5 February 2014
EMA/72273/2014

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

## GVP - Risk minimisation measures - selection of tools and effectiveness indicators (EMA/204715/2012)

The draft of this module was released for public consultation between 7 June and 5 August 2013. The module has been revised, taking the comments received into account.

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

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

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

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An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| AESGP |

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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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | The guideline does not read well – there are a number of redundancies and many cross references to the different sections of the guideline (in particular between part B structure and process and part C operation of the EU regulatory network). Is part C even needed at all? | |
| | Risk minimisation measures should not apply to non-prescription medicines as this would be contrary to the mere action to switch.<br><br>The same would apply to well-established medicines. In the rare cases where risk minimisation measures may apply to well-established medicines, no specific guidance is given contrary to generic which are cited, for example in relation to the absence of routine PSURs. | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| XVI.A. Introduction | | Comments: The legal status of a medicine can only be changed (from prescription to non-prescription) if the risk of serious adverse reaction is extremely low and the safety profile sound and well-known. Hence the mere action of asking for risk minimisation measures for a medicine available without prescription would be a paradox. It should hence not normally occur.<br><br>Proposed change (if any): **Risk minimisation measures would not be expected for non-prescription medicines given that all existing and potential risks have been carefully assessed before the change of legal status could occur.** | |
| XVI.B.4 Effectiveness of risk minimisation measures | | Comment:<br>This seems to be a burden not only on the MAH but also on the healthcare systems. Healthcare professionals would be involved in several surveys and studies. As described in section XVI.C.1.3 "Healthcare professionals and patients hold no legal obligations with respect to the implementation of the pharmacovigilance legislation.". Moreover, they are no legal obligation with respect to the participation in a study or survey measuring the effectiveness of risk management measures. What happens if the administrative burden is too high and patients and/or HCP are not willing to be part of that kind of studies or surveys anymore? | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | In our opinion it is not possible to perform a survey or study for every single DHPC. DHPC should be excluded from evaluating the effectiveness of risk minimisation measures. Communication practices and communication tools for DHPC distribution are currently quite different in the EU member states. GVP Module XV should be updated accordingly.<br><br>Proposed change (if any): | |
| XVI.C.2 Impact of risk minimisation measures effectiveness on RMP/PSUR | | Comments: In principle no risk minimisation measures should be expected for well-established medicines given their well-known safety profile. In the rare event in which risk minimisation measures may apply to well-established medicines, no specific guidance is given contrary to generic which are cited, for example in relation to the absence of routine PSURs – see lines 604 to 612.<br><br>Proposed change (if any): **In general well-established medicines would not be expected to be subject to risk minimisation measures, or only in very rare instances**. In general, generic **and well-established** products are exempt from routine PSUR reporting. … | |
| XVI.C.2 Impact of risk minimisation measures effectiveness on RMP/PSUR | | There seems to be redundancies between RMP and PSUR in this section – why should both documents include a summary evaluation of the outcome of specific risk minimisation measures? We understand that the focus would be different and use of common module can be made but why is this allowed only in case of parallel submission (cf. lines 577-578) | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change (if any): the approach should be simplified to avoid duplication of the providing of the same or similar information. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05.08.2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

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

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

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 284 - 289 | | **Comment**:<br>Regarding "Direct health care professional communication" (DHPC) it would be highly appreciated if the preferred way of distribution would be electronically in order ensure a fast, effective and cost-effective delivery. Furthermore, this very important tool for "risk minimization" should only be used for genuinely important issues (e.g. withdrawal) to ensure the particular sensitive relevance of such letters. GVP Module XV should be updated accordingly. | |
| | | Comment:<br><br>Proposed change (if any): | |

Please add more rows if needed.

