15 April 2013
EMA/239763/2013
Patient Health Protection

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

GVP Module X –Additional Monitoring

The draft of this module was released for public consultation between 27 June and 24 August 2012. The module has been revised, taking the comments received into account.

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

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

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

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17 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
AESGP

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It is not completely clear under which circumstances can the period of additional monitoring be less than 5 years, e.g. if the conditions are fulfilled. This should be possible and explicated in the GVP Module.
	We have a concern on the readability of information, i.e.: SPC and RMP published on national web-portals if published in national languages only: this information should be posted in national language AND in English.
	We understand that the black symbol may apply to centrally authorised medicines, medicines approved through MRP or DCP and medicines subject to EMA referrals. We are hence wondering how the coexistence of this black symbol with similar national monitoring scheme (e.g. black triangle in the UK) for purely national medicines will take place in order to minimise confusion for patients/consumers. It should be ensured that the meaning of the black triangle existing at national level is the same as the one proposed to be used EU-wide. According to Article 23, NCEs, new biologicals, medicines authorised under conditional approval, medicines subject to PASS or PAES as post-marketing requirements or RMS should bear this black symbol. From an MHRA perspective, the black symbol is used primarily to flag medicines containing new active substances. However medicines containing previously authorised APIs may also be monitored and assigned a black triangle status if it meets one or more of the following criteria: - new combination of active substances; - administration of the drug via a new route of administration or drug delivery system - a significant new indication which may alter the established benefit-risk profile of that drug - an established medicine which is to used in a new patient population. MHRA had the policy that any product with a black triangle could not be switched by definition of the product being “new” and therefore the safety profile not sufficiently established (the black triangle being applied to all NCEs for the first 3 years). Although we would expect situations of having a black symbol on non-prescription medicines extremely rare – basically in case a risk management system is requested to be put in place on an existing medicine – as such the

Stakeholder number *(To be completed by the Agency)*	General comment
	symbol should not be understood as a barrier to changing the legal status from prescription to non-prescription (for prescription medicines) or a systematic trigger to back-switch (for non-prescription medicines).

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
155-158		Comment: It should be made clear that this statement only applies to CAP medicines, not those approved at national level. Proposed changes: The scope of Article 23(2) of Regulation (EC) No 726/2004 does not only include centrally authorised medicinal products which are authorised or for which conditions are established after entry into force of the new pharmacovigilance legislation but also centrally authorised medicinal products which were authorised or made subject to conditions before such date, provided they fall within one or more of the above described situations.	
185		Comment: The title of this section includes "...or deletion from the list." However there is no reference to deletion in the text for that section. Proposed change (if any): Consistency between title of section and content of text	
275-276; 365-366		Comment: Our preference would be not to submit a new stand-alone variation but to be able to group it with the next one. Alternatively a type IA notification with no registration fee would also be fine.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: “shall submit the relevant variation to include/remove the black symbol, the statement, and the standardised explanatory sentence from the SmPC and PL, where applicable. The variation shall be free of charge if it cannot be grouped with another variation.”	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<24th August 2012>

Submission of comments on Guideline on good pharmacovigilance practices: Module X – Additional monitoring EMA/169546/2012

Comments from:

Name of organisation or individual
British Association of Quality Assurance

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 Agency and the Member States will set up, maintain and make public a list of medicinal products that are subject to additional monitoring. These medicinal products will be identified by the statement "*This medicinal product is subject to additional monitoring*" preceded by a standard black symbol and followed by an explanatory statement in their summary of product characteristics (SmPC) and package leaflets (PL). The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and to increase awareness about the safe and effective use of the medicinal products. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected adverse reactions while supervising or receiving treatment with a medicinal product subject to additional monitoring. After a medicine is placed on the market, its use in the wider population requires continuous monitoring. Additional monitoring status can be assigned to a medicinal product at the time of granting MA or at any time of the product life cycle. The additional monitoring status is particularly important when granting MA for medicinal products containing a new active substance and for all biological medicinal products. NCAs may also require additional monitoring status for a medicinal product which is subject to specific obligations. Mandatory inclusion applies to: • Medicinal products authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU • Any biological medicinal product not covered by the previous category and authorised after 1 January 2011 Optional inclusion may also be requested by the EC, NCAs, or following consultation with the PRAC in situations including but not limited to: • conditions or restrictions with regard to the safe and effective use of the medicinal product

Stakeholder number *(To be completed by the Agency)*	General comment
	• to conduct PASS or PAES • conditional approval • MA under exceptional circumstances • When a NCA imposes an obligation on a MAH to operate a risk management system for a medicinal product approved before 2 July 2012 The decision should also consider the usefulness of the additional monitoring status in relation to other additional PV activities proposed in the RMP e.g. in relation to the objectives of PASS. Due consideration should be given to include any generics of the reference medicinal product in the list The MAH must ensure that the PV system functions properly and effectively, that the roles, responsibilities and required tasks are conducted in a timely manner and are clear to all parties involved with regards to additional monitoring. The initial period of time for inclusion is 5 years, but the EC or NCA may extend that period following the recommendations of the PRAC. Consideration of removal from the list at the five year time point will normally be linked with the renewal procedure. In case a medicinal product is added to the list for an initial defined period of time following a recommendation from the PRAC, consideration of removal of the medicinal product from the list will depend on the fulfilment of the conditions placed on the marketing authorisation and on the knowledge of the safety profile gathered by that time. If there is no recommendation to extend the time period of additional monitoring of the reference medicinal product, removal from the list should apply to all generic medicinal products, unless different conditions and milestones have been agreed. This list will include the names and active substances of all medicinal products approved in the EU subject to additional monitoring irrespective of the approval procedure. Each Member State shall make publicly available on their national web-portal the list of medicinal product authorised in their territory that are subject to additional monitoring. Once the medicinal product is included or removed from the list, the marketing authorisation holder must update the SmPC and the package leaflet. The frequency for reviewing the statistical outputs from EudraVigilance for competent authorities should

