigens
	The assessment of vaccine efficacy will require not only the assessment of benefit at the individual but at the community level with the impact of vaccination campaign on herd immunity and on the decrease of the targeted disease even in non vaccinated subjects. Cooperation of MAH with competent authorities and implementation of epidemiology surveillance at the country level will be necessary.
	Are all specificities linked to the vaccine be continued and in which section (e.g. reports with fatal outcome, drug interactions, overdose, drug abuse and misuse, vaccine errors, vaccine schedule errors, vaccine route of admin errors, use during pregnancy?

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 246 & 976-977		Comment: The text reads "Request from competent authorities should be included in the PSUR" (l. 246) and "...to ensure that the requests made by the competent authority(ies) during the time of their PSUR assessment are properly addressed" (l.976-977). We would like to clarify whether it means that requests from countries outside Europe should not be included in the report Proposed change: We would like to suggest clarifying that it is limited to the assessment reports received in Europe and adding a comment on the reports outside Europe as well. Questions from health authorities received during the period are not to be included, these requests might be analysed with signals.
Lines 276-280		Comment: The PSUR should provide summaries of significant safety and efficacy information from all data sources, …-findings from active surveillance methodologies (e.g. data mining in internal or external databases)" For the larger pharma databases, there are adequate numbers of records to justify data mining in company internal, as well as external, databases when all products are pooled. However, for the larger vaccine databases, where the number of AE reports are substantially smaller, there may not be a statistical justification for such internal data mining. Proposed change : Change the text as follows "These ~~should~~ *may* include (as appropriate) …"
Lines 614-615		Comment: The concept of fixed combination therapy may not apply to all vaccines: especially the sub section of PSUR summarizing safety information from each individual component.
Line 655		Comment: As already stated in module VI, the concept of "Lack of efficacy" is included in this section and other modules

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		but nevertheless, a definition is excluded from Annex I and from the Modules. Proposed change : As proposed in Module VI, CIOMS/WHO has recently issued a professional and well structured guidance lack of efficacy of vaccines ("Definition and Application of Terms for vaccine Pharmacovigilance, 2012, section 3.2 "Vaccination failure"). The definition issued by the CIOMS/WHO should be used.
Lines 827-828 & 891-896		Comment: We would like to understand whether for combined vaccines which protect against several disease this means that the analysis on the incidence of each disease should be analyzed at individual level and at population level. Proposed change: The RMP should include monitoring of the benefit for new products. For the older vaccines it is suggested to limit to new publications on the topic if available.
Lines 1065-1072		Comment: We would prefer not to change the DLP of our PSURs. At least for centrally authorised products, the Union Reference Date should be based on the currently agreed start dates, recorded in the SIAMED database. For influenza vaccines, the data lock points and special frequency – specified in the Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines applications in the centralised procedure and in guideline on fast track procedure for human influenza vaccines – should be used for consistency. Proposed change: Specify that vaccines are excluded from this worksharing procedure.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

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

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Consistently use either benefit-risk or risk-benefit, not a mixture of both throughout the document
	Clarify the differences between annexes and appendices and exactly what information should be found in each
	What implications does this guidance have concerning the need for PSURs at renewal?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 5 – line 149		Comment: add "be" into the sentence Proposed change (if any): normally be specified in the request,
Page 5 – line 156		Comment: Remove extra s from PSUR Proposed change (if any): PSUR reporting should therefore be
Page 6 – line 166		Comment: add "the" before basis Proposed change (if any): State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active
Page 6 – line 166		Comment: What are the circumstances that are referred to concerning lack of PSURs. Why would there be a lack of PSURs? Proposed change (if any): Clarification of the above
Page 7 – line 220		Comment: In the phrase - Critically summarising relevant new safety, efficacy and effectiveness information that could have – please clarify what effectiveness means in this context. Proposed change (if any): clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 7 –line 222		Comment: The following sentence does not make sense - Conducting an integrated benefit-risk analysis for authorised indications based on the cumulative information available since the international birth date (IBD), the date of the first marketing authorisation in any country in the world / development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. Proposed change (if any): The addition of an "and" or and "or" make improve the sense.
Page 7 – section VII B.3.		Comment: This section only discusses products with one active substance. Proposed change (if any): Include medicines with multiple actives
Page 7 – line 235		Comment: Add the word "safety" before information and change "on" to "covering" before all Proposed change (if any): containing the same active substance with safety information covering all the authorised indications, route of
Page 8 – line 253		Comment: Remove the comma after "both" not required Proposed change (if any): should be used as the reference for both, the benefit and the risk sections of the PSUR. The core safety
Page 11 – line 356		Comment: Specify who should be the signatory Proposed change (if any): clarification
Page 11 – line 366		Comment: What about countries where an authorisation system is not in place e.g. US monograph system

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): further information
Page 12 – line 406		Comment: Add "for safety reasons" to the end of the sentence Proposed change (if any): marketing authorisation application for safety reasons;
Page 12 – lines 418 and 419		Comment: Add "for safety reasons" to the end of the sentences Proposed change (if any): failure to obtain a marketing authorisation renewal for safety reasons; withdrawal or suspension of a marketing authorisation for safety reasons ;
Page 12 – line 424		Comment: Add consumers to this bullet point Proposed change (if any): communications to health care professionals and consumers; and
Page 15 – line 516		Comment: include post-marketing data in the scope for this section, as it is discussed later in the section Proposed change (if any): The objective of this PSUR section is to present clinical and post-marketing safety data through summary tabulations of
Page 18 – line 630		Comment: Progress or final study reports generated during the reporting interval for post-authorisation safety 630 studies should also be included in the regional appendix of the PSUR (see VII.B.5.20.) –this sentence refer to PASS, but the title to this section refers only to non-interventional studies

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): clarify
Page 18 – line 634		Comment: Change "is" to "are", as the sentence discusses the plural "sources" Proposed change (if any): medicinal product from other clinical trial/study sources that are accessible[11] by the marketing
Page 18 – line 644		Comment: Change the order of this sentence slightly Proposed change (if any): This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.
Page 18 – line 646		Comment: add "of" after "aware" Proposed change (if any): the medicinal product that the marketing authorisation holder became aware of during the reporting
Page 20 – line 709		Comment: Delete "important" as important safety concerns have not been referred to previously Proposed change (if any): The purpose of this PSUR sub-section is to provide a baseline summary of safety concerns
Page 20 – lines 721-723	3	Comment: Change "safety specification" to "RMP" Proposed change (if any): For products with a RMP (see Module V), the information included in this sub-section should be equal to the summaries provided in the version of the RMP current at the beginning of the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		PSUR reporting interval.
Page 20 – lines 728 to 732		Comment: Add important to the bullet points Proposed change (if any): Important interactions with other medicinal products; •important identified medication error where no adverse events occurred, or near misses of medication errors Important interactions with foods and other substances; • important occupational exposure; • important pharmacological class effects.
Page 22 – line 791		Comment: Define the "sentinel" adverse reaction Proposed change (if any): clarification
Page 23 – line 815		Comment: Change "has" to "have" Proposed change (if any): important identified risks that have become available during the reporting interval should be
Page 26 – line 939		Comment: Add as applicable Proposed change (if any): In addition, as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate 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')*
Page 26 – line 946		Comment: Does this refer to the Reference Safety Information? Proposed change (if any): 1. Reference Safety Information
Page 27 – line 991		Comment: - what does this sentence mean? "and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;" Proposed change (if any): clarification required
Page 27 – line 988		Comment: Should have a small "p" after a colon Proposed change (if any): poor quality reports: poor documentation or insufficient information or evaluation provided to
Page 27 – line 996-997		Comment: This documentation should be available at all times. – available to whom, where and in what context Proposed change (if any): clarification required
Page 28 – line		Comment: State that this is the responsibility of the QPPV Proposed change (if any): It is the responsibility of the person responsible for the pharmacovigilance system (the QPPV) to ensure that the
Page 30 – line 1048		Comment: Remove extra s from PSURs

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Optimisation of the management of PSURs and PSUR assessments within the EU:
Page 31 – line 1087		Comment: addition of "is" Proposed change (if any): Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU
Page 31 – line 1093		Comment: What are the circumstances that are referred to concerning lack of PSURs? Why would there be a lack of PSURs? Proposed change (if any): Clarification of the above
Page 32 -		Comment: Explain that the diagram does not apply to all products – i.e. some products will not be included in the list Proposed change (if any):
Page 35 – line 1162		Comment: Doesn't immediately usually mean within 90 days? Proposed change (if any): Marketing authorisation holders shall submit PSURs immediately upon request (usually 90 days) from a competent
Page 38 – line 1230		Comment: Add an "s" to PSUR Proposed change (if any): Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 39 – line 1247		Comment: Change to "an EU" Proposed change (if any): list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from
Page 42 – line 1334		Comment: change "hold" to held" Proposed change (if any): whether or not held by the same marketing authorisation holder and for which the frequency and dates
Page 44 – line 1344		Comment: Change "has" to "have" Proposed change (if any): have been granted in accordance with the centralised procedure;
Page 44 – line 1376		Comment: Change "from" to "of" Proposed change (if any): and to the Member States concerned [DIR Art 107e(2)], within 60 days of the start of the
Page 45 – line 1409		Comment: Change "from" to "of" Proposed change (if any): meeting following the PRAC adoption. Within 30 days of receipt, the CHMP shall consider the PRAC
Page 50 – line 1577		Comment: VII.C.5.3. PSUR EU regional appendix, sub-section "Company core safety 1577 information and summary of product characteristics" – is this country specific?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): clarification
Page 50 line 1591		Comment: This section assumes that you have a RMP in place – what happens if there is not a requirement for a RMP? Proposed change (if any): clarification
Page 51 – line 1634		Comment: How often will the EU reference list of dates and frequencies be updated? Proposed change (if any): further information
Page 52 - line 1645		Comment: Add an "s" to the first risk Proposed change (if any): authorisation holder should maintain on file a specification of important identified risks, important
Page 53 – line 1696		Comment: Remove "s" from program Proposed change (if any): consistent, sustainable and efficient records management program and it has been developed in
Page 53 – line 1714		Comment: Change "on" to "of" Proposed change (if any): information in cases of non-compliance and take appropriate regulatory actions as required.
Page 53 – line		Comment: Change to "an " EU

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1716		Proposed change (if any): only one Member State and containing an active substance for which an EU reference date and
Page 54 – line 1724		Comment: Remove the "s" from communication Proposed change (if any): communication across the EU regulatory network and the actions to be taken regarding the variation,
Page 54 – line 1735		Comment: Add a full stop at the end of the sentence Proposed change (if any): EudraVigilance database or other data used to support the PSUR assessment.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
166		Comment: What pharmacovigilance concerns would result in a request for a PSUR? Proposed change (if any): Please provide examples.
226		Comment: Please clarify if this is a cumulative list of risk minimization actions or an interval list of risk minimization actions during the period of the PSUR.
487-488		Comment: Please consider that it is not currently possible to present post-marketing sales data by age, sex, indication, dose, and formulation.
528-573		Comment: Please provide templates for all required cumulative and interval summary tabulations.
784-785		Comment: Please provide guidance on how to estimate relative risk and absolute risk as well as how to determine the precision of the estimates.
1163		Comment: Regarding “immediately upon request” – please provide timelines as PSURs take time to compile if not being routinely prepared.
1287-1288		Comment: Please note that if listings of individual cases retrieved from the EudraVigilance database are created by the Agency and made available to the PRAC Rapporteur, there is the potential for discrepancies to arise against information included in the PSUR by the MAH.
1356-1358		Comment: Please note that if listings of individual cases, summary tabulations, and other relevant data are created and retrieved from the EudraVigilance database by the Agency and made available to the PRAC

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Rapporteur or Member State, there is the potential for discrepancies to arise against information included in the PSUR by the MAH. This could be an issue in audits.
1633-1635		Comment: How often is the MAH required to check the list of EU reference dates and frequency of submission published in the European medicines web-portal to ensure compliance with the PSUR reporting requirements? Please clarify the criteria for the submission criteria to be changed.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
H. Lundbeck A/S

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PSUR submission timelines are changed; however has this been aligned with international guidelines?
	Are line listings for case reports no longer a requirement in the PSUR?
	Is it correctly understood that narratives only should provided in case of scientific evaluation of a signal/safety concern?
	Clinical trials: The requirement of inclusion of All Serious Adverse events regardless of the causality to the treatment/exposure to IMP is strange and beyond the normal scope of the PSUR were only related information is included. The difference between the DSUR and the PSUR seems is not clear
Page 13 section VII.B.5.5.1	Clinical trial information if several partners are involved can be a challenge

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')*
Figure VII 1		Comment: Figure is difficult to understand Proposed change (if any): Should be followed up by text
Figure VII 5		Comment: Not clear when the MAH can expect to receive a final response from the CHMP Proposed change (if any): Day XXX to be stated
Figure VII 6.		Comment: The figure is unclear. Why does the left arm "Opninion sent to EC, MAH and NCAs divide into "for Non-CAPs" and into "CAPs if regulatory action". In the middle of the flow chart the arms are already divided accoding to "CAP included" yes/no Proposed change (if any):

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
149		Comment: Proposed change (if any): add "calendar" in the sentence "within 90 calendar days"
231		Comment: Proposed change (if any): add "and package leaflet" in the sentence "approved summary of product characteristics and package leaflet for the product(s) "

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
April 16th, 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	What are the transitional measures allowing putting in place this new template?