17/07/2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| C.B. Fleet Company |

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 390-392 | | Comment: It is difficult to understand the explanation, what should be the outcome indicator(s)?<br><br>Proposed change (if any): | |
| 147-148 | | Comment: Are “Additional minimisation activities” proposed *only* when they are laid down as a condition?<br>Does it mean that “Additional minimisation activities” can not be an initiative of the MHA?<br><br>Proposed change (if any): | |
| 156-158 | | Comment: The paragraph says: “if additional minimisation activities are requested (…)”. Who makes the request? The Authorities, the PRAC, the MAH?<br><br>Proposed change (if any): | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5th August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Celgene Europe Ltd |

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | Celgene would like to highlight our primary areas of concern, with text specific comments following in this document:<br><br>• Clarification of language throughout Module XVI to distinguish between 'routine' and 'additional' risk minimisation measures, and between 'risk' and 'safety concern', as appropriate and where referenced.<br>• Clarification that a controlled access programme as a risk minimisation measure, even if it is organized data collection, does not fall under the definition of a PSP (patient support programme) and spontaneous, instead of solicited, reporting should be followed.<br>• It would be beneficial to have a flexible approach to the method(s) used to measure effectiveness of risk minimisation measures, without a full PASS study being required for all situations. Not all assessments of risk minimisation measures are appropriate to be assessed via a PASS (i.e. process indicators, adherence to risk minimisation measures), which would then be subject to the PASS protocol template, and the reporting (including a full study report) requirements, etc. For example, use of a PASS may be a complex approach to monitor implementation of a DHPC letter or to answer a simple question. Flexibility to use other methods is proposed. Further, as routine risk minimisation measures are captured in the corresponding sections of GVP Module XVI, all non-interventional studies (i.e. drug utilisation studies) would qualify by default as a PASS as, for example, drug usage according to the SmPC is investigated which falls under routine risk minimisation measures (pack size, legal status, wording in the SmPC such as indication, precautions or warnings).<br>• Clarification on the presentation of risk minimisation measures in the RMP as relates to 'Guidance on format of the risk management plan (RMP) in the EU part V: Risk Minimisation Measures' (EMA/715019/2012) | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 113 | | **Comment:**<br>Paper based information is also the SmPC and the PL and the educational materials are targeting focused additional information.<br><br>**Proposed change (if any):**<br>Delete: paper-based information<br>Should read:<br>…gain prominence in the future in addition to the paper based **additional** educational materials | |
| 129 | | **Comment:**<br>The “risk minimisation plan” is not a part of the RMP it is a subpart in Module V and no longer on the Guidance on Format of the RMP Part V.<br><br>**Proposed change (if any):**<br>**The risk minimisation measures,** an integral part of the RMP, should therefore give appropriate consideration to the following parts: | |
| 139 - 140 | | **Comment:**<br>Implementation plan is newly introduced in this context and not part of Module V nor in Guidance on Format for Module V of the RMP. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **Proposed change (if any):**<br>**The section Proposed actions/components** should provide a detailed proposal…… | |
| 141 - 143 | | **Comment:**<br>Evaluation plan is newly introduced in this context and not part of Module V nor in Guidance on Format for Module V of the RMP.<br><br>**Proposed change (if any):**<br>**Planned dates for assessment:** This section should provide… | |
| 156-158 | | **Comment:**<br>Request is not defined in the module.<br><br>**Proposed change (if any):**<br>If additional risk minimisation activities are **suggested, the rationale should** be clearly documented, should be linked to a specific safety concern and sufficiently detailed in the RMP part risk minimisation measures. | |
| 159 | | **Comment:**<br>Distinguish between routine and additional risk minimisation measures. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **Proposed change (if any):**<br>*XVI.B. describes **additional** risk minimisation measures that should be considered in addition to the routine measures, including:* | |
| 170, 181-182,190,216<br>230<br>239<br>324 | | **Comment:**<br>Risk is sometimes used instead of safety concerns as the RMP represents only important risks and not all risks.<br><br>**Proposed change (if any):**<br>replace “risk” with “**safety concerns**” | |
| 172 | | **Comment:**<br>Important risk is selected here instead of safety concerns as this would not capture i.e. important missing information.<br><br>**Proposed change (if any):**<br>...and that applying this measure is considered important for minimising **safety concerns**/or for… | |
| 174 | | **Comment:**<br>Safety concerns is missing in the sentence.<br><br>**Proposed change (if any):**<br>.., can address more than one **safety** concern and ... | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| 175 | | **Comment:**<br>Materials are mentioned but not defined.<br><br>**Proposed change (if any):**<br>Ideally, **additional educational materials**... | |
| 198-199 | | **Comment:**<br><br>**Proposed change (if any):**<br>.., in order to minimise **selected important** risks | |
| 234-259 | | **Comment:**<br>Please clarify that a controlled access programme as a risk minimisation measure, even if organized data collection, does not fall under the definition of a PSP (patient support programme) and spontaneous reporting should be followed.<br><br>**Proposed change (if any):** | |
| 261-267 | | **Comment:**<br>Please clarify that a Pregnancy Prevention Programme with a controlled access programme as a risk minimisation measure, even if organized data collection, does not fall under the definition of a PSP (patient support programme) and spontaneous reporting should be followed.<br><br>**Proposed change (if any):** | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | | |
| 277 | | **Comment:**<br>Supply should only be limited to the population at risk i.e. woman of childbearing potential.<br><br>**Proposed change (if any):**<br>Prescription limited to a maximum of 30 days supply **for the population at risk.** | |
| 278 | | **Comment:**<br>Monitoring of the programme performance would qualify as an effectiveness study and therefore as a PASS.<br><br>**Proposed change (if any):**<br>Monitoring of the programme performance **i.e. pharmacy self audits, and compliance measuring to the programme i.e. pregnancy test results checks, do not qualify for an effectiveness measure and therefore PASS as these are only process indicators.** | |
| 281-283 | | **Comment:**<br>This section does not fall under a Pregnancy Prevention Programme as it is a pregnancy registry focusing on the outcome of an exposed pregnancy and would qualify as a PASS.<br><br>**Proposed change (if any):** | |