Stakeholder number *(To be completed by the Agency)*	General comment
	be every 2 weeks for the duration of the additional monitoring. With regards to existing legislation, this guidance represents an extension of the approach used in the UK with the Black Triangle scheme. Some differences being the scope of application (Community vs. UK) and duration of the inclusion in this scheme (5 vs. 2 years). Exactly how many additional reports this scheme generates remains unknown.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<24/8/2012>

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
Boehringer Ingelheim GmbH

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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')*
Line 42- 45 Line 76 - 77		Comment: However, not all risks can be identified at the time when an initial authorisation is sought and **~~many of the~~** risks associated with the use of a medicinal product can only be discovered or fully characterised post-authorisation. Proposed change (if any): It is questioned whether many of the risks are seen post-authorisation. Therefore a more neutral formulation would be preferred e.g. **additional risks** Similarly we would replace the word harm with risks in line 77. All medicines are authorised on the basis that the benefit of treatment is judged to outweigh the potential **risks ~~harm~~**
Line 170 - 173		Comment: Is it, and how is it, planned to co-ordinate the exchange of information or risks between the countries and possibly between different reference medicinal products? Proposed change (if any):
Line 258- 264		Comment: To be consistent with the information in section X.C.4.3 the following information needs to be included Proposed change (if any): • recommends upon request of the European Commission or a national competent authority, the time period that a particular nationally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 is to remain in the 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')*
Line 266 -269		Comment: We are in agreement with the use of the proposed black symbol. Nevertheless, we would like to emphasize that only one common symbol should be defined, i.e. the symbol should not be country- or language- specific. Furthermore shaded or two-dimensional symbols should be avoided. The use of a simple, one-dimensional symbol will enhance readability and printability. In case the size of the symbol is pre-specified, it should be considered that not only it must be easily legible, but also that space limitations may apply to multilingual package leaflets. Proposed change (if any):
Line 275/276		It is unclear if a variation that should be submitted when introducing and/or deleting the black symbol would be classified as a type I or type II variation and if this variation should be submitted a separate variation or can it be included in the next upcoming variation? It should be specified within which timeframe such revised SmPC and PIL should be availabe.

Please add more rows if needed.

17. August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional Monitoring' (EMA/169546/2012)

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
	No comments.

2. Specific comments on text

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24. August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
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')*
252-254, 283-284, 370-371		Comment: In the draft guideline it is suggested that National competent authorities "shall make publicly available in their national web-portal the list of medicinal products authorised in their territory that are subject to additional monitoring." According to art.23 (1) of Regulation (EC) No 726/2004 the Agency shall, in collaboration with Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring. In art. 106 (d) of Directive 2001/83/EC it is given that each Member State shall by means of their national webportal make public available the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004. The text currently included in the GVP module suggests the generation and maintenance of individual national lists of medicinal products authorised in the territory. This is beyond the mandate of the legislation only referring to the list. Proposed change (if any): The text in the guideline should be changed so that national competent authorities "shall make publicly available by means of their national webportal the list of medicinal products subject to additional monitoring published on the European web-portal"
		Comment: 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')*
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
[redacted], Dr Reddy's Laboratories UK

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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')*
80		Comment: Proposed change (if any): delete extraneous full stop
101		Comment: Proposed change (if any): ...alarm and without discouraging appropriate prescribing and use of the medicinal product.
147		Comment: every MAH should have an adequate pharmacovigilance system. This suggests infers that almost every medicinal product will be subject to additional monitoring Proposed change (if any): delete
241-246		Comment: these two sections suggest that the same active may be subject to additional monitoring in some, but not all countries Proposed change (if any): strengthen the role of the PRAC in determining what actives are listed to ensure consistency across Europe
268		Comment: "This medicinal product is subject to additional monitoring" is probably meaningless to most patients and is potentially alarmist. It may discourage use of the product, putting the patient at risk. Has this phrase been tested with patients?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): rephrase to be more meaningful and test with patients before finalising
269		Comment: what is the standardised explanatory sentence? Proposed change (if any):
345		Comment: what is the European pharmacovigilance issues tracking tool? Proposed change (if any):
363-366		Comment: what is the timeline for submission of the required variation by the MAH, its approval by the competent authorities, and its implementation in labeling? Proposed change (if any):
377		Comment: “enhances” is an unsubstantiated claim Proposed change (if any):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

EFPIA

[redacted] EFPIA

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We fully support the intent that publication of the list of products subject to additional monitoring should not create undue alarm. This is particularly important given the diversity of the safety profiles of products that will be included in the list, and the fact that products may be included, removed and re-included in the list. The "appropriate communication" proposed on line 104 will have to be carefully worded to explain the purpose of the list and the reasons for which products have been included. We welcome the confirmation that the decision to include products in the list based on the optional scope should take into account a number of factors, and not simply the fact that the product is subject to one of the conditions that is within scope. To ensure that this principle is applied in a consistent manner, it would be helpful to further develop some guidance, in consultation with interested parties, on the factors to be taken into consideration. If it is decided that a product will be added to the list under the optional scope then a full explanation of the reasons for including it should be provided to the MAH. From a public health perspective, further consideration should be given to the inclusion of preventative medicines on the list, considering the negative public perception that this may invoke, potentially leading to a reduction in adherence to immunisation programmes. The procedural aspects for consultation of the PRAC in case of optional scope products is unclear, specifically the timeframes needed for consulting with the PRAC. Based on experience, conditions for the MA are decided at a late stage during the approval procedures and we are very concerned that significant delays will occur while the additional consultation step with the PRAC will be implemented. A fast and swift consultation process with the PRAC - even outside its scheduled Committee meetings cycle - may be necessary to avoid those delays. We fully support simple removal of the black symbol and additional monitoring statements from the product information. The amendments to the PI should be made during any ongoing procedure. If the removal occurs outside an open procedure we propose that the MAH could opt for removal of the statements as part of any upcoming variation for that product as a grouping. From the first publication of the additional monitoring list, an appropriate transition period for implementation of the required changes should be defined. Implementing the changes in the SmPC and the package leaflet (i.e. variation application and update of SmPC and package leaflet) within a very short timeframe following the