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')*
146		Comment: Based on the significant changes in the template and on the amount of new information to provide, the timelines for submission should be longer. Proposed change (if any): Within 90 calendar days whatever the period covered
233		Comment: those principles are not applicable to plasma derived medicinal products. Proposed change (if any): It would be good to have such principles adapted for such specific products

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

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

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
	Transitional Arrangements There is concern relating to the timelines and process for implementation of the new EU PV legislation. We would seek clear guidance on this and ask for a transitional period that allows time for updating of processes, procedures, templates and reprogramming of the safety database, and also fits in with implementation of ICH E2C.It is not clear that from 02 Jul 12, if all PSURs submitted for centrally authorised products will need to be in new format. This would mean database lock in April / May, so giving very short timelines for implementation. We would propose a phased implementation for PSURs with database lock after July 2012.
	Modular approach We would ask for further clarification with regards to the “modular approach” referred to. Will this mean standalone sections that may be updated, and also requested by Regulatory Authorities to be updated, independently on an ongoing basis? Updating stand alone sections could be difficult in such a comprehensive and interconnected report – changing one section may have a knock on effect on other sections.
	Addendums & Summary Bridging Reports (SBRs) There is a lack of information in the GVP guidance on Addendums and SBRs for license renewals (in fact we could not find any reference). ICH E2C states that Addendums and SBRs may no longer be required. Further clarification is sought as to whether Addendums and SBRs will be required and how these, or other updates, will be managed. We are aware that a draft guidance has been released by the Agency regarding processing of renewals for centrally authorised products, but no similar guidance has been released for nationally authorised products. Furthermore, the recent Agency guidance suggests that although addendums and summary bridging reports are no longer required much of the data and analyses is still required as part of the renewal documentation. The requirement to now prepare this separately will create a significant additional administrative burden on companies. Provisions should still be made to refer to the PSUR for this data.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 151-153		Comment: Further clarification is required for transitional arrangements concerning line listings. Line 152 states “detailed listings of individual cases should not be included routinely” however this can only be implemented when the Eudravigilance database is fully operational. Proposed change: A continuation of the current process of interval line listing would be recommended rather than appending cumulative data.
Lines 162-164		Comment: “The new legislation also waives the obligation to submit PSURs routinely for generic medicinal products, well-established use medicinal products, homeopathic medicinal products and herbal medicinal products.” What is the definition of a “well-established product”? Will a list of such generic / well-established products not requiring PSURs be published? If so, when? Proposed change: Clarification of the definition of a “well-established product” not requiring a PSUR and / or details of where this information can be found.
Lines 244-245		Comment: The following statement is open to interpretation: “Case narratives must be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR”. .” The use of the term “relevant” seems arbitrary and will ultimately be decided by the author of the PSUR. Proposed change: The word “must” be changed, as this wording may make Marketing Authorisation Holders feel inclined to

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		include far more narratives than are necessary. For example: “Case narratives should be provided at the discretion of the MAH where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR”. Also, please provide further guidance regarding the nature of the term “relevant”? How extensive should the narrative be and if there are limits?
Lines 246 - 247		Comment: “Additional pharmacovigilance data, in particular, in relation to requests from competent authorities should be included in the PSUR. This may include analysis of cases classified as non-serious.” Further clarification on requirements is sought. Proposed change: Please clarify further what additional PV data may be sought.
Lines 263 - 265		Comment: “The marketing authorisation holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorised product information. These meaningful differences should be included in PSUR regional appendix”. Proposed change: Definition or guidance on the term “meaningful differences” is requested, similar to the guidance for Core Safety Profiles.
Lines 267 - 269		Comment: “A PSURs shall contain cumulative data starting from the granting of the marketing authorisation, though with the focus on new information emerging in the period since the data lock point of the last PSUR” Proposed change: “PSURs shall contain cumulative data starting from the granting of the....”

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Please confirm that this refers to International Birth Date, rather than EU marketing authorisation date. Line 562 may provide further clarification "from the IBD to the data lock point of the current PSUR". We would ask for consistency and clarity in terminology to ensure correct use of IBD rather than EU marketing authorisation date.
Lines 285, 294, 300		Comment: Information from co-marketing or co-distribution partners may be presented in their PSURs, or may not be shared with partners, depending on the contractual agreements in place; therefore inclusion of the wording "as applicable" is suggested. Proposed change: "information from co-marketing or co-distribution partners as applicable, where relevant to the marketing authorisation holder's approved product"
Line 322		Comment: "6.3 Cumulative and Internal summary Tabulations from Post-Marketing Data Sources". Does this mean the present "core" cases for PSURs – serious listed and unlisted and non-serious unlisted cases? Proposed change: Please provide additional guidance as to what should be included here
Lines 369 - 370		Comment: "actions taken and proposed for safety reasons including significant changes to the investigator brochure and post-authorisation product information or other risk minimisation activities" Proposed change: "actions taken and proposed for safety reasons including significant changes to the ~~investigator brochure and post-authorisation product information~~ reference safety information or other risk minimisation activities"
Lines 438 - 439		Comment: "PSURs shall provide an accurate estimation of the population exposed to the medicinal product including all data relating to the volume of sales and volume of prescriptions."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: "PSURs shall provide an ~~accurate~~ estimation..." Comment: For established products, it may be challenging to obtain cumulative data for clinical trial exposure. Draft ICHE2C acknowledges the challenges for established products but there is no recognition of this in Module VII of GVP. Proposed change: Guidance should be amended to acknowledge of the challenges in obtaining cumulative data for clinical trial exposure for established products and advice on approaching this.
Lines 487-488		Comment: "Data should be routinely presented by sex, age, indication, dose, formulation, and region where applicable." Is this optional depending on the methodology of each MAH to obtain exposure data? If the MAH routinely doesn't present the exposure data in this manner, will they be obligated to do so? Proposed change: Add the following statement to clarify that this is a suggestion only. "<u>The precise presentation of the data will depend on the methodology each MAH uses to obtain exposure data</u>."
Lines 513 - 514		Comment "For purposes of identifying which patterns of use are off-label, the marketing authorisation holder should reference the CCDS in the PSUR." Add the word "indications". Proposed change: Amend the text to reflect this "…the marketing authorisation holder should reference <u>the indications</u> in the CCDS"
Line 713		Comment: With regards to "frequency" in this section - Should this be based on reporting rates from post-marketing safety data, incidence rates from clinical trials data, or epidemiology data? Proposed change: Please provide additional guidance on this point

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 758 - 759		Comment: " all risks detected during the reporting period……" 'Detected' could refer to different types of activities. Proposed change: Please clarify what is meant by 'detected' (e.g., evaluated in an ad hoc report, Safety Management Team meeting, etc)
Line 776		Comment: The definition for "identified risks" and "potential risks" is provided in Annex I – Definitions. Proposed change: These terms should be defined here or cross referenced with the definitions provided in Annex I.
Line 824		Comment: What constitutes "baseline information"? Is this clinical trials data from the application submission? Proposed change: Please provide additional guidance as to what is considered to be "baseline information."
Line 952		Comment: "Listing of all post-authorisation safety studies". This list should only include those studies that the marketing authorisation holder is sponsor for or providing some support (as defined in Module VIII). Proposed change: include clarification e.g. "Listing of all <u>marketing authorisation holder</u> post-authorisation safety studies"
Lines 1019 - 1020		Comment: Should timelines be 70 / 90 days, as per lines 144 – 145?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Propose change: Please amend to ensure consistency.
Lines 1424-1428, 1481-1484		Comment: Clarification regarding the procedures and timings to follow for both the MAHs ***and*** Competent Authorities regarding variations that may result from the assessment of the PSUR should be provided.
Line 1538		Comment: Due to the common modular nature of the RMP and PSUR, is it anticipated that the RMP will be updated every three years, in line with the PSUR, as Section 2 and Section 3 of the PSUR are likely to change during the period, which then would be reflected in Sub-section of part I – "Product overview" and Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason" of the RMP, respectively? Proposed change: Please clarify whether the RMP should be updated in line with the PSUR.
Lines 1581-1580		Comment: Does this include ongoing changes, where variations are currently under assessment, in line with line 434 of the proposed Guideline? Proposed change: Amend text to clarify whether ongoing changes under assessment at the time of submission are in scope for this section.
Line 1583		Comment: Will the proposed amendments to the SmPC be approved as part of the PSUR assessment? If so, will ongoing changes currently under assessment consequently be approved? Proposed change: Please provide additional clarity as to how the submission of this information will impact ongoing changes

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 April 2012

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

Comments from:

Name of organisation or individual
CBG-MEB (Medicines Evaluation Board – the Netherlands)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	VII.B.5.3. PSUR section "Actions taken in the reporting interval for safety 387 reasons" A point relevant for products that are authorized via DCP or NP, especially for those products that are not part of PSUR worksharing: Very often the MAHs update a national SPC on request of local authorities, e.g. add a new ADR in section 4,8, and these changes are not always incorporated in the RSI. Therefore, apart from changes on the RSI, it would be useful to know which new changes on national SPCs have been requested by national authorities in other Member States during the PSUR interval. Some of the changes may not be relevant for each MS, but having an overview of requests from different agencies (e.g. to add some new ADRs in section 4,8) to their national SPCs may help to identify some relevant issues and will assist with assessment of PSURs.
	VII.B.5.5.2. PSUR sub-section "Cumulative and interval patient exposure from marketing 473 experience" Guidelines on estimation of patient exposure should be more specified for prescription-only medicines. Very often MAH use sales data to estimate patient exposure which may result in overestimation of exposure due to stockpiling, etc. For prescription-only medicines, volume of prescriptions should be provided, if available or feasible to estimate. Preferably, patient exposure should be estimated based on prescription volumes instead of sales data.
	VII.B.5.15. PSUR section "Overview of signals: new, ongoing, or closed" The presentation of signals as "new, ongoing or closed" seems to be at the discretion of the MAH. However, a signal that is regarded as "closed" by the MAH might be regarded as "ongoing" by the national competent authority. In this section VII.B.5.15 it should be made more clear that the signal status assigned by the MAH might be further assessed by national authorities. It should be more clearly indicated that the presentation of signals as "new, ongoing or closed" is the MAH's own assessment and might be different from the signal detection outcome of the national competent authority.
	VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information" It is not clear from this section VII.B.5.16.3 how the risks should be evaluated. At the moment this sub-section VII.B.5.16.3 implies that the MAHs should simply list and describe the risks. It would be useful if the MAHs provided some additional information next to listing the new potential or identified risks, such as : a) is there a known mechanism explaining the link between the product and the risk? b) is the risk supported by spontaneous reports only or is there evidence supported by epidemiological data?

Stakeholder number *(To be completed by the Agency)*	General comment
	VII.B.5.16.4. PSUR sub-section "Characterisation of risks" It is not clear how the following variables should be measured: 1) precision of estimate, 2) quality of life, and 3) risk factors. 1) More information should be provided regarding the precision of estimate: this will not be always easy to estimate, e.g. if based on spontaneous reports only. 2) Impact of identified or potential risks on the individual patient including quality of life is important. However, it is not clear which methods should be used to assess the impact on quality of life. Usually this is measured using standardized questionnaires and is not feasible for routine implementation. 3) It is not clear how the risk factors should be identified, i.e. in a descriptive way or shall the MAHs perform some basic analyses in their databases to identify the risk factors in a more reliable way?
	VII.B.5.16.4. PSUR sub-section "Characterisation of risks" In contrast to previous sections, this section should provide information on cumulative data of the important identified, potential risks and missing information. But signals are only closed during reporting interval. Are they analysed for cumulative period?
	VII.B.5.16.5. PSUR sub-section: "Effectiveness of risk minimisation (if applicable)" If different national conditions have been agreed for the measurement of the effectiveness of risk minimisation activities a single EU assessment might be problematic. In some cases it would not be possible to assess this at EU level, so it has to be taken into account that a national assessment should be prepared prior to generalising the results to the EU level.