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|---|---|---|---|
| | | | |
| 290<br>304<br>307<br>429<br>559<br>568-569<br>576 | | **Comment:**<br>Routine and additional risk minimisation measures are mixed.<br><br>**Proposed change (if any):**<br>Insert "**additional"** before risk minimisation measures | |
| 316 | | **Comment:**<br><br>**Proposed change (if any):**<br>Outcome indicators **measurement would qualify for a PASS** | |
| 325-328 | | **Comment:**<br>It should be clarified that outcome indicator as an objective qualifies for a PASS.<br><br>**Proposed change (if any):** | |
| 340 | | **Comment:**<br>The concept of process and outcome indicators is not clearly defined and should be clearly defined or distinguished, as a process indicator is not measuring effectiveness; it is only a process or quality check. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **Proposed change (if any):**<br>The legislation defines “any study…measuring the effectiveness of risk **minimisation** measures” as a post-authorisation safety study. **Only studies measuring the effectiveness via outcome indicators of risk minimisation measures are considered to fall under this definition.** | |
| 414 | | **Comment:**<br>Replace the term “safety issue” with “safety concern” for consistency<br><br>**Proposed change (if any):**<br>… in response to a **safety concern** detected in the post-authorisation… | |
| 471 | | **Comment:**<br><br>**Proposed change (if any):**<br>…not imposed as a condition for marketing authorisation these **shall be** in the RMP | |
| 479 | | **Comment:**<br>The outcome is defined as outcome indicator in the RMP.<br><br>**Proposed change (if any):**<br>…of the outcome **indicator** of risk minimisation measures which comprise additional… | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | | |
| 484 | | **Comment:**<br>The outcome is defined as outcome indicator in the RMP.<br><br>**Proposed change (if any):**<br>..should evaluate the outcome **indicator** of **additional** risk minimisation measures,.. | |
| 488 | | **Comment:**<br><br>**Proposed change (if any):**<br>…the effectiveness of **additional** risk minimisation measures **focused on outcome indicators.** | |
| 552 | | **Comment:**<br><br>**Proposed change (if any):**<br>...shall monitor the outcome **indicator** of **additional** risk minimisation measures | |
| 609-612 | | **Comment:**<br>Please clarify if for a variation application only the proposed changes must be captured in the PSUR and an updated RMP must not be submitted and can be submitted with the next routine submission with the changes captured.<br>**Proposed change (if any):** | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Council for International Organisations of Medical Sciences (CIOMS) |