Stakeholder number *(To be completed by the Agency)*	General comment
	publication of the list could be impractical for many MAHs.. The GVP Module X has been developed based on the Article 23 of Regulation 726/2004 adopted in December 2010. However a revision of Article 23 is now under the ordinary legislative procedure for a possible adoption in September 2012. We would welcome confirmation that this revision will be taken into account with the initial adoption of the list. In addition, we would like to get confirmation that the existing lists for products under additional monitoring (e.g., ANSM list "Médicaments sous surveillance renforcée", MHRA list of current drugs under intensive surveillance (Black Triangle List)) will no longer exist when the new additional monitoring will be created. It is unclear if and when the MAH will be informed about the date of publication on Agency and National Competent Authorities web portal. There is a need to ensure that either the Agency or the National Competent Authority communicate to the MAH that the product will be on the list and in that case, the planned date of publication. Use the term "benefit-risk" instead of "risk-benefit" throughout the 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')*
Lines 100-106		Comment: We fully support the intent that publication of the list of products subject to additional monitoring should not create undue alarm. This is particularly important given the diversity of the safety profiles of products that will be included in the list, and the fact that products may be included, removed and re-included in the list. The "appropriate communication" proposed on line 104 will have to be carefully worded to explain the purpose of the list and the reasons for which products have been included.
Lines 110- 111		Comment: Amend the wording " that the roles , responsibilities and required tasks are conducted in a timely manner and are clear to all parties involved" Proposed Change (if any): .."that the roles and responsibilities are clear to all parties involved and required tasks are conducted in a timely manner"
Line 120 - 126		A statement is needed to clarify that changes to the active substances of seasonal influenza vaccines in the context of annual strain variations are out of the scope of the medicinal products for which additional monitoring is requested according to Article 23.1(a) of Regulation (EC) No 726/2004. The composition of seasonal influenza vaccines with respect to their active substances is changed/adjusted on a yearly basis in accordance with the WHO and EU recommendations, in order to match the strains of influenza virus expected to circulate during the following season. We consider that there is no need from a Public Health point of view to assign an additional monitoring status considering that long and outstanding experience has demonstrated that the safety profile of these vaccines is not altered by yearly strain changes/adjustments. Proposed change (if any): Clarify that influenza seasonal vaccines are excluded from the mandatory scope provided for under Article 23 1 (a) of Regulation (EC) No 726/2004. Add in section X.C.1.1: *"Exemptions from the mandatory scope (Article 23.1(a) of Regulation (EC) No 726/2004): seasonal influenza vaccines for which a variation is introduced to adapt to a new strain in accordance with official recommendations (annual variation), but for which the safety profile remains unchanged"*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 147		Comment: This may be a typo "the existence of an adequate pharmacovigilance system..." Proposed Change (if any): "the existence of an inadequate pharmacovigilance system..."
Lines 163-169		Comment: We welcome the confirmation that the decision to include products in the list based on the optional scope should take into account a number of factors, and not simply the fact that the product is subject to one of the conditions that is within scope. To ensure that this principle is applied in a consistent manner, it would be helpful to further develop some guidance, in consultation with interested parties, on the factors to be taken into consideration.
Lines 163-169		Comment: We welcome the confirmation that the decision to include products in the list based on the optional scope should take into account a number of factors, and not simply the fact that the product is subject to one of the conditions that is within scope. To ensure that this principle is applied in a consistent manner, it would be helpful to further develop some guidance, in consultation with interested parties, on the factors to be taken into consideration.
Lines 170-173		Comment: Unless a reference product is subject to a safety-related condition that is specific to that reference product (e.g. relating to an excipient that is not present in a generic), generics of that reference product should be subject to the same conditions and should, therefore, also be included in the list. The exclusion of generics from the list may lead to a perception that they are in some way safer than the reference product. The similar logic is applied for **removal** of generics from the list as outlined in Section X.C.3.2, lines 214-216. Proposed change (if any): Suggest adding the following to the end of this paragraph: "Generally, generics will also be included in the list unless the conditions for which the reference product is included are based on properties or characteristics specific to that product (e.g. related to an excipient that is not present in a generic).
Lines 181-184		Comment: The current text explains that the initial period of time for inclusion in the list is decided "taking account of the time considered necessary to fulfil the conditions" (emphasis added). This suggests that a longer period than is foreseen for fulfilment of the condition(s) may be applied. The Module should clearly state that the initial period of time for inclusion in the 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')*
		should be no longer than the period required for fulfilment of the condition(s). This period may be extended at a later date, if more time is necessary for fulfilment of the condition(s). Proposed change (if any): "...PRAC. This initial period will be no longer than ~~, taking account of~~ the time considered necessary to fulfil the conditions and obligations, as specified in ~~placed on~~ the marketing authorisation."
Line 190		Comment: Please correct the reference to Directive 2001/83/EC to be consistent with the reference to regulation (references to articles on renewal + risk management plan). Proposed change: "…that the conditions referred to in Articles 14a and 21(2) of Regulation (EC) 726/2004 or referred to in Articles 22c and 104a of Directive 2001/83/EC have been fulfilled.
Lines 198-204		Comment: The Module indicates that products in the mandatory scope may be maintained in the list for longer than 5 years "if justified in terms of increasing awareness about the safe and effective use of a medicinal product and/or providing any additional information for the evaluation of the product". Article 23(4) of the Regulation clearly states that the period of inclusion may be extended until such time as it is concluded that the relevant conditions have been fulfilled. Those conditions are the same as those that determine the optional scope for inclusion in the list. Products included in the list because they fell under the mandatory scope should, therefore, only be retained in the list for longer than 5 years if they meet one of the criteria for optional inclusion after 5 years. See also the comment on lines 210-213. Proposed change (if any): "During the renewal, the European Commission or the national competent authority, as appropriate, should indicate if the medicinal product should be maintained in the list if justified on the basis that one of the criteria for optional inclusion applies beyond that point in time (i.e. the MA is subject to one of the conditions for the optional scope that has yet to be fulfilled). ~~in terms of increasing awareness about the safe and effective use of a medicinal product and/or providing any additional information for the evaluation of the product. The criteria for extending the period of inclusion should take into account the frequency of submission of PSURs and the need for an additional renewal.~~ In order to determine the length of the extension, the period of time needed for completion of milestones for the relevant conditions included in the RMP should be taken into