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')*
VII.B.5.7. PSUR section "Summaries of significant findings from clinical 574 trials in the reporting interval"		Comment: Providing information on sponsored interventional trials to measure the effectiveness of risk minimisation measures in this section is not appropriate/confusing. Proposed change (if any): This information is already requested in section B.5.16.5. Therefore, the request for this information in section 5.7 is duplicate and should be removed.
VII.B.5.12. PSUR section "Other periodic reports"		Comment: 'The purpose of this section is to 'Summarise significant findings from other PSURs'. What is the difference with section VII.B.5.7.5? Furthermore, the same problems are foreseen for this section. Proposed change (if any): Integrate this section with section VII.B.5.7.5.
VII.B.5.16.2. PSUR sub-section "Signal evaluation" (line 754)		Comment: Regarding the last point: "… conclusion, including proposed actions". It would be also useful to list actions. Proposed change (if any): Adapt line 754 into: "… conclusion, including proposed **and undertaken** actions". For example, SPC updated.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

MSSO

MedDRA Maintenance and Support Services Organization (MSSO)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Consider to mention somewhere in the module VII - Periodic safety update report the application of The Standardised MedDRA Queries (SMQs) as a potential method for signal detection.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
532		Comment: Sentence in line 532 starting with …The tabulation(s) should be organised by MedDRA SOC…..may want to add " listed in the internationally agreed order" Comment; as stated in the MedDRA Introductory Guide to facilitate consistency irrespective of language or alphabet Proposed change (if any): The tabulation(s) should be organised by MedDRA SOC listed in the internationally agreed order
564		Comment: as stated in the MedDRA Introductory Guide to facilitate consistency irrespective of language or alphabet Proposed change (if any): The table should be organised by MedDRA SOC listed in the internationally agreed order.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
MHRA

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
222 and 1542		Comment: The section describing Principles for the evaluation of the benefit –risk balance (line 222) states "Conducting an integrated benefit-risk analysis for authorised indications based on cumulative information". This is inconsistent with the section describing EU-specific requirements where it states that "The scientific evaluation of the risk-benefit balance shall be based upon all available data, including data from clinical trials in unauthorised indications". Proposed change (if any):	
290		Comment: "Therapeutic use of an investigational medicinal product" should be defined. The guideline later clarifies this may include expanded access, compassionate use programmes, particular patient use and other organised data collection. It would be helpful to define this here since without the definition it is not clear what is actually required. Proposed change (if any):	
386		Comment: It may not be suitable to describe all territories where a product is authorised in the narrative format. The reader should be directed to the appendix.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
422		Comment: The strike-through text should be deleted. It is not relevant to reference the development programme here. Proposed change (if any): - significant safety-related changes in labelling documents ~~that could affect the development programme~~, including restrictions on use or population treated;	
429		Comment: It would be useful to describe all labelling changes relating to adverse reactions and not just those which are serious and/or special interest. Proposed change (if any): "Such changes might include information relating to contraindications, warnings, precautions, ~~serious~~ adverse drug reactions, ~~adverse events of special interest~~, and interactions; important findings from ongoing and completed clinical trials; and significant non-clinical findings (e.g. carcinogenicity studies)."	
435		Comment: Delete strikethrough text below for clarity	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "The marketing authorisation holder should also provide information on any final and ongoing changes to the national/local authorised product information ~~based on the most recent version of the CCSI~~ in the regional appendix, see VII.B.5.20..	
453		Comment: Cumulative subject exposure in Clinical Trials – It does not seem relevant to also include cumulative subject exposure to placebo and/or active comparator(s) since DIBD. Propose deleting this text. Proposed change (if any): "cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, ~~placebo, and/or active comparator(s)~~ since the DIBD. It is recognised that for older products, detailed data might not be available;	
525		Comment: Why is this section entitled "Reference Information" when the only guidance relates to the version of the coding dictionary? Propose amended heading.	
535		Comment: Reproducing cumulative SAE tabulations for active comparator and placebo does not seem meaningful. Although this may place the SAE tabulation for the investigational drug	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		in context, this may result in unnecessary effort given that a PSUR is "a tool for post-authorisation evaluation". It should not be the mechanism to compare AE rates in clinical trials. This information could be requested if required by a CA. Consider removing text. Proposed change (if any):	
545		Comment: Same comment as above regarding comparators and placebos.	
548		Comment: It would not be meaningful to include blinded clinical trial data in the tabulations since this information can not be used for objective evaluation. Proposed change (if any): Allow inclusion in PSURs once unblinded.	
685		Comment: New individual cases may not in themselves be an important index case but may add to the evaluation of a safety issue presented in the PSUR. Suggest amending text as below. Proposed change (if any): New individual case reports should not routinely be included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal, or where they	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		may add to the evaluation of safety issues already presented in the PSUR.	
697		Comment: A signal which is newly identified may still be under evaluation at the data lock point and therefore can not be handled as a closed signal as proposed in this section. Proposal: Delete text: ~~Signals that are 696 both newly identified and closed during the reporting interval should be handled in this section as closed signals (i.e., signals detected during the reporting period, with evaluation completed within the reporting period).~~	
955		Comment: It would be helpful to include a section here on PSUR submission i.e. where to submit and how with cross-reference to the transitional arrangements (Section VII.C.8.1)	
956		Comment: For clarity, "Section VII.B.6 Quality Systems for PSURs at the level of Marketing Authorisation Holders" should be integrated with "VII.C.6.1 Quality Systems and record management systems at the level of the marketing authorisation holder" since these are essentially the same topic.	
1118		Comment: For clarity, it may be useful to include the section on submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products prior to	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		VII.C.2, since it is not necessarily clear under what circumstances "standard submission schedule" and "Figure VII.2. "Conditions for PSURs submission as general requirement" actually apply.	
1226		Comment: It is not feasible to "continuously" check the European medicines web-portal. Proposal: "Marketing authorisation holders shall ~~continuously~~ periodically check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures"	
1539 - 1628		The sections describing "EU-Specific requirements for periodic safety update reports" should be included in the earlier section which provides guidance on inclusion for the different sections of the PSUR e.g. at line 955 with reference to the regional appendix.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 18 Jun 2012 10:24:00

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

Comments from:

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	• In the Structure and processes section, the use of data from IBD, DIBD, interval data or cumulative data should be consistently specified. Instances of inconsistencies were noted as well as areas which can benefit from clarification as to which duration of data to use. • In the Operation of the EU network section, the comments were primarily comments for more guidance. There was one topic which was not addressed in this document, which the MAH finds helpful to include. In Volume 9A, section 6.2.4.b addresses the submission of PSURs for the renewal of marketing authorizations. Although, the renewal process is independent of the PSUR process, with the elimination of PSUR addendum reports and PSUR bridging documents as noted in the ICH-E2C(R2), the MAH would require additional guidance on how the MAH can continue to meet the PSUR requirements (e.g. submission of safety information covering 4 years and 4 months) in the renewal process. Also, information is needed on if PSURs which are submitted for renewal will be included in the List of EU reference dates. • Further details are provided in the special comments on text below.

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')*
162-164		**Comment:** In the interest of clarity, it would be useful to provide a definition for "well-established use medicinal products." If the reference document is to DIR Art 10a, then would suggest making reference to it in the text. **Proposed changes:** The new legislation also waives the obligation to submit PSURs routinely for generic medicinal products, well-established use medicinal products (DIR Art 10a), homeopathic medicinal products and traditional herbal medicinal products [DIR Art 107b (3)].
220-221		**Comment:** It is stated that new safety, efficacy and effectiveness information is to be critically summarized, but does not specify if this is interval data or cumulative data from IBD/DIBD. As noted in Section 16.3 (Evaluation of risks and new information) and 17.2 (Newly identified information on efficacy and effectiveness), it is interpreted that this review should be against interval data. **Proposed change:** Critically summarising relevant new safety, efficacy and effectiveness information during the report interval that could have an impact on the risk-benefit balance of the medicinal product.
234-237		**Comment:** It is stated that the MAH should prepare one single PSUR for all its medical products containing the same active ingredients. Additionally, exceptional scenarios where separate PSURs may be appropriate are provided; however there is no guidance on how this requirement would apply to combination products (ie. would the MAH need to place separate requests for authorization from the authorities?). For completeness, it is suggested to consider adding the handling of combination products as a scenario. Further clarification will be useful. **Proposed change:**
222-225		**Comment:** This paragraph states that the integrated benefit-risk analysis should be conducted for authorized indications. Line 252-253 states that the CCDS is the reference document to be used for the benefits and risks section of the PSUR. As there are situations where the CCDS may not encompass all authorized indications and if the intent of the statement is to include all authorized indications, then it should be stated as such for the purposes of clarity. **Proposed change:** Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since...
261-262		**Comment:** Depending on PSUR's periodicity, the CCDS and the coding dictionary may have been updated more than once. Therefore clarification is needed on what time point the version of the coding dictionary should reflect. Additionally certain types of products such as over-the-counter products, a coding dictionary may not be available. It would be helpful to understand the purpose for having the version of the coding dictionary noted in the CCDS.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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:
267-270		**Comment:** In the interest of consistency within the document, DIBD should be included. **Proposed change:** A PSUR~~s~~ shall contain cumulative data starting from the granting of the marketing authorisation and the DIBD, though with the focus on new information emerging in the period since the data lock point of the last PSUR …
298-299		**Comment:** As stated, it may be interpreted by MAHs that competitor data is needed in order to obtain data on relevant efficacy or safety findings for products the same therapeutic class. However, it is clarified in line 659 that this is in reference to literature data. **Proposed change:** literature for any ~~other source of~~ relevant efficacy or safety findings for products in the same therapeutic class
309		**Comment:** It would be useful if it was specified which individual(s) should sign this document. **Proposed change:** Title Page including signature of … **Comment:** This document does not address electronic signatures. Is an electronic signature acceptable? **Proposed change:**
381		**Comment:** As part of the Introduction, it is stated that a brief description of the population being treated and studied should be included. In ICH-E2C (R2), it is specified for approved populations. If population "studied," refers to unauthorized use then further clarification would be useful. **Proposed change:** a brief description of the authorized population(s) ~~being treated and studied~~
382		**Comment:** "A brief description and explanation of any information that has not been included in the PSUR" is rather broad, but if it is in reference to a similar statement in Volume 9A which states that "exclusions should be explained (for example, they may be covered in a separate PSUR (e.g. for a combination product)," then it would be useful to include a similar statement or provide examples. **Proposed change:** a brief description and explanation of any information that has not been included in the PSUR; for example, the product may also be covered in a separate PSUR (e.g. for a combination product).
493		**Comment:** It is stated that where post-authorization use has occurred in special population, then available information regarding cumulative patient exposure should be included. This can be interpreted as the MAH will need to conduct such studies for all products which are authorized in special populations. If this is not the intent, then it would need to be stated that it will need to be discussed if data is available. **Proposed changes:** Where post-authorisation use has occurred in special populations, ~~available information regarding~~ cumulative patient numbers exposed and the method of calculation should be provided if the information is available.
522-524		**Comment:** As stated, it is interpreted that the seriousness of the adverse events/reactions should be the seriousness assigned at the case level, which would imply that a non-serious event in a serious case would be categorized as a serious event. As the summary tabulation is presented on an event level, further clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		would be needed to understand why the association is on a case level. It further states that “seriousness should not be changed specifically for the preparation of the PSURs.” Is this in reference to the seriousness of the adverse event or the case? **Proposed changes:**
530-537		**Comment:** Although reference is made to an example of summary tabulations in ICH-E2C(R2) appendix B table 6, it would be useful to provide specific information that is required in the text (ie. seriousness, listedness, causality, report source, etc.). **Proposed changes:**
543-545		**Comment:** As stated it is unclear what information should be included; if it is in reference to including all serious events and not just suspected serious events, then would suggest stating as such. **Proposed change:** Therefore, the summary tabulations should include all serious adverse events and not just suspected serious adverse reactions for the investigational drug, comparators and placebo.
321, 574		**Comment:** The section title is not aligned with the section title used in the ICH-E2C (R2). **Proposed change:** Summaries of significant safety findings from clinical trials in the reporting interval
658		**Comment:** “Non-clinical safety results” is very broad especially when referring to literature data. It would be useful if examples were provided. **Proposed change:**
825-826		**Comment:** This paragraph states that the baseline information on both efficacy and effectiveness should be related to the authorized indication of the medicinal product as listed in the CCDS. Similar to the comment made on line 222-225, as there are situations where the CCDS may not encompass all authorized indications and if the intent of the statement is to include all authorized indications, then it should be stated as such for the purposes of clarity. **Proposed change:** This information should relate to all authorised indication(s) of the medicinal product~~, listed in the CCDS~~.
829-830		**Comment:** It is stated that when there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, the summary should be succinct, essentially the content of the CCDS. As the CCDS will be included in the appendix, rather than repeating information in CCDS, would suggest making reference to the appropriate CCDS sections. **Proposed changes:** When there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, reference can be made to the appropriate sections of the CCDS ~~the summary should be succinct, essentially the content of the CCDS~~.
840		**Comment:** As stated, it is unclear if “comparator” refers to data from other companies and literature or if it refers to the comparators in MAH studies. Further clarification would be useful. **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')*
845-848		**Comment:** It is stated that if additional information on efficacy and effectiveness in authorised indication become available during the reporting interval, it should be included in this section. Further clarification is needed to understand what “additional information” encompasses (e.g. only from studies or inclusive of literature). **Proposed change:**
889		**Comment:** It is stated that this section should provide a brief description of the medical need for the medicinal product in the authorised indications and summarised alternatives (medical, surgical or other; including no treatment). As there are indications and products such as over-the-counter products in which there can be many treatment alternatives, further clarification advising the extent of content in the summary would be useful. **Proposed change:**
1009-1010		**Comment:** It is stated that training should cover legislation, guidelines, scientific evaluation and written procedures. In the interest of clarity, would state the legislation and guideline that is being referred to here. **Proposed changes:**
1034-1035		**Comment:** With regards to the list of EU reference dates, it would be useful to indicate who is responsible for inclusion of the active substances as well as how this list will affect the Work sharing and Synchronization lists. **Proposed changes:**
1068		**Comment:** In earlier sections, reference is made to the IBD (e.g. when conducting an integrated benefit-risk analysis), however, this section states that the EU reference date would be the date of the first market authorization in the EU. As the PSUR would be used in regions outside the EU and in the interest of harmonization, would strongly suggest using the IBD in the EU reference dates list. **Proposed changes:**
1163-1164		**Comment:** It is stated that the MAH shall submit PSURs immediately upon request from a competent authority in a Member state. Is this in reference to the submission of an ad hoc PSUR (line 148-150) or to a previously submitted PSUR? Further guidance would be useful. **Proposed changes:**
1224-1227		**Comment:** It is stated that the updated list of EU reference date is published the week following adoption by the CHMP or the CMDh which is expected to be monthly. Additionally, the MAH shall continuously check the EMA web-portal for relevant updates. As this information is intended to be available electronically, would it be feasible for the MAH to receive automatic notifications (e.g. news feeds); to check continuously without knowing when the updates will specifically be made will provide an added burden to the MAH. **Proposed changes:**
1232 - 1233		**Comment:** It is stated that when appropriate, MAH shall submit the relevant variation within six months before the updated list of EU reference dates takes effect. As a change to the data in this list is administrative

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		in nature and to avoid the burden from the frequent submission of variation requests, would propose to not submit a stand alone variation for such a change, rather to submit with the next significant variation. **Proposed changes:**
1538		**Comments:** Table VII.1 provides the common sections between the PSUR and RMP. As the DSUR is another regulatory document (line 158-161) with common modules, it would be useful to also present the common modules between the DSUR and PSUR within the table. Additionally, further guidance on how the modular approach works is useful, including how common sections are updated, especially when review periods for all three documents are not aligned and if it is sufficient to cross-reference? If another document exists to address the modular approach, it is suggested to reference it in this document. **Proposed changes:**
1588		Comment: It is stated that the proposed SmPC text should be provided in the appendix, however, since this proposed text will be included in a subsequent labeling variation and may be subject to comments from Authorities, would it be acceptable to provide a summary of proposed changes to the SPC instead, rather than attaching a proposed SPC text? **Proposed changes:** ~~The proposed SmPC and package leaflet should be included as an appendix to the PSUR~~.
1603-1604		**Comment:** It is stated that progress reports and final study reports generated from PASS during the reporting interval should be also included as an annex to PSUR. As no caveat is noted for the lack of progress reports, it can be interpreted that progress reports should be prepared for all PASS for the purpose of the PSUR; this can be an added burden to the MAH, especially when interim analysis can provide limited, if any, value to the benefit-risk profile as blinded data may be involved. Any significant safety finding from ongoing PASS would have been addressed in either section 7 or 8; therefore, not clear what other information would be need in the Annex to support the benefit-risk analysis. Further clarification on the purpose of the progress reports is useful. **Proposed changes:**

Please add more rows if needed.