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		account."
Lines 210-213		Comment: Similar to the comment above, the Module should be clear that the period of inclusion in the list will only be extended in cases where additional time is necessary to fulfil the condition(s) that led to the product's inclusion. Proposed change (if any): "As part of the evaluation of the data submitted by the marketing authorisation holder (i.e. renewal procedure, PSURs, study reports, RMP updates) the European Commission or the national competent authority, as appropriate, following a recommendation of the PRAC, may propose to extend that period of additional monitoring for the time considered necessary to fulfil the relevant condition(s)."
Lines 271-272		Comment: The wording "all efforts" are too difficult to define and it can always be disputed what to include in this ominous expression. Proposed change: "…should make all efforts to encourage reporting…" to "…should ~~make all efforts to~~ encourage reporting…"
Lines 273-274		Comment: The RMP should be the primary document through which any safety commitments shall be updated and communicated. This should be made clearer in the text. Proposed change: To add "…Commission **through the RMP**";
Line 275 and 365		Comment: Please clarify that any such variation should always be 1A $(_{IN})$ and that this could be grouped with other variations as appropriate. Proposed change: "…the relevant variation…" to "…a type 1A (IN) variation with possibility to group with other variations…"
Line 285 -343		Comment: With regard to process, further details of the precise timelines should be provided for each step in the 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')*
Line 334-338		Comment: There should also be a provision for informing the MAH that the product is to be removed so that action can be taken at the earliest opportunity to remove the black symbol and other relevant information from the product labelling and related materials.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'GVP Module X – Additional monitoring' (EMA/169546/2012)

Comments from:

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The EGA welcomes this opportunity to comment on the GVP proposal regarding additional monitoring incorporating new elements coming from the new pharmacovigilance legislation. Although we fully understand and support the intention of proposed module, the EGA members have a few comments.
	A lot of provisions are described under which circumstances additional monitoring is necessary. There are concerns that a huge number of products will fall under the optional provisions. The guideline does not reflect the implementation time. If a whole group of products with hundreds of leaflets has to be changed this brings an enormous workload for companies. The EGA is concerned that the implementation of additional text and symbols will lead to massive recalls of batches to fulfil the requirements which are under the scope of supervision and inspection.
	The guideline is currently under review and soon final without mentioning when the black symbol will be available. Again concerns exist about the implementation time, huge costs to discard old package material and resources to change the bigger parts of the generic portfolio.
	The authorities expect better transparency to the public including patients with more and better spontaneous reports. Usually sentences like "product is subject to additional monitoring" do not support the compliance of patients to trust the medicinal product. General concerns are that the products with a black symbol are avoided from prescription or even not taken by the

Stakeholder number *(To be completed by the Agency)*	General comment
	patients and thus decrease compliance. All stakeholders including the authorities should therefore also collect all refusals and denials to use the products by HCP and patients to evaluate the effectiveness of these measures, especially when more reports are expected.
	Even though the timelines to implement the additional monitoring in the SmPc and PI are detailed in the QRD template, it should be mentioned in this GVP module where the MAH may find that information, such as: for details in the timelines to implement the black symbol and update the SmPC and PI.

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 62-64		Comment: The sentence "The concept of….. specific medicines." is not clear and raises questions on the real need for additional monitoring. Proposed change (if any):
Line 80		Comment: There is a duplicate dot at the end of the sentence. Proposed change (if any): Delete the repeated dot (.): "population and/or after long term use.. In addition …"
Line 120 – 126		Comment: Pursuant to Section X.C.1.1., as currently written, biosimilars of reference biological products approved before 1 January 2011 will be mandatorily included in the additional monitoring list and carry the black symbol, while their reference biological products will not. As the Agency stated in *EMA Procedural advice for users of the centralized procedure for similar biological medicinal products applications*, '[t]he active substance of a similar biological medicinal product is a **known** biological active substance…' and [a] similar biological medicinal product and its reference medicinal product **are expected to have the same safety and efficacy profile** and are generally used to treat the same conditions' (emphasis added). Unless there are safety related reasons that are specific to the molecule, there is no science-based reason to subject a biosimilar product to additional monitoring if its reference product is not subjected to the same monitoring program. By subjecting biosimilars to additional monitoring and to carrying the black symbol in their label without any special safety reasons while not requiring the same of their reference product, EMA will put an undue and unfair burden on the biosimilars that is not based on science because biosimilar products are explicitly approved as equally safe and effective as their reference 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')*
		As stated in **Section X.B.2. Communication and transparency**, additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions **but without creating undue alarm** (emphasis added). Imposition of additional monitoring that is not based on science or specific safety concerns but is instead directed at a class of new drugs will create precisely the undue alarm that EMA is trying to avoid. **Section X.C.1.2. Optional Scope** covers products which do not fall into the Mandatory Scope but which should be included on the additional monitoring list as a result of a special safety concern. This section addresses special scientific needs and provides a sufficient regulatory vehicle for EMA to include in the additional monitoring list, on a case by case basis, those biosimilars which do not fall into the Mandatory Scope, but which in EMA's estimation should nevertheless be included in the list due to a special safety concern. Proposed change (if any): **X.C.1.1. Mandatory Scope** According to Article 23(1) of Regulation (EC) No 726/2004, it is mandatory to include the following two categories of medicinal products in the list: 1. medicinal products, including biological medicinal products, authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU; 2. any similar biological medicinal product, if its reference biological product is already included in the list of products for which there is additional monitoring ~~not covered by the previous category and authorised after 1 January 2011~~
Line 178		Comment: What is the rational to select the date "1 January 2011"? Shouldn't it be used the date when the new legislation became in force (Jul 12)?
Lines 273-274		Comment: The MAH shall provide evidence on the status… It is unclear what evidence should be provided and to whom.

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

Please add more rows if needed.

22 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional Monitoring' (EMA/169546/2012)

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
	No comments.

2. Specific comments on text

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases (Eurordis) [redacted]

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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')*
120-125		Comment: not only active substances, but maybe also new excipients as they might also expose patients to adverse reactions Proposed change: **X.C.1.1. Mandatory scope** 120 According to Article 23(1) of Regulation (EC) No 726/2004, it is mandatory to include the following two categories of medicinal products in the list: 1. medicinal products authorised in the EU that contain a new active substance or excipient which, on 1 January 2011, was not contained in any medicinal product authorised in the EU; 2. any biological medicinal product not covered by the previous category and authorised after 1 January 2011.
120-125		Comment: biological medicinal products are not defined in this module, neither in the module on definitions.
134-147		Comment: Clarification needed: it is optional when a marketing authorisation is granted subject to the existence of an adequate pharmacovigilance system [DIR Art 21a (e)]. Isn't it the case for all marketing authorisations? Are there cases where a marketing authorisation is granted in the absence of an adequate pharmacovigilance system?
181-184		Comment: if the initial period can be decided by the national competent authority, is there a risk that different national competent authorities decide on different periods? This could be confusing and detrimental in the communication to the public. 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')*
		X.C.2.2. Optional scope The initial period of time for inclusion in the list of medicinal products authorised subject to conditions can be decided by the European Commission or the national competent authority, as appropriate, following recommendation from the PRAC, taking account of the time considered necessary to fulfil the conditions and obligations placed on the marketing authorisation. When the decision is made by the national competent authority and the period differs from one Member State to the other, the PRAC will ultimately decide on the duration.
282-284		Comment: the Member States should also encourage patients and health care professionals to report Proposed change: In addition, as defined in Article 106 of Directive 2001/83/EC, each Member State shall make publicly available on their national web-portal the list of medicinal product authorised in their territory that are subject to additional monitoring, and take all appropriate measures to encourage patients and health care professionals to report any suspected adverse drug reactions.
Not in the text		Comment: magistral formulas also called extemporaneous mixtures are not in the scope of this proposal, although many chronic patients are treated with such preparations and some may require additional monitoring in terms of their quality, safety or efficacy.

Please add more rows if needed.

August 7, 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
[redacted] Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237MH 's-Hertogenbosch The Netherlands

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
	Line 74 It is important to keep in mind that additional monitoring should be something special, so that health care professionals and patients do report when they encounter ADRs due to these drugs. If the number of drugs being monitored is too large, it will make it less special and therefore not prompt reporting.
	Line 99-106 It is not clear who is responsible for the communication towards health professionals and patients regarding products that are under additional monitoring
	Line 127 Optional scope If a product is chosen for additional monitoring by the route: suggestion national competent authority, PRAC, EC, is it than mandatory for all countries to monitor this drug?
	Optional scope If a national competent authority suggests a drug for additional monitoring but the PRAC does not find it necessary to include the drug to the additional monitoring list. Is there than any possibility for the country to include the drug on a national additional monitoring list?
	Line 170 If it is deemed necessary to add a product to the additional monitoring list, all generic versions of this drug should also be monitored.
	Line 177-179 It would be advisable to say that 5 years the minimum time is for monitoring a drug. In some countries the marketing date isn't the same as the date of approval. Furthermore, the use of the drug can be delayed due to its reimbursement status. It also needs to be considered that some of the drugs also have a very limited use (orphan drugs for example) which

Stakeholder number *(To be completed by the Agency)*	General comment
	might warrant a longer monitoring period in order to collect data. In order to correct for this, it might be suggested not to have a fixed monitoring period for all drugs but also take drug exposure into account when deciding on the monitoring period. If the period is set to 5 years, long-term effects would be more difficult to identify.
	Line 267 It should be stated in which time frame the MAH shall include the information about additional monitoring in the SmPC and PL after it has been decided that a product is subject to additional monitoring.
	Line 333 In maintaining the list, will there also be a reason given why a drug (that falls under the category optional) is subject to additional monitoring and why a drug after the initial 5 year period will be removed form additional monitoring?
	What implications will additional monitoring have on the use of disproportionality measures in EV? If a product is subject to additional monitoring during its first 5 years of marketing one can assume that it will generate more reports than if the drug was not followed by additional monitoring. If the additional monitoring stops after 5 years, the reporting rate would probably go down. If statistical measures will be used for signal detection, it will be difficult to find signals after the additional monitoring stops since the number of reports in the first 5 years will hamper the usefulness of disproportionality measures in the periods thereafter.