16th April 2012

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

Comments from:

Name of organisation or individual
OPTUMInsight

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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')*
142-148		Comment: Does 70 days or 90 days apply to PSURs of exactly 12 months duration? Proposed change (if any):
142-148		Comment: In terms of transitional arrangements, do the new timelines of 70/90 days apply to PSURs with a DLP from July 2012 or those submitted from July 2012 (i.e. a DLP in May 2012)? Proposed change (if any):
142-148		Comment: As this section states that 'MAH should submit PSURs to the Agency according to the following timelines', do PSURs being submitted to national agencies during the transition period follow the previous 60 day timeline? Does 60 days apply to purely national PSURs? Proposed change (if any):
264		Comment: Will the new format apply before the finalisation of ICH E2B (R2)? Harmonisation of PSUR format across the ICH regions should be a serious consideration in terms of resource burden. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module VII – Periodic safety update report) is very comprehensive and provides detailed and helpful guidance on the preparation, submission, and assessment of periodic safety update reports. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.
	Participation by the Agency in international consensus forums, such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), creates efficiencies and promotes protection of patient safety in the EU through global consensus guidelines, e.g., the ICH Periodic Benefit-Risk Evaluation Report (VII.B.5.)
	Since the initialism “PSUR” is introduced in Section VII.A. (line 127), it is not necessary to spell out “periodic safety update report” in subsequent text. It is also unnecessary to reintroduce the initialism, e.g., on line 189.

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')*
405-406 418 419		**Comment**: Since the PSUR is a safety document, actions related to the failure to obtain a Marketing Authorisation (MA), renewal of a withdrawal or suspension of an MA should only need to be included in the PSUR if they are due to safety or lack of efficacy reasons; commercial reasons for these actions should not need to be included in the PSUR. **Proposed change:** Revise lines 405-406 to read: "*failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a marketing authorisation application* ***for safety or lack of efficacy reasons****;*" Revise line 418 to read: "*failure to obtain a marketing authorisation renewal* ***for safety or lack of efficacy reasons****;*" Revise line 419 to read: "*withdrawal or suspension of a marketing authorisation* ***for safety or lack of efficacy reasons***;"
643		**Comment**: Section VII.B.11. notes the review of special types of safety information to be included, such as special populations. However, this module does not specifically mention these populations elsewhere. **Proposed change**: Provide examples (to be considered when relevant).
673-678		**Comment**: Data are expected to be included in the PSUR on lack of efficacy relative to established therapies from clinical trials. Further details are needed to clarify exactly what is expected to be provided

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		here. Unless it is a stated objective of the trial's protocol, comparing efficacy data from a clinical trial to real-world use of a product is not scientifically sound. **Proposed change**: Provide scientific rationale for this section or entirely delete lines 673-678, i.e., "~~*Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses could reflect a significant risk to the treated population and should be summarised in this PSUR section.*~~".
724 – 734		**Comment**: Subsection VII.B.5.16.1. only mentions medication errors and occupational exposure (VI.A.2.1.2. includes overdose, misuse, abuse, in addition to medication errors and occupational exposure). There should be more consistency between Modules VI and VII regarding special situations. **Proposed change**: Revise line 731 to read: "***Reports of exposure in utero, lack of therapeutic efficacy, overdose, abuse, misuse, dependency, medication error, off-label use, or*** *occupational exposure* ***should be considered when those reports constitute safety issues impacting on the benefit-risk balance of the medicinal product;"*** Revise lines 733-734 to read: "*The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or special populations* ***(may include, but not limited to, paediatric, elderly, pregnancy or lactating women, patients with hepatic and/or renal impairment)*** *that use the medicinal product."*
911- 913		**Comment:** Add text to make this subsection consistent with other descriptions of benefit-risk analysis. **Proposed Change**: "*With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		*from **clinical trials in unauthorized indications or populations,** off-label use, or misuse."*
928 -931		**Comment**: When little new information has become available there is little guidance as to the evaluation required. **Proposed Change**: Revise line 929-931 to read: "*Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of ~~an evaluation~~ **a general overview** of updated interval safety data.*"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 9, 2012

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

Comments from:

Name of organisation or individual
Pharmiceutics LLC

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
252 - 253		Comment: This text requires that a MAH uses specifically a “CCDS” as the reference document for both the benefit and risk sections of the PSUR. The CCDS continues to be defined in the Glossary document as a “document prepared by the marketing authorisation holder containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.” For the purposes of our comments, we call this type of document a “full-fledged CCDS”. The proposed requirement is based on 3 assumptions, all of which are incorrect: Assumption A: All MAHs do have a CCDS for all products that may require a PSUR. This assumption is not correct. Many companies, for many products, may have used so far another type of document to provide reference safety information (RSI) for PSUR purposes. Until now, this is in line with Volume 9, which asked for “RSI” to be provided and calls the CCDS (with its CCSI) a “practical option”. A RSI document other than the CCDS is, for example, provided for products that are only registered in the EU and export markets where the product is registered to come with EU-labeling. In this case, usually the EU SmPC is used as the RSI. Assumption B: All MAHs have full-fledged CCDS that are suitable for submission along with a PSUR. This assumption is not correct. There are companies that hesitate to provide a full-fledged CCDS (which may contain extremely confidential information that is not relevant for PSUR purposes) as RSI for a PSUR, out of concerns that, for example, confidential information gets somehow in the public domain and to competitors. Such companies may provide as RSI for PSURs instead a customized document (a “CCDS excerpt”) which is essentially limited to the required CCSI. However, the draft guideline, by virtue of the definition in the glossary, appears to ask for the full-fledged CCDS.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Assumption C: All MAHs include in their CCDS all locally approved indications and information on the clinical data in support of these indications. This assumption is not correct. Many MAHs do not list all approved indications in their CCDS and, for the indications listed, do not necessarily include a description of the underlying clinical data. It should be noted that CCDS are primarily company-internal global labelling governance tools that function in a framework of - other documents that provide information to country organizations, and - associated policies and business rules. This framework determines which content needs to be carried in a CCDS. Therefore, many CCDS will not meet the definition in the glossary document, which comes from ICH and CIOMS. So far, this discrepancy was not relevant, because CCDS were only ONE option for PSUR purposes. An overview of industry core labelling practices is available as a free on-line “training” session (approx. 2 hours) at our website (http://pharmitrain.com/course3.html). We understand that the draft guideline now requests reference information not only for safety but also for approved uses and efficacy. This should, however, be achieved in a fashion that does not (appear to) require that MAHs change the character of their established CCDSs, with potentially adverse consequences for their global labelling governance system. We propose, therefore, that the guideline be changed to refer to a CCDS only as one option for providing this reference information. This gives MAHs the necessary flexibility to use - a CCDS, where this document happens to be fully suitable for this purpose, or - a CCDS with appendices, or entirely separate, additional documents (i.e., documents *not* appended to the CCDS). Calling the use of a CCDS “one option” would also permit that companies with full-fledged CCDS that contain

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		critical confidential information, continue to use “CCDS excerpts”. We would also like to point out that efficacy information (clinical studies) in local labelling and CCDS may not necessarily be written so that the robustness of the total body of evidence in support of claimed benefit is discussed or easily visible. Clinical studies information in CCDS, if present at all, usually represents the set of information in the local labeling of one major market (e.g., EU or US). For products, for which original approval was based on a rather limited data set (as is the case for many older products), additional evidence for benefit that was accumulated in the postmarketing phase may not be presented in a CCDS (or local labeling). Therefore, the information in a CCDS or local labeling may “under-represent” the robustness of actual evidence for a benefit. Proposed change (if any): We propose to use, throughout all Guidelines, the term “Reference Product Information (RPI)” or “Reference Safety and Usage Information (RSUI)” instead of CCDS and mention that the use of a CCDS for this purpose may be a practical option. The Guidelines should also permit that the reference usage information is incorporated in the PSUR itself (e.g., in the section designed to capture the worldwide marketing authorization status).
261 - 262		Comment: The draft guideline assumes that adverse reaction lists in a CCDS/CCSI are based on MedDRA terminology and that all terms in a list can be referenced to a MedDRA version. This assumption is incorrect. In fact, CCDS/CCSI that is optimized as a company internal governance tool for local labelling may not use MedDRA terms throughout. This is in the interest of providing country organizations with terms that best communicate risks to the reader of labelling (optimized for risk communication by labelling, not optimized to serve as listedness checklist in the context of periodic reporting).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		We propose that the guideline not request that each CCDS names the coding dictionary used (which implies that the terms are taken from the dictionary) but, as needed, allow for (and encourage the use of) attachments to the CCDS that "translate" terminology in the CCDS' Adverse Reactions section into MedDRA terminology and names the dictionary version. Such attachments are increasingly used by MAH's anyway. Proposed change (if any): See above
426 - 436		Comment: This paragraph could be mis-read to mean that a CCDS is expected to contain adverse events of special interest or important findings from on-going clinical trials. To clarify that this information is expected to be found in an Investigator Brochure rather than in a CCDS, the wording should be clarified as shown below. Note that this proposed wording avoids portraying the CCDS as the only acceptable document to be submitted as reference document for approved product uses. Proposed change: "This PSUR section should list any significant changes made to the reference safety information (Investigator Brochure and/or other reference safety information for approved product uses) within the reporting interval."
513 - 513		Comment: The draft guideline assumes that CCDS are suitable reference documents for determining off label use. For the majority of CCDS, this assumption is incorrect. CCDS do not necessarily list all approved uses, or even all uses a MAH considers ethical and justifiable. In addition, in many CCDS for older marketed products, the spectrum of uses may be described in rather general terms, to cover a spectrum of similar (but not identical) approved uses in a "single line". This is done when such "condensation" is considered sufficient and appropriate for providing the reader of the CCDS with the necessary information to understand the safety profile described 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')*
		the CCDS. For additional information see our comments on lines 252 - 253. Furthermore, regulatory off-label use must generally be determined based the specific local indication and use pattern in approved labeling, and requires a meticulous comparison of observed use with conditions of use in the Indications, Dosage and Administration and possibly others sections (e.g., for requires safety precautions). Determining off label use vis-à-vis a global document is only possible if local approved uses are sufficiently similar and reflected in the MAH's global reference document. And a suggestion regarding the term "off-label use". Off-label use is more than just use outside the spectrum of approved indications. If the agency is interested in information on use outside the spectrum of approved indications, then the term "non-indicated use" or another, equivalent construction should be used. Proposed change: "For purposes of identifying which patterns of use are ~~off-label~~ not in accordance with approved indications, the marketing authorisation holder should reference the reference information for approved uses provided in the PSUR or as an attachment to the PSUR (e.g. in a CCDS) ~~in the PSUR~~.
824 - 825		Comment: See our comments on lines 252 - 253.
829 - 830		Comment: See our comments on lines 252 - 253.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Module VII – Periodic safety update report.
	In general we want to point out that the overall timeframe of the consultation was very short for an in-depth analysis and commenting on this comprehensive guidance documentation.
	The terms appendix and annex are used several times throughout the document. Please use a more consistent wording or define the differences.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
169		Comment: risk-benefit balance Proposed change (if any): benefit- risk balance
352		Comment: PSUR title page Proposed change (if any): Please provide a template
383		Comment: Worldwide marketing approval status Proposed change (if any): Please provide a template
1020		Comment: 60/75/90 days Proposed change (if any): Where or when are the 60/75 days applicable?
1050 - 1053		Reference: For active substances or combinations of active substances included in the list, marketing authorisation holders shall vary, if applicable, the condition laid down in their marketing authorisations in order to allow the submission of PSURs in accordance to the frequency and submission date as indicated in the list [DIR 107c(4)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		to (7)]. Comment: Please provide examples and define conditions of MAs Proposed change (if any):
1559		lack of marketing authorisation, including explanation, by competent authorities in Member States; Comment: Please clarify if refusal of MA is meant instead of lack of MA Proposed change (if any):

Please add more rows if needed.

<17 March 2012>

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

Comments from: Pierre Fabre Group

Name of organisation or individual
Pierre Fabre Group

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Efficacy data and benefit risk ratio analysis Pierre Fabre recognises that the draft PSUR GVP module is in line with the Step 2 ICH E2C (R2) guideline in terms of reinforcement of the benefit risk ratio analysis aspect but would like to emphasize the burden to implement the efficacy and benefit risk ratio analysis as currently defined in VII B 5 18 2 for “old company products ” or for products where the company has no specific efficacy knowledge based clinical trials data as the MA were essentially based on bibliographic or generics applications . It should made be clear if a comprehensive reevaluation of the benefit risk ratio, via the existing efficacy data in all clinical trials available to MAH, is awaited in the psurs even when there has been no new efficacy data emerging from a clinical trial during the reporting interval. **Transitional Arrangements** Pierre Fabre has another concern relating to the transition period that will be allowed to implement these new psurs. To achieve writing of the new PSUR format, companies will need to make extensive changes in existing processes, write new SOPs, create new templates and retrain the concerned staff’s departments, as well as involve more departments outside the main pharmacovigilance department. Pierre Fabre recognises that the implementation of the GVP modules may be required by EMA within a short period of time but given the major changes in the format and companies processes changes needed to implement the new one, Pierre Fabre proposes that the new PSUR format applies at the earliest to all reports whose data lock points occur after January 2013. It is deemed moreover useful for global companies that the mandatory implementation date is posterior to Step 4 of ICH E2C (R2) .

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 229-232		Comment : It is mentionned : "*should conclude the psur with consideration as to the need for changes and/or actions, including implications for the approved SmPCs for the product(s) for which the psur is submitted*" For products authorised in Europe with different national procedures, as the psur is global, it does not seem relevant to detail these implications. The reference safety document towards which the necessity for change has been assessed should be rather mentionned. Proposed Change : "*should conclude the psur with consideration as to need for changes and/or actions to be implemented,* ***compared to the reference safety document , if relevant, in the national approved SmPCs"****. If a need for revision of the existing safety reference document has been concluded at the end of the psur, it should be mentionned with major safety modifications highlighted"*
Lines 261-262		Comment: The PSUR GVP module states that "*The CCDS/CCSI should be dated, version controlled and it should state the version of the coding dictionary used"* The aim of providing the version of the coding dictionary and how this information would be useful is unclear . Furthermore, for PSUR covering long periods , there will be multiple versions of MedDRA used and this will impose a time consuming burden for the MAH to verify which MedDRA version was in place when a particular adverse effect was added to the CCDS/CCSI Proposed Changes: "*The CCDS/CCSI should be dated, version controlled and provided as a track changes version that identifies changes made over the reporting period ~~and it should state the version of the coding dictionary used."~~*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 353-354		Comment : It is mentionned that the title page must include the name of the medicinal products. For some psurs, including several medicinal products including the same active substance , the list of names , including invented names, could be long and will be available in the annex table of marketing status Moreover, psurs may be aligned to the EU reference date following previous work sharing process and in accordance with the published list of EU reference dates. The mention , in addition to the MAH IBD, of the EU reference date in the title page could make sense. Proposed change : "*should include the ….**common name of the active substance, ie either the INN or if not existing the usual common name***." Add "***international birth date, and EU reference date if relevant***, "
Lines 369 - 370		Comment: "*significant changes to the investigator brochure and post-authorisation product information* "may be confusing , particularly as post authorisation product information may differ according to regions or countries (for ex US PI versus EUSPC) To avoid misunderstandings and to ensure consistency with the title of section 5.4 of the PSUR (**Changes to the Reference Safety Information),** it is proposed to use rather the term "Reference Safety Information" . This recommendation should also apply in section 5.4 . Proposed change: "*actions taken and proposed for safety reasons including significant changes to the Reference Safety Information ~~investigator brochure and post-authorisation product information~~ or other risk minimisation activities"*
Lines 435-436		Comment : This sentence needs to be clarified . It could be understood that status of all variations submitted or approved following a change of the CCSI/CCDS should be presented here. This sentence seems also to request different information that the one requested in lines 263-264

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 : could you clarify the intent and the type and format of information to be provided
Lines 438-442		Comment: This section can be interpreted as requiring drug utilisation studies on all products . If this interpretation is in line with the underlying intent, it seems inconsistent with the risk proportionality principle . Proposed change : "*PSURs shall provide an accurate estimation of the population exposed to the medicinal product including all available data relating to the volume of sales and volume of prescriptions. Where data available to the MAH allow the analyses to be made, ~~T~~this estimation of exposure should be accompanied by a qualitative and quantitative analysis of actual use including how it may differ from indicated use ~~based on all data available to the marketing authorisation holder including~~. Sources of information for the analyses should include the results of observational (e.g. registries) or drug utilisation studies when these have been conducted".*
Lines 450-451		Comment: The consolidation of all finalised studies in the R&D database may not be performed at frequencies and timelines corresponding to the DLP of the psurs. There would be an unnecessary burden , especially for old products when only occasional phase IV studies are being conducted , to add an actualisation of cumulative data based on our psurs DLP Proposed changes : Add after the first sentence :" *When presented in tabular format from pooled clinical trials database, the data lock point of the cumulative data should be mentionned* ***and may not correspond to the PSUR data lock point***"
Lines 487-488		Comment : There may not be available drug use utilisation data for all products as mentionned in a previous comment; moreover , companies may have different levels of access to IMS data . Proposed change : "*In addition the data should be ~~routinely~~ presented by sex age indication , dose, formulation and region ~~where~~*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		~~*applicable*~~ ***when available*** "
Line 525		Comment : It is recognised that the title of this section is the one mentionned in ICH E2C R2 step 2 document but it does not seem to completely fit with the purpose of this section Proposed change: PSUR sub-section "*ADRS and AEs coding dictionnary* "
Lines 574-585		Comment: Section VII.B.5.7 is entitled "**Summaries of significant findings from clinical trials in the reporting interval"** appears to refer to findings from all interventional clinical trials. However, the first paragraph requires the inclusion in an appendix of *"sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during the reporting interval"* (i.e., those qualifying as a Post Authorisation Safety Study) Therefore, clarification is needed on the data to be included in this section (i.e. from all clinical trials or from just interventional PASS) Proposed changes: *This section of the PSUR should provide summaries of significant findings from all the marketing authorisation holder`s interventional clinical trials. In addition, t~~The~~ marketing authorisation holder should include as an appendix a listing of the sponsored interventional trials with the primary aim of…….*
Lines 576-581		Comment: the first stentence of the paragraph seems to restrict the followed subsections to interventional studies with primary criteria on safety assessement while it semms further that the section B 5 7 refers to all interventional studies Proposed change : Remove lines 576-581 at the end of the introduction after Line 587
Line 1006		Comment: It is mentionned that the staff should be trained "*according to the applicable guidelines"* and it is unclear what guidelines are being referred to. If the " applicable guidelines " refer to ICH E2C and/or the PSUR

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		GVP module, it would be helpful to clarify it Proposed change : Add the references in parenthesis: "*and trained according to the applicable guidelines (ICH E2C (R2) and this GVP PSUR module)"*
Lines 1019-1020		Comment : In the timelines for psur finalisation , D60 and D75 appear in figure VII.1 while in the text are only mentionned D 70 and D90 Proposed change : harmonisation needed with change 60/75/90 days to 70/90 days in the figure
Lines 1098-1099 Lines 1224-1225		Comment: "*The list should be updated" …*As the companies will have to identify their products in the list and any changes towards the previous list published, it would be useful to publish updates with track changes Proposed change : "*In case of amendment, the updated list should be published* ***, with visible track version changes*** *, …"*
Lines 1581-1589		Comments: This section evokes the needed modification of the SmPC , when during the psur period new safety information triggered the need to change the CCSI. It is requested that proposed new SmPC and leaflet be provided as an appendix to the psur. In case of different national SPCs (old products) , this may lead to a very long appendix. Moreover , if the current wordings are different across EU in locals SPCs, MAH may need to submit appropriate variations apart from the PSUR after a complete evaluation of all modifications needed in all national "old SPCs" Proposed change : "*The ~~proposed SmPCs and package leaflet~~* ***updated CCSI*** *with highlights on the changed sentences, paragraphs …should be appended as an appendix to the psur*"
Lines 1605-1626		Comment: In this appendix are detailed what should be done as a result of a new safety finding in a PASS or another non interventional study. This would seem to be more appriopprate in section VII B 5 8 as it should apply to all MS where there is a MA. Moreover the title of the section is restricted to PASS while other studies

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		are discussed inside the section . Proposed change : Deleted lines 1605-1626 from section VII C 5 5 and replace them in section VII B 5 8 after Line 631
Lines 1661-1664		Comment : This section concludes on the necessary record retention time for psurs related document Proposed change : It should be helpful to remind this record retention time in the sentence

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	General concern how they will address the lack of data on non-serious cases in the transition period.
	Do we have to switch format immediately on 2nd / 20th July.
	The new requirements apply to the EU but if countries outside EU will not accept new format. MAHs will need to produce 2 formats of PSUR moving forward - are the EMA discussing this new format with non EU Authorities to gain worldwide acceptance?
	BRIDGING REPORTS AND ADDENDUMS REPORTS: What safety information has to be provided for renewals? Contents of the addendums reports and SBR will be adapted to the PSUR template?
	ELECTRONIC PSUR: Do you have an estimated data for the submission of PSUR electronically? When will be the pilot phase launched between Regulatory Authorities and the Pharmaceutical companies?
	It says we don't include line listings. However non-serious cases up to June 2012 will not have been submitted to Eudravigilance. For 3 year PSURs for the next couple of years, it could be a lot of cases. Are we going to have to a) submit the backlog of non-serious cases b) submit supplementary line listings as a transition phase c) just summarise them.
	For mature products (i.e. licensed over 20years ago) that are not licensed under DIR Art 10a; will there be the possibility of not having to include sections pertaining to risk management systems. These products have not to date required risk management plans.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 317		Comment: Is interval data also required for clinical trial exposure? Proposed change (if any):

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Procter & Gamble

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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
	Consistently use either benefit-risk or risk-benefit, not a mixture of both throughout the document
	Clarify the differences between annexes and appendices and exactly what information should be found in each
	What implications does this guidance have concerning the need for PSURs at renewal?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 5 – line 149		Comment: add "be" into the sentence Proposed change (if any): normally be specified in the request,
Page 5 – line 156		Comment: Remove extra s from PSUR Proposed change (if any): PSUR reporting should therefore be
Page 6 – line 166		Comment: add "the" before basis Proposed change (if any): State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active
Page 6 – line 166		Comment: What are the circumstances that are referred to concerning lack of PSURs. Why would there be a lack of PSURs? Proposed change (if any): Clarification of the above
Page 7 – line 220		Comment: In the phrase - Critically summarising relevant new safety, efficacy and effectiveness information that could have – please clarify what effectiveness means in this context. Proposed change (if any): clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 7 –line 222		Comment: The following sentence does not make sense - Conducting an integrated benefit-risk analysis for authorised indications based on the cumulative information available since the international birth date (IBD), the date of the first marketing authorisation in any country in the world / development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. Proposed change (if any): The addition of an "and" or and "or" make improve the sense.
Page 7 – section VII B.3.		Comment: This section only discusses products with one active substance. Proposed change (if any): Include medicines with multiple actives
Page 7 – line 235		Comment: Add the word "safety" before information and change "on" to "covering" before all Proposed change (if any): containing the same active substance with safety information covering all the authorised indications, route of
Page 8 – line 253		Comment: Remove the comma after "both" not required Proposed change (if any): should be used as the reference for both, the benefit and the risk sections of the PSUR. The core safety
Page 11 – line 356		Comment: Specify who should be the signatory Proposed change (if any): clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 11 – line 366		Comment: What about countries where an authorisation system is not in place e.g. US monograph system Proposed change (if any): further information
Page 12 – line 406		Comment: Add "for safety reasons" to the end of the sentence Proposed change (if any): marketing authorisation application for safety reasons;
Page 12 – lines 418 and 419		Comment: Add "for safety reasons" to the end of the sentences Proposed change (if any): failure to obtain a marketing authorisation renewal for safety reasons; withdrawal or suspension of a marketing authorisation for safety reasons ;
Page 12 – line 424		Comment: Add consumers to this bullet point Proposed change (if any): communications to health care professionals and consumers; and
Page 15 – line 516		Comment: include post-marketing data in the scope for this section, as it is discussed later in the section Proposed change (if any): The objective of this PSUR section is to present clinical and post-marketing safety data through summary tabulations of
Page 18 – line		Comment: Progress or final study reports generated during the reporting interval for post-authorisation safety

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
630		630 studies should also be included in the regional appendix of the PSUR (see VII.B.5.20.) –this sentence refer to PASS, but the title to this section refers only to non-interventional studies Proposed change (if any): clarify
Page 18 – line 634		Comment: Change "is" to "are", as the sentence discusses the plural "sources" Proposed change (if any): medicinal product from other clinical trial/study sources that are accessible[11] by the marketing
Page 18 – line 644		Comment: Change the order of this sentence slightly Proposed change (if any): This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.
Page 18 – line 646		Comment: add "of" after "aware" Proposed change (if any): the medicinal product that the marketing authorisation holder became aware of during the reporting
Page 20 – line 709		Comment: Delete "important" as important safety concerns have not been referred to previously Proposed change (if any): The purpose of this PSUR sub-section is to provide a baseline summary of safety concerns