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')*
239-256		Comment: It is not clear whether a national competent authority has to follow the recommendation from the PRAC in their decision to include a medical product on the list for additional monitoring. Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Section X.C.5. includes a lot of repetition as compared with the other parts of the GVP 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 43		Change: <…> all risks can be identified at the time when an initial authorisation is sought and ~~many of the~~ sometimes risks <…>
Line 62-64		Comment: This phrase is not very clear. Which proportionality is meant? What is meant by a `differentiated view of specific medicines`? Proposed change : Please clarify or delete this phrase.
Line 81		Change: <…> everyday medical practice where patients may have more than one disease or treatment is ~~frequently~~ often <…>
Line 83		Change: <…> wider population requires continuous monitoring. ~~As for all medicinal products~~therefore, marketing <…>
Line 83-90		Comment: The fact that patients and HCP are encouraged to report by adding text to all medicinal products is not correctly reflected here. Proposed change : Discuss the addition of the information to encourage the spontaneous reporting of ADRs and then the concept of additional monitoring of certain medicinal products.
Line 91-92		Change: Additional monitoring status can be assigned to a medicinal product ~~at the time of granting marketing authorisation or~~ at any time of the product life cycle.
Line 91-97		Comment: information about the period of time for inclusion on the list is missing for both the mandatory and the optional scope.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 100		Change: <…> such a way that it increases reporting of suspected adverse reactions ~~but~~ _without creating undue
Line 103-106		Comment: This is already taken care of by the black symbol, why phrase it like this here? In addition, encouraging HCP and patients to report all suspected adverse reactions is not different for products subject to additional monitoring, where a statement is included in the SmPC with the new legislation, than for all products. Therefore it does not seem to add valid information here. Proposed change : Please delete this phrase.
Line 134		Comment: Please highlight that meeting criteria below line 134 definitely does **not** imply in all cases additional monitoring should be assigned.
Line 147		Comment: According to the Directive a marketing authorisation can be granted under the condition that an adequate PV system is in place. It should not be a possibility, to make up for an inadequate PV system by the black symbol and additional monitoring, since if the system is inadequate, it can not be sure that the spontaneous reports really are processed in a good way. The scope of additional monitoring is meant to monitor and not meant to reflect an inadequate PV system. Proposed change (if any): Please clarify that the condition of an adequate PV system is usually not a reason for including a product to the list of additional monitoring.
Line 170-173		Comment: Monitoring and identifying the spontaneous reports might be valuable also for the generics, e.g. if during the lifetime additional monitoring is decided to be necessary. Additional monitoring status should apply to the active substance and not only the innovator product.
Line 181-184		Comment: It is not clear how long the medicinal products falling under the optional scope should remain on the list. Proposed change :Products under the optional scope should be removed from the list once 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')*
		condition has been fulfilled, or otherwise a default period could be considered.
Line 186-190		Comment: For the extension of the period it could be useful to add the default period of five years. Proposed change: Consider default extension of the period of time (e.g. 5 years).
Line 239-256		Comment: The wording about the final decision is not very clear. E.g. line 247 states that NCAs decide, based on a PRAC recommendation, This implies that a medicinal product could be on the list in one MS but not in the other MSs. Proposed change : it should clearly be stated who is responsible for final decision regarding the additional monitoring and clarify whether it it possible that the list differs between countries
Line 273-274		Comment: It is not clear to whom the MAH shall provide evidence on the status of any conditions imposed by the NCAs or the EU. Proposed change: Please clarify.
Line 275-276		Comment: It is not clear to whom and in what time period the MAH shall submit the relevant variation to include/remove the black symbol, the statement, and the standardised explanatory sentence from the SmPC and PL, where applicable. Proposed change: Please clarify.
Line 292-297		Comment: Article 57(2) requires the Agency to establish lists of all human medicines authorised in the EU. Thus, in principle the EMA should have all information available for the products. But what if the information in article 57 is not in line with the information in the different MSs? Or is each MS only responsible for the correct information for the product as available in that MS? Proposed change: Please clarify.
Line 319-320		Comment: It is not clear in case of MRP/DCP whether the CMDh is involved.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change : Please clarify.
Line 323-327		Comment: It is not clear in case of NAP who is responsible for the correct information being send to the EMA: RMS, pRMS or each NCA where the product is authorised. Proposed change : Please clarify.
Line 334-343		Comment: In order to include the product on the list – optional scope – will there be requirements or templates for submission to the PRAC? Will removal from this list for the mandatory scope not always be 5 years unless? Proposed change : Please clarify.
Line 339-341		Comment: In the case where the CHMP or NCA(s), as applicable, does not follow the PRAC recommendation <…>. It is not clear in what case, only in the case of extension? Proposed change: Please clarify.
Line 345-349		Comment: As commented before, where does this leave article 57? Proposed change (if any): Please clarify.
Line 359-366		Comment: It is not clear if a medicinal product – both mandatory and optional – will be included or removed from the list, what the timelines are to implement this in the SmPC and the PL. Proposed change (if any): Please clarify.
Line 368-373		Comment: The list EMA will make publicly available can differ from the list the NCA will make publicly available?
Line 373		Change: ~~to~~ the summary of the RMP are publicly available.
Line 375-378		Comment: It is not clear why this is relevant in this context, this does not concern the impact on the overall Pharmacovigilance activities?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Please clarify.
Line 378-383		Delete: ~~The main goal is to facilitate the ready identification of medicinal products that require collection of additional information in a timely manner. As for all medicinal products, marketing authorisation holders and competent authorities should continuously monitor any information that becomes available and assess the impact on the risk-benefit profile of the medicinal product. However, in the light of the direct relevance of spontaneous adverse reaction reporting to signal detection activities,~~ <…>

Please add more rows if needed.