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 20 – lines 721-723	3	Comment: Change "safety specification" to "RMP" Proposed change (if any): For products with a RMP (see Module V), the information included in this sub-section should be equal to the summaries provided in the version of the RMP current at the beginning of the PSUR reporting interval.
Page 20 – lines 728 to 732		Comment: Add important to the bullet points Proposed change (if any): Important interactions with other medicinal products; •important identified medication error where no adverse events occurred, or near misses of medication errors Important interactions with foods and other substances; • important occupational exposure; • important pharmacological class effects.
Page 22 – line 791		Comment: Define the "sentinel" adverse reaction Proposed change (if any): clarification
Page 23 – line 815		Comment: Change "has" to "have" Proposed change (if any): important identified risks that have become available during the reporting interval 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')*
Page 26 – line 939		Comment: Add as applicable Proposed change (if any): In addition, as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the
Page 26 – line 946		Comment: Does this refer to the Reference Safety Information? Proposed change (if any): 1. Reference Safety Information
Page 27 – line 991		Comment: - what does this sentence mean? "and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;" Proposed change (if any): clarification required
Page 27 – line 988		Comment: Should have a small "p" after a colon Proposed change (if any): poor quality reports: poor documentation or insufficient information or evaluation provided to
Page 27 – line 996-997		Comment: This documentation should be available at all times. – available to whom, where and in what context Proposed change (if any): clarification required
Page 28 – line		Comment: State that this is the responsibility of the QPPV

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): It is the responsibility of the person responsible for the pharmacovigilance system (the QPPV) to ensure that the
Page 30 – line 1048		Comment: Remove extra s from PSURs Proposed change (if any): Optimisation of the management of PSURs and PSUR assessments within the EU:
Page 31 – line 1087		Comment: addition of "is" Proposed change (if any): Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU
Page 31 – line 1093		Comment: What are the circumstances that are referred to concerning lack of PSURs? Why would there be a lack of PSURs? Proposed change (if any): Clarification of the above
Page 32 -		Comment: Explain that the diagram does not apply to all products – i.e. some products will not be included in the list Proposed change (if any):
Page 35 – line 1162		Comment: Doesn't immediately usually mean within 90 days? Proposed change (if any): Marketing authorisation holders shall submit PSURs immediately upon request

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		(usually 90 days) from a competent
Page 38 – line 1230		Comment: Add an "s" to PSUR Proposed change (if any): Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six
Page 39 – line 1247		Comment: Change to "an EU" Proposed change (if any): list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from
Page 42 – line 1334		Comment: change "hold" to held" Proposed change (if any): whether or not held by the same marketing authorisation holder and for which the frequency and dates
Page 44 – line 1344		Comment: Change "has" to "have" Proposed change (if any): have been granted in accordance with the centralised procedure;
Page 44 – line 1376		Comment: Change "from" to "of" Proposed change (if any): and to the Member States concerned [DIR Art 107e(2)], within 60 days of the start of the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 45 – line 1409		Comment: Change "from" to "of" Proposed change (if any): meeting following the PRAC adoption. Within 30 days of receipt, the CHMP shall consider the PRAC
Page 50 – line 1577		Comment: VII.C.5.3. PSUR EU regional appendix, sub-section "Company core safety 1577 information and summary of product characteristics" – is this country specific? Proposed change (if any): clarification
Page 50 line 1591		Comment: This section assumes that you have a RMP in place – what happens if there is not a requirement for a RMP? Proposed change (if any): clarification
Page 51 – line 1634		Comment: How often will the EU reference list of dates and frequencies be updated? Proposed change (if any): further information
Page 52 - line 1645		Comment: Add an "s" to the first risk Proposed change (if any): authorisation holder should maintain on file a specification of important identified risks, important
Page 53 – line 1696		Comment: Remove "s" from program

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): consistent, sustainable and efficient records management program and it has been developed in
Page 53 – line 1714		Comment: Change "on" to "of" Proposed change (if any): information in cases of non-compliance and take appropriate regulatory actions as required.
Page 53 – line 1716		Comment: Change to "an " EU Proposed change (if any): only one Member State and containing an active substance for which an EU reference date and
Page 54 – line 1724		Comment: Remove the "s" from communication Proposed change (if any): communication across the EU regulatory network and the actions to be taken regarding the variation,
Page 54 – line 1735		Comment: Add a full stop at the end of the sentence Proposed change (if any): EudraVigilance database or other data used to support the PSUR assessment.

Please add more rows if needed.

19.04.2011

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

Comments from:

Name of organisation or individual
La Roche

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Roche supports the comments EFPIA has sent in. The modules are in general well written but would benefit from consistency checks across in terms of definitions and requirements for the quality system. In particular Module I describes that, in each module, particular quality aspects will be discussed, and as this is clearly the case in a number of modules, it is less obvious in other modules. We have no comments in addition to the EFPIA comments, however we do have some questions for clarification that were raised while reviewing the draft modules. In line with the presentation of safety data (clinical trials and post marketing) through summary tabulations (see VII B.5.6.1 & VII B.5.6.2), we assume that we will no longer be required to submit listings of individual cases within the PSUR and that the Agency will assume responsibility for retrieval of this information from the EudraVigilance database and providing this to the PRAC Rapporteur or Member state (VII.C.4.2.1, 1283-1284 and VII.C.4.2.2, 1352-1354), please confirm. Per VII.C.8.3, and until the procedure detailed in VII.C4.2.2, VII.C4.2.3 and VII.C4.2.4 is in place, we assume that the current requirements for submission of the PSUR and related documents (ie proposed Core Safety Profile, CSP vs RSI comparison and HMA cover letter) should continue to be submitted to the assigned P-RMS under the present EU Work Sharing Procedure – please confirm? And a related question; for EU synchronised products for which there is no assigned P-RMS or until the procedure detailed VII.C4.2.2, VII.C4.2.3 and VII.C4.2.4 is in place, that they should continue to be submitted to Competent Authorities for assessment where the product is licensed in individual member states – please confirm?

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
175-176		QUESTION: Union Reference date list – do we know when this will be available and where it will be stored?
356		If the signature of the EUQPPV is required on the title page it is important that this is clarified here.
1577		Has the notion of Core Safety Profile disappeared and should a comparison with all local SmPCs be performed?

Please add more rows if needed.

<Date of submission>

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The exact date from which the new PSUR content should be used is not fully clear. It would make sense if it is not July 2012 since it takes a long time to revise templates and working instructions and implement/finish related training plans. Besides, the new PSUR standard no longer requires linelistings and thus it would make sense that the EV database first has its functionality that all member states receive non-serious reports.
	It would make sense if the new EU reference dates are aligned with the already existing EU-HBDs in order to avoid additional workload with respect to planning of upcoming PSUR periods and related variations
	A detailed standard for signal detection is currently missing. There are many open questions such as “which methods are legally accepted for companies with a small number of reports where statistical methods do not make any sense due to the low number of cases” or “should literature reports where only the active substance is known and the product could have been produced by several MAHs be included into signal detection”, etc.
	A separate appendix for the new proposed SmPC and the entire study reports does not make any sense since it is too detailed for the purpose of a PSUR. A summary of proposed SmPC changes and a summary of relevant study results would be enough.
	The requirements for renewal PSURs are not fully clear, e.g. How detailed should renewal PSURs be? Will they have the same structure as common PSURs? Will an addendum report still be accepted for a renewal?
	What about non-EU countries? Will they all accept the new PSUR format?

2. Specific comments on text

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

Please add more rows if needed.

17.04.2012

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
	In reference to v 210-213, could you please specify if there is any frequency for this evaluation established? How it should be performed/documented if PSURs are not required?
	In reference to v 639, we would like to suggest that it should be clearly stated whether safety findings originating only from studies performed by MAH or also from studies found in the literature (for an active substance) should be described in this section.
	In reference to v 649, please provide more detailed explanation if during PSUR preparation MAH should review all available literature data, or only some of them as examples. What about literature searches for PSURs for substances for which EMA will perform literature searches – are EMA results will be available to MAH's and they will be allowed to use this data in PSURs, or they will be obliged to perform their own literature searches?
	In reference to v 1128 and v 1254, could you please specify whether the result of PSUR assessment will be obligatory for all MAHs of product (e.g. generic) with the same active substance (what exactly does the word "concerned" in v 1254 means)?
	Generally the module does not clarify how PSURs should be submitted during transitional period: should PSURs for generics be submitted after 02.07.2012, if yes , up to which date? What kind of format should these PSURs have?

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The new PSUR format is too complex, it contains too many sections and subsections (previously there were 10 sections, now there are 20)
	Furthermore to avoid inconsistency and confusion we do strongly recommend waiting with finalising this GVP module on PSURs until the new ICH guidance is approved.
	Most of the data/documents requested for a regional PSUR appendix will be difficult, time-consuming and impossible to consolidate for the PSUR. The PSUR is not the appropriate document to record the local SmPCs, PILs and changes made to them should be appended.
	Since for a lot of products the requirement for writing PSURs for generics is waived, the complexity and difficulties for now creating PSURs for generic products are not taken into account. In some sections below wesuggest what should be exempted for generics. For products for well established use and generics there is usually a variety of indications and dosage schedules present in all different SPCs – therefore generic companies do not have a CCDS, but work with a CCSI. The PSUR should not be considered as a document to discuss the correct indications and posology – so a thorough review and reassessment of that should not be expected.
	It would be useful to attach a template of the cumulative tables as required

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')*
146		Comment: Considering all the new analysis and requirements to be covered in the PSUR, which will require significant multiple cross-departmental inputs, PSUR submission deadline should be longer than 70 days (for PSURs up to 1 year). Proposed change: Change to at least 3 months.
157-161		Comment: Regarding modular approach of the PSUR - it is still not efficient to repeat and maintain the same information in 2 documents. Furthermore, only a link to the RMP is needed when available. Proposed change: Instead of copying sections from the RMP, it should be sufficient just to make cross-references to the RMP, when available and relevant.
231		Comment: PSUR conclusion(s) should primarily indicate whether any actions or changes are needed to the CCDS/CCSI, and not to the approved SmPC(s). Relevance for the individual SmPCs should be discussed separately from the PSUR procedure. Proposed change: Replace "summary of product characteristics" with "CCDS/CCSI".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
252 - 254		Comment: "The latest CCDS in effect at the end…..sections of the PSUR" Since generic companies do in general not have a CCDS, the CCSI should also be mentioned as possible reference document. For summary tables from clinical trials consideration should be given to the use of the IB as a reference for safety information Proposal: Change to: "The latest CCDS *or CCSI* in effect at the end…..sections of the PSUR" "for summaries from clinical trials the IB can be used as reference.
261-262		Comment: Generic MAHs have CCSIs created in general from EU CSP/CAPs/referral. Since those documents use an unspecified version of the coding dictionary, the MAH will not be able to say which coding dictionary was used for the CCSI. Proposed change: Remove the requirement to indicate the version of coding dictionary.
263-265		Comment: Differences between the SmPC & the CCSI should not be submitted within the PSUR, there should be a separate procedure for this. Large generic companies may have many different local SmPCs for the same active substance, PSURs are usually written centrally, hence the SmPC/CCSI comparison should be done by the local MAHs, outside the PSUR. Proposed change (if any): remove the requirement to include the SmPC/CCSI comparison in the PSUR appendix.
353, 378		Comment: In some companies PSURs are numbered in a non-sequential way - such as based on the active substance internal number and/or data lock point. Sequential numbering would also cause confusion for several products

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		with overlapping PSURs written for different countries/regions with different periodicity. Proposed change (if any): remove the word "sequentially"
354-355		Comment: A large generic company may have many different MAHs for the same product, it is impractical to name them all on the title page. Proposed change (if any): MAHs should be indicated in the registration status of the PSUR, not on the title page.
385-386		Comment: What does it mean "where authorised, if applicable"? Do we need to list all countries where the product is authorised or not? Proposed change: Clarify whether MAHs need to indicate where each product is authorised, or not.
422-423		Comment: In the phrase "safety related changes in labelling documents that could affect the development programme" - it is unclear why the development programme is mentioned here when those changes concern actions related to already marketed drugs i.e. the development programme has long since been completed? Proposed change (if any): remove this requirement from the section "marketed products" because it concerns products under development, and not marketed products.
434-436		Comment: PSUR is not the appropriate document to record changes made to the local SmPCs. This is done locally, in local language.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Remove the requirement to report changes made to local SmPCs in the PSUR (regional appendix).
475		Comment: "When possible, separate estimations should be provided for cumulative exposure (since the IBD) and interval exposure (since the DLP of the previous PSUR)" For generic companies which grow through acquisitions the cumulative sales going back to first sales for any particular product is not usually available. The phrase "when possible" will be interpreted that it should in fact be available, which for the general safety profile of the product is not needed. The sentence should be rephrased to indicate that most important are the sales during the PSUR period. Proposed change to: "Interval exposure since the DLP of the previous PSUR should be provided. When readily available and considered relevant when there is only one MAH in the EU, separate estimations could be provided for cumulative exposure (since the IBD)
487-488		Comment: If patient exposure is derived from sales data, the data on indication, sex and age are sometimes not available. Proposed change (if any): Add "where such information is available" for data on sex, age and indication
514		Comment: Some companies maintain and attach CCSI but not CCDS to the PSUR. Proposed change (if any): Add the option to attach CCSI if CCDS is not available.
611-616		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')*
		Please specify or give examples of what "important safety findings" for a combination product should be included in the single-substance PSUR and vice versa.
630-631		Comment: For PASS studies conducted locally as a local requirement the progress/final study reports are usually available in the local language only. Proposed addition: "Progress or final study reports…. Appendix in the PSUR. *If the report is not in English, a summary in English is sufficient"*
844		Comment: It is unclear if the new information on efficacy and effectiveness, as mentioned in this section, refers to MAH's own data, or MAH is expected to search the literature. Proposed change: Clarify the scope of new information.
888		Comment: Some of the data requested in this section are overlapping with the data in subsection "Important baseline efficacy and effectiveness information". It would be clearer to present them together. Proposed change (if any): The requested data in this section should be added to the section on "Important baseline efficacy and effectiveness information", and the section "Benefit-risk context-medical need and important alternatives" should be deleted.
1000		Comment: The agreement should specifically detail the options to audit the PSUR preparation process.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1050 / 1106 / 1232		Comment: The URD list to be published as well as the DIR and the REG determining the periodicity changes are required by the legislation and as such legally binding documents. The intentions of the new legislation include better protection of patients, simplification, reduction of duplication, and reduction of bureaucracy. Submitting variations to move to either no PSURs (for generics) or other dates (from the URD list) appears to be an inefficient use of MAHs time, money and resources.. There is also a real danger that such new obligations would waste resource at hthe CA level too. Proposal: It is proposed to remove the PSUR DLP and periodicity out of the definition of "MA condition"
1079		Comment: It would be useful to also add in the URD list the name of the company that is responsible for preparing the PSUR for a particular substance. Proposed change: see above
1111 and 1155		Comment: Often in generic companies one PSUR is prepared for a group of MAHs and not for individual MAH where each MAH in the group holds an MA for products containing a particular substance. Proposed change (if any): add: *one marketing authorisation holder or a group of MAHs*
1158-1161		Comment: It is not efficient, to always have to contact and agree with the competent authorities upfront whether it is appropriate to write a stand-alone PSUR for a combinational product, or this information should be submitted in the same PSUR for the single substance product.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Provide the flexibility for the MAH to choose the preferred way to report this information , without the need to agree with the relevant authorities.
1163		Comment: the minimum deadline (after the request from the competent authority) for ad hoc PSUR submission should be defined. Proposed change (if any): Replace "shall submit PSURs "immediately" with a mutually agreed deadline, taking into account the amount of data and analysis necessary for PSUR preparation.
1164 - 1166		Comment: "To facilitate the EU assessment….. the competent authorities in the MS may make use of the list of EU reference dates……" To eliminate and facilitate requests as much as possible "may" should be replaced by "should" unless justified. Proposed "To facilitate the EU assessment….. the competent authorities in the MS ~~may~~ should make use of the list of EU reference dates……"
1226		Comment: The agency's webportal should enable the possibility to subscribe to email notifications after an update in order to make sure MAHs will receive essential information important for the safety of their products. Proposed change "*The agency shall facilitate the possibility to subscribe to automated notification after the Agency's portal is*

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		updated so MAH shall *be notified* ~~continuously check the European medicines portal~~ about any relevant updates…"
1538		Comment: It is good to have such a table to allow for a direct comparison between common sections of the PSUR and RMP. However, the PSUR modules that are interchangeable with RMP modules could have the same title/name to make it easier to recognize parts of report that are interchangeable. Proposed change (if any): Please change names to the PSUR/DSUR and/or RMP titles/sections to make them more similar and easier to cross-reference.
1588		Comment: It is impractical to attach hundreds of proposed local SmPCs and package leaflets in the PSUR (regional appendix). There should be a separate, PSUR-independent process for submission of these local documents. Proposed change (if any): Remove the requirement to attach local SmPCs & PILs in the PSUR appendix.
1661 1664		Comment: Does this mean that at a given typical life-cycle of 30 years of a product, PSURs including sales figures etc should be kept up for 40 years ? A PSUR includes cumulative data which are interesting during the life cycle of a PSUR. But PSURs older than two 3-years periods are out-dated and might have only historical value. Proposed change (if any): PSURs should be required to be kept only for 6 years max.
1715-1719		Comment: For products which are not included in the URD list, how will an MAH know if this is due to the fact that no

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		PSURs are needed for this substance, or if this is due to the fact that it is purely nationally authorized product registered only in one member state, so such products are not considered in the EU single assessment project? Proposed change (if any): Include in the URD list also those substances for which no PSURs are needed at all, and mark them appropriately in the list. This would be more transparent.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<18 April 2012>

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

Comments from:

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

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Some headers in the proposed Table of Contents for the future PSUR (PBRER) appear slightly misleading or even contradictive to the content of the body of the text underneath. Misleading titles may lead to significant uncertainty in how to practically write the respective PSUR sections. Proposed header name changes will be addressed for each header individually starting in line 318 below. With regards to section 7 of the PSUR the issue is illustrated by the discrepancy between the header names in ICH E2C (R2) and the GVP module: in ICH E2C (R2) it reads "Summaries of Significant *Safety* Findings from Clinical Trials in the Reporting Interval", whilst the term "Safety" has been omitted in the draft GVP module. Uncertainty may arise where to depict lack of effect data / efficacy data, particularly since a separate section on Lack of efficacy as section 13 of the PSUR has been maintained. In some subsections to section 7 depiction of both efficacy and safety findings (or "important information" in general) is requested, thus inferring that section 7 should include both, and that the term "Safety" has been intentionally omitted in the GVP header opposed to the ICH E2C (R2) header. This discrepant situation illustrates two principal issues: • The guidance in the GVP text under each header may differ from the header, rendering practical writing of these sections difficult • Whilst headers 10, 11, and 12 are limited to the data source alone therewith rendering the TOC easy to read, headers 7, 8, 9 and 13 each represent a mixture of data source and the expected content for these sections – unfortunately in a slightly inconsistent way (terms used are "Significant findings", "Findings" and "Information", which do not always adequately reflect the expected information in these subsections). Proposals: • Merge sections 7 and 13 • Simplify the table of contents depictions for sections 7 through 13

Stakeholder number *(To be completed by the Agency)*	General comment
	Accordingly the table of contents could look as follows: 7. ~~Summaries of Significant Findings from~~ Clinical Trials ~~in the Reporting Interval~~ 7.1. Completed Clinical Trials 7.2. Ongoing Clinical Trials 7.3. Long-term Follow-up ~~7.4. Other Therapeutic Use of Medicinal Product~~ → [pasted to 8.1 - justification see line 603-607] 7.~~5~~. 4. New Safety Data Related to Fixed Combination Therapies 8. ~~Findings from~~ Non-interventional Studies 8.1. Other Therapeutic Use of Medicinal Product 9. ~~Information from~~ Other Clinical Trials and Sources 10. Non-clinical Data 11. Literature 12. Other Periodic Reports ~~13. Lack of Efficacy in Controlled Clinical Trials~~ → [could be merged with section 7]

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
160-162 Figure VII.2 and figure VII.3 (lines 1103 and 1145, respectively)		The new legislation also waivers the obligation to submit PSURs routinely for generic medicinal products, well established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products. Comments: 1.) Please confirm what the definition of a well established medicinal product is in the GVP definitions module. Will MAHs need to seek confirmation with each individual Competent Authority that a PSUR is not required for a well established product in case that product is not on the URD list? We propose this should not be the case and the system as described in the Regulation, Directive and GVP module should be clear and subsequently followed. 2.) The flowcharts included in Figures VII.2 and VII.3 conflict in that for medicinal products without a condition on the frequency of PSUR submission *and* the active substance(s) of which are also not in the URD list, Figure VII.2 indicates that PSURs are required as per Directive 2001/83/EC until eternity (unless the active substance will be included in the EURD list), where as Figure VII.3 indicates that these medicinal products do not require a PSUR at all. It is our understanding that the EURD list will not contain all substances for which MA s exist, but only those for which PSURs will be needed. Therefore the presentation in Figure VII.2 does not reflect the spirit of the key concept of the whole New Legislation which – among others – aimed to both simplify and therewith strengthening Pharmacovigilance by focus on a risk-balanced approach. Proposal: Figure VII.2 should be modified to match Figure VII.3.The rightmost box should read "No PSUR required".
201		Comment: Why should a PSUR never be used to provide initial notification of new safety information or provide the means by which new safety issues are detected? There may be circumstances where a PSUR serves for these

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		purposes as outlined in Module VII, line numbers 198, 214 ff, and 1521-1522. In case, during the preparation of PSUR the critical evaluation of the safety data (see line numbers 214 and 215) leads to the identification of new potential or identified risks etc., this will be explicitly stated in the "Executive Summary", a section of the PSUR that has been introduced in the table of contents of a PSUR also for this purpose.
261-263 and 432-434 and 1574-1583		GVP text: The marketing authorisation holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorised product information. These meaningful differences should be included in the PSUR regional appendix (see VII.B.5.20). And GVP text: The marketing authorisation holder should also provide information of any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI in the regional appendix, see VII.B.5.20. And GVP text: The marketing authorisation holder should include in this section the meaningful differences between the CCSI and their proposals for the summary of product characteristics (SmPC). When the marketing authorisation holder considers that changes to the SmPC are required in line with the provisions established in Article 16(2) of Regulation (EC) No 726/2004 and Article 23(2) of Directive 2001/83/EC, the proposed amendments to the SmPC should be submitted with the PSUR provided these changes are in relation to the new safety information regarding the new interval covered. If not directly related to the new safety information, the amendments should not be delayed. It is the obligation of the marketing authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		marketing authorisation. The proposed SmPC and package leaflet should be included as an appendix to the PSUR. Comment: For MAHs with multiple national procedures for a medicinal product (DCP, MRP), the inclusion of each proposed local product labeling (in the local language?) and current variation status will create a large administrative burden. Highlighting of meaningful differences as requested in the first text above appears of value to maintain oversight on non-compliance with the CCSI for both regulators and companies, whilst a detailed depiction at the member state level as requested in the second text may exceed the scope of what should be in a Europe-wide document. Before the PSUR repository is established, such information might rather belong into the cover letter. It is also beyond scope of the more detailed depiction of the European procedure which is outlined in the third quoted text above. Proposal: The second text presented above should be rephrased as follows: The marketing authorisation holder should also provide information on meaningful differences and – where applicable – proposed amendments of the SmPC of any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI in the regional appendix, see VII.B.5.20.
263, 434		Comment: Not all regulatory agencies may request highlighting meaningful differences between CCSI and the local product information (→ regional appendix). Purpose of the regional appendix according to VII.B.5.20 is to comply with national or regional requirements. Similar comment for line 434.

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		Proposed change (if any): Add "if requested by national legal requirements "in line 263: These meaningful differences should be included in PSUR regional appendix if requested by national legal requirements (see VII.B.5.20.).
318		The only information that should be provided in the section with the header "Reference Information" is information about the version of the coding dictionary used. Therefore, the header name is misleading. It also implies a link to section 4 with the header "Changes to Reference Safety Information". Proposal: Change header name from "Reference Information" to "Coding Dictionary Information".
319-320		Depiction of the two headers 6.2 and 6.3 do not follow the same logic, because 6.2 includes what is to be presented (SAEs) in the ST, whilst 6.3 does not tell. For clarity, section 6.3 should reflect that adverse reactions are to be depicted. Proposal (change/addition underscored): Change header name of 6.3 to read "Cumulative and Interval Summary Tabulations of Adverse Reactions from Post-marketing Data Sources".
337		When writing PSUR sections 16.2 and 16.3 clear distinction needs to be made regarding which signals/new risks go into which of these two sections. The text makes clear that 16.2 is exclusively intended for depiction of each closed signal *individually*. Opposed to that section 16.3 is to include an evaluation of *all* risks (not just these completed during the interval) in the light of new information. Therefore, this section will likely rather present summarising information opposed to individual depictions of single signals. Unfortunately the header name of section 16.2 does not reflect the expectation of depicting closed signals from the interval. In addition, use of the term "evaluation" in both section headers for 16.2 and 16.3 adds to

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		the level of uncertainty. Proposal: Change header name of 16.2 from "Signal Evaluation" to "Closed Signals".
351-353		GVP text: The title page should include the PSUR number (reports should be numbered sequentially), the name of the medicinal product(s), international birthdate, reporting interval, date of report, marketing authorisation holder details and statement of confidentiality of the information included in the PSUR. Comment: Please clarify if 'the name of the medicinal product' refers to the active moiety or to each licensed worldwide tradename. Proposal: If so, the term "active substance(s)" should be used instead of "medicinal product(s)" Comment: Please clarify if 'marketing authorisation holder details' could be replaced with 'details of the author of the report'. This is worthwhile for companies for which one global PSUR is written on behalf of multiple local MAHs. Proposal: Use the phrase 'Details of the author of the report'.
597-600		GVP text: VII.B.5.7.3. PSUR sub-section "Long term follow-up" Where applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

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		Proposed change: For clarification of the sentence it is proposed to have "beyond their clinical trial participation" inserted as follows: Where applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs beyond their clinical trial participation, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).
602-605		The subsection B.5.7.4. "Other therapeutic use of medicinal product" is located under the main section B.5.7 "clinical trials", but does not refer to clinical trial information. At present the GVP text in this subsection reads as follows: This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D (e.g. expanded access programmes, compassionate use programmes, particular patient use and other organised data collection). Proposal: The subsection B.5.7.4. should be allocated to section B.5.8 "Non-interventional studies" instead of B.5.7 "clinical trials".
609-611		GVP text: If the product that is the subject of the PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy.