<Date of submission>

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
Medicines and Healthcare Products Regulatory Agency (MHRA)

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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')*
Line 80		Comment: There are two full stops at the end of the sentence. Proposed change (if any):
Line 92		Comment: Proposed change (if any): Consider adding - In some rare cases, additional monitoring may also be useful when a new safety concern is identified for a product/active substance which has been on the market for some time. In which case an RMP may be requested.
Line 147		Comment: It may be useful to indicate that additional monitoring could be a rare requirement if the condition relates to the pharmacovigilance system (condition e), because there may be no specific safety concerns about products. Proposed change (if any):
Line 193		Comment: Proposed change (if any): Five year should read five-year
Line 275		Comment: Would it be useful to state the type of variation required to introduce the changes or provide a link to the appropriate variations classification guidance? Also, is there an expectation regarding how quickly an MAH should submit variations to include this information once 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')*
		have been notified that their product is subject to additional monitoring? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 July 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from:

Name of organisation or individual
Nilesh Sheth MRPharmS, Regulatory Consultant

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
	In common with the previous draft GVP modules, there is a general issue concerning the use of unnecessarily long sentences, poor grammar, sentence construction and punctuation in the document. All of these factors detract from the readability of the document. It would appear that the writer(s) do not have a thorough command of the English language to be able to convey the subject matter clearly and succinctly. More time and thought should be invested in delivering a well written document that engages the reader.

2. Specific comments on text

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

Please add more rows if needed.

<20 August 2012>

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

Comments from: Novartis AG

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Additional monitoring as described in GVP X is only about the means of ensuring better spontaneous reporting of ADRs. With exception of the two-weekly check of EV data by NCAs, no other means of ensuring the additional monitoring of medicinal products are described. While the effort for collecting more spontaneous reports in the early years of marketing of a new product is welcome, it would be interesting to also design/outline the means of measuring how effective this effort is, and the means of using the data thus collected for an enhanced monitoring of the safety of medicinal products.
	Some local Health Authorities already have schemes, such as the Black Triangle scheme in the United Kingdom. There is a need to understand how these will be affected, for example will they be retired once GVP Module X comes into force? If yes, then this should be stated and some timelines given.
	Novartis welcomes the role of the PRAC as gatekeeper to entry into the list. However, there still seem to be some way for local Health Authorities to use GVP X to impose inclusion into a local list without consultation of the PRAC. There is a need to understand if these 'locally monitored' products would then be included into the central list.
	Keeping newly authorised products on the additional monitoring list for five years can be too long for products for which the safety profile can be reliably and quickly established. There is a need for a process to review inclusion into the list before the 5-year point and for criteria to use to decide whether to shorten the period.
	Additional monitoring as described in GVP X concentrates on establishing and publishing list(s) of products, and how the product information will be affected. But other activities will also be needed to handle how this is presented to the public, patients and healthcare professionals. Clarification is needed on further communications: • Communications published alongside the list(s),

Stakeholder number *(To be completed by the Agency)*	General comment
	• What to communicate when a product comes back on the list, especially if the reason for coming back on the list is linked solely e.g. to the addition to the label of a new indication, • Communication in advertising and promotional materials.

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')*
104		Comment: The list should be published 'together with appropriate communication to encourage healthcare professionals and patients to report all suspect adverse drug reactions. It is key that no undue alarm is raised in patients whose medicine is placed on the list. The way the additional monitoring is described in communications should be consistent throughout the network, both for regulators and MAHs. Proposed change (if any): The appropriate communication needs to be defined to ensure a common understanding among all actors (regulators and MAHs), in terms of content and language(s).
121-122		Comment (1): Pursuant to Section X.C.1.1., as currently written, biosimilars of reference biological products approved before 1 January 2011 will be mandatorily included in the additional monitoring list and carry the black symbol, while their reference biological products will not. As the Agency stated in *EMA Procedural advice for users of the centralized procedure for similar biological medicinal products applications*, '[t]he active substance of a similar biological medicinal product is a **known** biological active substance…' and [a] similar biological medicinal product and its reference medicinal product **are expected to have the same safety and efficacy profile** and are generally used to treat the same conditions' (emphasis added). Unless there are safety related reasons that are specific to the molecule, there is no science-based reason to subject a biosimilar product to additional monitoring if its reference product is not subjected to the same monitoring program. By subjecting biosimilars to additional monitoring and to carrying the black symbol in their label without any special safety reasons while not requiring the same of their reference product, EMA will put an undue and unfair burden on the biosimilars that is not based on science because