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		This sentence is slightly confusing because a "product" cannot be authorised or developed as a component of a fixed combination product. Proposal: The term product in the following sentence should be replaced by "active substance": If the ~~product~~ active substance that is the subject of the PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy.
713		Comment: Typo: "public heath" Proposed change (if any): Change heath to health
776-779		The introductory text in sub-section VII.B.5.16.4 reads as if *every* important risk that has been identified in the time period since the IBD needs to be presented *individually* including all assessment elements presented in lines 778 through 793. This understanding arises also because – opposed to ICH E2C (R2) - the GVP uses the term "should" instead of "may" in line 777. It is understood that the elements listed are similar but not equal to the elements in section 1.5.2 of the present RMP template. At present ICH E2C (R2) in Appendix D does not consider this a module to be shared between PBRER/PSUR and RMP. Based on the above expectation sub-section VII.B.5.16.4 might become excessively long. Obviously a risk-based approach should be taken, and the extent of information to be provided will depend on whether every important identified risk from the beginning of time has to be depicted in its full characterisation, or whether such risks which may have been removed from the RMP over time may be depicted in a very concise manner.

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		The GVP module text should foresee such options. Proposal: One sentence added at the end of the introductory paragraph. In addition the text in line 777 should read as in ICH E2C (R2) and use the term "may": This sub-section will characterise important identified risks and important potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe important missing information. The level of detail to be portrayed for each identified risk should be greater for more recent risks compared to those which are acknowledged for many years and adequately established in the CCDS/CCSI since then. Where applicable, taking into account the data source, risk data ~~should~~ may include the following:
818-819		GVP text: Results of evaluations that became available during the reporting interval should be provided in the regional appendix (see VII.B.5.20.), to comply with national or regional requirements. Comment: This text likely refers to results of local evaluations confined to one or more EEA member states and which may therefore be of limited relevance for the international PSUR document. This may be made slightly clearer. Proposal: Results of evaluations that became available during the reporting interval and refer to individual member states only should be provided in the regional appendix (see VII.B.5.20.), to comply with national or regional requirements.
976-978		Comment: What is expected regarding "source data verification"? Which source of data should be checked (safety database entries or source documents on which the safety database entries are based?) and to what extent

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		(full dataset?) Proposed change (if any): please clarify
1001		Comment: The "person responsible for the Pharmacovigilance system" - is this the EU-QPPV or is this also the local responsible person for the Pharmacovigilance system according to national regulations such as German Drug Law (Arzneimittelgesetz), section 63a (§63a, Graduated Plan Officer)?. If yes, how should this responsibility be addressed by a local QPPV within a global pharmaceutical company? Proposed change (if any):
1018		Comment: Typo in Figure VII.1.: "Directive 2010/84/EU amending Directive 2011/83/EC (Dir)" Proposed change (if any): Change 2011/83 EC (Dir) to 2001/83 EC (Dir)
1160		Comment: "Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a Member State". How is "immediately" defined? Does an "immediate" submission refer only to already available PSURs? According to line 146-149 of Module VII, "… the ad hoc PSURs should be submitted within 90 days of the data lock point". Proposed change (if any): Use the same wording as in lines 146–149.

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1202		Comment: Figure VII.4.: The two arrows leading from the box "PRAC recommendations on the amendment of the list …" do not have labels. So it is not clear in which situation the arrow to the box "END" is applicable and in which situation the arrow to "CHMP opinion or CMDh position". Proposed change (if any): Add appropriate labels next to the two arrows
1229-1230		GVP Text: Where appropriate, marketing authorisation holders shall submit the relevant variation within these six months in order to reflect the new information in their marketing authorisations [DIR 107c(6)]. Comment: It is understood that this refers to proposed variations to amend the PSUR submission schedule. Because the schedule has already been agreed through the EU URD list amendment of the MAH's authorization thereto represents a formality and should be managed with the least possible administrative effort in the interest of both MAHs and authorities. Proposal: Where appropriate, marketing authorisation holders shall submit a variation if they cannot implement the new information in their respective PSUR reporting system within these six months. ~~the relevant variation within these six months in order to reflect the new information in their marketing authorisations.~~ Additional comment: The reference to [DIR 107c(6)] should be deleted as this refers to an application to deviate from an agreed schedule to trigger discussions at CHMP and CMDh following PRAC consultation. Lines 1229 and 1230 refer to a new published date AFTER an agreement is reached at that level. This is in a sense imposed on 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')*
		Deviation of the new date (e.g. implementation outside of the 6 months) should trigger a variation.
1550		Presentation of the renewal date is requested in sub-section "EU marketing authorisation status" that is part of the PSUR EU regional appendix. That sentence can be misread due to the use of the term "subsequent" in two ways: • either to refer to the first ever renewal (not the most recent one if multiple) • or to require a renewal date to be provided in any case. We trust that only outstanding renewals should appear in the list. This is because all past renewals are of no relevance for the PSUR assessment procedure. Disclaimer: Just in case the above assumption is inaccurate, the following needs consideration: For products that historically had (or products which in future might have) more than one renewal date, guidance is needed as to which renewal date should be presented in the regional appendix. For practical reasons the latest renewal date appears more meaningful than historical earlier renewal dates, as it is the one to most likely trigger regulatory decisions (if any). Proposal: This information should contain the following: • dates of marketing authorisation and subsequent outstanding renewals
1576-1582 (1580)		GVP text: When the marketing authorisation holder considers that changes to the SmPC are required in line with the provisions established in Article 16(2) of Regulation (EC) No 726/2004 and Article 23(2) of Directive 2001/83/EC, the proposed amendments to the SmPC should be submitted with the PSUR provided these changes are in relation to the new safety information regarding the new interval covered**. If not directly related to the new safety information, the amendments should not be delayed.** It is the obligation of the marketing authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 variations to the terms of a marketing authorisation. Comment: The intent of the sentence highlighted bold above is not clear. Changes directly related to new safety information require timelier variations compared to non-safety changes. The sentence should therefore be rephrased. Proposal: If not directly related to the new safety information, the amendments of the SmPC may ~~should not~~ be delayed.
1583		GVP text: The proposed SmPC and package leaflet should be included as an appendix to the PSUR. Comment: Clarification on this sentence is requested. 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? Proposal: The proposed new text parts for the SmPC(s) and package leaflet(s) should be summarised into one document and included as an appendix to the PSUR.
1764-1776		Comment: Until the Agency can ensure the functionalities agreed for the repository, MAHs submit PSURs to all competent authorities in Member States in which the medicinal products are authorised, according to lines 1764-1771. According to line 1772 -1776, from 12 months after the functionalities of the repository have been established, the MAH shall submit the PSURs electronically to the Agency.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		It is not completely clear whether the MAH can/shall then stop to send the PSURs to the other authorities as stated in line 1764-1771. Proposed change (if any): Include a statement whether or not the MAH shall stop sending PSURs to all competent authorities in Member States in which the medicinal products are authorised from 12 months after the functionalities of the repository have been established.
1764-1769		"Until the Agency can ensure the functionalities agreed for the repository, marketing authorisation holders under the obligation to submit PSURs irrespective of whether the medicinal product is authorised in one Member State only or more than one Member State and irrespective of whether the active substance or combination of active substances is on the EU reference date list shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised [DIR Art 2(7)]. Comment: This sentence may be read in such way that PSURs have to be submitted to all active substances even if they are not on the EU reference date list. This may not be the intent of the text (the intent may be to indicate that in case a PSUR is needed, submit to all competent authorities). However, this should be clarified. Submission of PSUR for all active substances is not in the spirit of the key concept of the whole New Legislation which – among others – aimed to both simplify and therewith strengthening pharmacovigilance by focus on a risk-balanced approach. The reference to DIR Art 2(7) does not appear entirely correct, as this refers to Directive 2010/84, not Directive 2001/83 as amended as all other references to the DIR. For 2001/83 reference to Transitional provision number 7 would need to be made; alternatively the reference might read DIR 2010/84 Art 2(7).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposal: "Until the Agency can ensure the functionalities agreed for the repository, marketing authorisation holders under the obligation to submit PSURs shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorized [DIR 2010/84 Art 2(7)]. This requirement to submit PSURs holds irrespective of whether the medicinal product is authorised in one Member State only or more than one Member State and irrespective of whether the active substance or combination of active substances is on the EU reference date list ~~shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised [DIR Art 2(7)]~~.
1782-1784		Comment: Within 60 days from the start of the procedure the preliminary assessment report created by the Rapporteur will be circulated to the Agency and the members of the PRAC. The Agency will send the report to the concerned marketing authorisation holder(s). Since the deadline for the marketing authorisation holder to submit comments on the Rapporteur's preliminary assessment report is by Day 90, the marketing authorisation holder should receive the Rapporteur's preliminary assessment report as soon as possible. Proposed change (if any): Include in line 1784 a statement on the timeline/deadline by which the Agency shall send the Rapporteur's preliminary assessment report to the concerned marketing authorisation holder(s).

Please add more rows if needed.

<Date of submission>

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Question: The DLP for my PSUR is < 2 / 21 July 2012, the submission date is > 2 / 21 July 2012. Do I have to submit a PSUR if my product is not on the EURD list? Which format should I use for my PSUR if the DLP is in the above mentioned period, volume 9A or GVP module VII?

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 222 - 225		Comment: it is not really clear what the starting point for the cumulative data is. It should not be necessary to include the definition of IBD or DIBD here. Also, this should take into account that not all MAH who need to write PSURs have a comprehensive database (e.g. MAHs for Generics). Proposed change (if any): Conducting an integrated benefit-risk analysis for authorised indications based on the cumulative information available i.e. since the international birth date (IBD), or the date of the first marketing authorisation for the MAH in any country in the world or the development international birth date (DIBD) or the date of first authorisation for the conduct of an interventional clinical trial sponsored by the MAH in any country.
Line 356		Comment: It would be useful if it could be specified who is expected to sign – the QPPV or designee? Can there be more than one signature? Proposed change (if any):
Line 522 – 524		This paragraph states that the seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to the ICSR. The does not take into account that ICSRs may contain serious and non-serious events/reactions. If non-serious reactions are categorised as serious because they are part of an event episode that included a serious event, incorrect conclusions might result from the presentation of data in summary tables in this way. Proposed change (if any):
Line 625 – 629		This paragraph states that any MAH sponsored non-interventional study with the aim of measuring the effectiveness of risk management measures which was completed or ongoing during the reporting interval (i.e.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		post-authorisation safety studies). For the scenario where one of the risk management measures is controlled distribution, there may be studies which do not involve patients or the drug use, but look at compliance with operational measures (for example what happens at the pharmacy level). It would be very helpful if it could be specified whether this type of study should or should not be included in the relevant appendices.
Line 823		What is the difference between 'efficacy' and 'effectiveness' in this context? Could definitions be included in Annex 1?
Line 829 - 830		It is not clear what is meant with 'the summary should be succinct, essentially the content of the CCDS'. As the CCDS should be appended, could the MAH in this scenario refer to the CCDS?
Line 1032-1033		Comment: it is stated here that "PSURs shall also be submitted at any time immediately upon request by the national competent authority(ies) or the Agency." It is mentioned in Section VII.A that the timeline for the submission of ad hoc PSURs requested by competent authorities will be normally specified in the request, otherwise the ad hoc PSURs should be submitted within 90 days of the data lock point. It would be helpful to repeat this here, instead of only stating "immediately".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Zeincro Hellas S.A.

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We generally agree with the provisions described in this Module

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 267		Comment: Plural form instead of singular used. Proposed change (if any): "A PSUR~~s~~ shall contain"
Line 308		Comment: Full stop is missing at the end of the sentence. Proposed change (if any): "be stated."
Lines 309-351		Comment: Bullet points are not summarised under a title. Proposed change (if any): the text "PSUR structure:" shall be included after the line 308 and before line 309 as to refer to all bullets following in lines 309-351.
Line 657		Comment: The term "near misses" is used but the meaning of the term is not explained in the document, nor explained in the Annex I – Definitions. Please clarify the meaning of the term "near misses". Proposed change (if any):
Line 968-969		Comment: Proposed change (if any): "There ~~will~~ should be documented procedures"
Lines 1003-1006		Comment: Provisions in lines 1003-1006 are confusing for marketing authorisation holders, since there is a reference to the "person responsible for the pharmacovigilance system" and to the "assessment" of PSURs.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The QPPV is the person referred to in line 1003 for marketing authorisation holders whereas assessment of the PSUR is made by competent authorities and the Agency. In case provisions are laid down in this way as to be addressed to marketing authorisation holders as well as to the competent authorities and the Agency, we consider a clarification to be introduced. Proposed change (if any): "For all organisations (as applicable) it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSURs are adequately qualified, experienced and trained according to the applicable guidelines."
Lines 1158-1161		Comment: Provisions in lines 1158-1161 are misleading since no reference to VII.B.2. is relevant to the specific provisions and no other section of the document refers to an agreement with the competent authority(ies) for the submission of PSURs for fixed combination products. However, provisions in VII.B.3. as well as in VII.B.5.12. refer to products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority. We consider there is no need for an agreement between the marketing authorisation holder and the competent authority(ies) for submitting PSURs for fixed dose combination products. Proposed change (if any): Lines 1158-1161 should be omitted.
Line 1538		Comment: The Table VII.1. under PSUR section – Section 2, refers to an "EU Regional Appendix". Furthermore the "EU Regional Appendix" is not listed in VII.B.20. A clarification is needed whether the "EU Regional Appendix" is the same as the "Regional appendix" referred in VII.B.20. Proposed change (if any):
Lines 1550-1551		Comment: "EU marketing authorisation status" in lines 1550-1551 is referred as "EU marketing approval

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		status" in Table VII.1. under PSUR section – Section 2. We propose the term "EU marketing approval status" to be used according to "Worldwide marketing approval status" in line 313. Proposed change (if any): "VII.C.5.2. PSUR EU regional appendix, sub-section "EU marketing approval ~~authorisation~~ status"