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		biosimilar products are explicitly approved as equally safe and effective as their reference products. As stated in **Section X.B.2. Communication and transparency**, additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions **but without creating undue alarm** (emphasis added). Imposition of additional monitoring that is not based on science or specific safety concerns but is instead directed at a class of new drugs will create precisely the undue alarm that EMA is trying to avoid. **Section X.C.1.2. Optional Scope** covers products which do not fall into the Mandatory Scope but which should be included on the additional monitoring list as a result of a special safety concern. This section addresses special scientific needs and provides a sufficient regulatory vehicle for EMA to include in the additional monitoring list, on a case by case basis, those biosimilars which do not fall into the Mandatory Scope, but which in EMA's estimation should nevertheless be included in the list due to a special safety concern. Proposed change: 1. medicinal products**, including biological medicinal products,** authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU; 2. any **similar** biological medicinal product**, if its reference biological product is already included in the list of products for which there is additional monitoring** ~~not covered by the previous category and authorised after 1 January 2011~~ Comment (2): Clarify what is considered a new active substance, in particular in the case of - a seasonal influenza vaccine subject to a yearly strain change; a new strain should not be considered as a new active substance. - an active substance that could be marketed as a food supplement or a non-prescription medicinal product in some member states.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
124		Comment: To avoid any confusion that the PhV measures only apply to human medicines Proposed change (if any): 'not contained in any **human** medicinal product'
155-158		Comment: It is unclear how the retrospective application of the optional scope criteria will be handled, and how far back the PRAC may go when indentifying products for inclusion into the list. More guidance is needed.
170-173		Comment: If a medicinal product is included in the list, all generics of this reference medicinal product should also be included in the list regardless. If not there is a risk that a generic may be perceived as safer than the reference medicinal product.
178, 186 and 192-194		Comment (1): While line 178 describes the initial period to be included in the list as "five years after the Union reference date referred to in Article 107c(5) of Directive 2001/83/EC", this seems unsettled as on line 186, the text uses unclear terminology "Once a medicinal product is included in the list for a certain period of time the European Commission or the national competent authority, as appropriate, may extend that period following the recommendations of the PRAC ...". This text should be removed or some clarification added. Comment (2): There is no possibility to reduce this period especially for newly authorised products as the only criterion for removal from the list is a renewal. Setting a default 5-year period is not in the spirit of the additional monitoring, which should allow 'risk proportionate post-authorisation data collection'. There is a need for a process and criteria to allow for the rapporteur, RMS or MAH to petition the PRAC to remove the product from the list earlier than at the end of the 5-year period as appropriate, i.e. based on the data collected and an evaluation of

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the risk, or because the requirements imposed at the time of authorisation have been fulfilled. Proposed changes: "Once a medicinal product is included in the list the European Commission or the national competent authority, as appropriate, may extend **or reduce** that period following the recommendations of the PRAC" 'In the case where a medicinal product is automatically included in the list at the time of the granting of the marketing authorisation, **deletion from the list before the five year time point should be considered, upon recommendation from the PRAC based on [defined criteria]**. **If a product is still on the list at the end of the 5-year period,** removal from the list will be automatic at the time of the renewal.'
217-219		Comment (1): Re-entry of a product into the list is possible if 'new conditions are imposed'. This is vague and it is essential that the criteria for a product to re-enter the list are clearly defined as such an event will be very alarming for patients already taking the products. This is particularly significant if the re-entry is linked to e.g. a new indication that is not the reason for them taking it. The additional communication that will be needed (including standard text in the product information) should also be defined.. Comment (2): if a product re-enters the list, all generics using this product as reference medicinal product should also be re-listed.
220-276		Comment: None of the key stakeholders have any responsibility for monitoring if the recommendation of an increased spontaneous reporting by HCPs and patients in working. However, GVP Module IX chapter IX.C.2. clearly states that EMA and NCAs have the responsibility to monitor Eudravigilance outputs every two weeks for products subjects to additional monitoring.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Include the information on 2-weekly monitoring in under the paragraphs describing the responsibilities of the Agency and of NCAs.
231 241 and 252		Agency [231] "is responsible <u>for publishing the list of medicinal products that are subject to additional monitoring</u> on the European web-portal with an electronic link(s) to a webpage where the product information and the summary of the RMP are publicly available" National competent authority [241] "inform the Agency <u>on those particular nationally authorized medicinal products that are to be included in the list and provide the electronic links to the national webpage where the product information and the summary of the RMP</u> are publicly available" There will be parallel lists, one maintained centrally by the Agency, which is likely to be in English only, and local lists maintained by National Competent Authorities, likely to be in the local language. This duplication may lead to discrepancies and confusion. It is recommended that the local lists also include the products included in the central list. In addition, Product information and summary of RMP on NCA websites will probably be in local language. Is there a translation planned on Agency website or only a link to this information?
275-276, 365-366		Comment: As the list is established, adding the additional monitoring information to product information should not need a variation but it should be possible to group this with the next scheduled variation. Conversely, removing the statement should also be included in an upcoming variation. Alternatively, if there is no suitable variation planned, a variation could be filed that does not incur any charge. Proposed change (if any): 'shall submit the relevant variation [...] where applicable. **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')*
		variation will be free of charge if it cannot be grouped with another variation.'
344		Comment: The tool used for the maintenance of the list is EPITT, a system that is not shared with MAHs. It is unclear why a shared system such as the Art57 database is not used for the purpose.
380		Comment: There is no additional information being collected, this is simply about trying to increase reporting. The sentence needs reformulating. Proposed change (if any): 'the main goal is to facilitate the ready identification of medicinal products **for which** ~~that require~~ **spontaneous reports should be actively** collect**ed**~~ion of addtional information~~ in a timely manner.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'good pharmacovigilance practices module X – Additional monitoring' (EMA/169546/2012)

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 X – Additional monitoring.

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')*
80		Reference: population and/or after long term use.. Comment: Please delete the additional punctuation mark Proposed change (if any): population and/or after long term use.~~.~~
85		Reference: risk-benefit profile Comment: Please use the correct term benefit-risk profile Proposed change (if any): benefit-risk profile
Between 238/239 and 256/257		Reference: Roles and responsibilities of the Agency/NCA Comment: Please include an additional line with reference that the MAH has to be informed by the Agency/NCA if a MA under his responsibility is added to the 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')*
		Proposed change (if any):

Please add more rows if needed.