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | CIOMS highly welcomes the release of GVP Module XVI by the EMA and commends the Agency for introducing this important guidance in an area which is of primary importance to public health.<br><br>CIOMS is in parallel developing international guidance in the area of risk minimisation with medicinal product use in CIOMS Working Group IX 'Practical Approaches to Risk Minimisation for Medicinal Products' and the final output from this WG is expected at the end of 2013.<br><br>Membership of the WG has included both the EMA and EU National Competent Authorities in addition to other international regulatory authorities and pharmaceutical companies. Whilst CIOMS has an international scope it is our opinion that the CIOMS IX Guidance will be compatible with GVP Module XVI subject to finalisation of both these guidances. In addition, whilst GVP Module XVI concentrates on high level principles of risk minimisation, CIOMS IX takes an approach regarding practical application of related risk minimisation concepts in a 'Points to Consider' kind of approach. For this reason, CIOMS would like to suggest that the proposals and recommendations of CIOMS IX may in certain ways be complementary in approach to GVP Module XVI in the | The concept of interventions proportionate to the risk to be managed is already present throughout. Nonetheless, 'undue burden' is now specifically mentioned in "XVI.B.1. General principles" and "XVI.B.4. Effectiveness of risk minimisation measures"<br><br>Cross-reference to CIOMS guidance is beyond the purpose of the Good Vigilance Practices. |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | area of risk minimisation with the use of medicinal products.<br>***CIOMS therefore respectfully requests for the EMA to consider whether a specific reference to CIOMS IX, could be included in GVP Module XVI.***<br><br>Risk management plans which are part of pharmaceutical legislative requirements in the EU sometimes require additional activities on behalf of key stakeholders such as healthcare professionals, patients, their carers and the wider healthcare system. These activities may be burdensome when added to 'normal' practice and in certain circumstances such 'undue burden' may have inadvertent negative effects on patients and their access to safe and effective medicines. CIOMS IX considers this aspect to be important and proposes appropriate definitions for consideration in risk management planning and these will be provided for reference in the CIOMS IX book.<br>***CIOMS respectfully requests that the Agency specifically mention in GVP Module XVI 'undue burden' as an important area to be considered when planning and implementing additional risk minimisation measures and that CIOMS IX guidance may be consulted, regarding this aspect.***<br><br>CIOMS IX welcomes the emphasis on outcome measures | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | of assessing effectiveness of additional risk minimisation strategies but would like to put forward additional considerations for safety outcomes of interest (SOI). These SOI may include a range of outcome measures of a clinical nature including results of monitoring (e.g. laboratory testing) that can evaluate compliance with monitoring recommendations and aid early detection of risk thus facilitating its mitigation. For instance, monitoring white blood cell and neutrophil counts to detect early reduction is a relevant SOI that would allow intervention (such as dose reduction or drug discontinuation) rather than focussing the assessment of effectiveness on incidence of agranulocytosis, the latter being less feasible or appropriate to assess as an oucome in a study despite it being a 'harder' endpoint. In CIOMS's view the endpoints chosen for assessing effectiveness should be feasible to apply and relevant from a time perspective.<br>***CIOMS respectfully requests that GVP Module XVI considers inclusion of safety related outcomes of interest (SOI) as additional or alternative endpoints when assessing effectiveness of risk minimisation measures and that a cross-reference be made to CIOMS IX guidance.***<br><br>The GVP Module XVI may imply wide application of formal safety studies to quantify ADRs and such an | Markers for a safety outcome are now referred to in "XVI.B.4.2. Outcome indicators" |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | approach may not always be feasible or justified in all situations from an ethical, public health, timing or resource perspective.<br>***CIOMS encourages the Agency to clarify the approach regarding the types of studies to be required for assessing effectiveness of risk minimisation measures. Use of drug utilisation studies and assessment of SOI could be useful additional or alternative approaches to be highlighted, particularly early in the lifecycle of medicinal products. A stepwise approach may also be considered that is proportionate to the medicinal product and risk to public health.*** | The module already refers to the proportionality of interventions |
| | Module XVI does not describe the additional risk minimization strategy of (informational) communication, which is considered in CIOMS IX (and in Module XV – Safety communication). This is an important aspect that should be addressed either directly in Module XVI, or at least referred to in Module XVI. It should be noted that an “educational programme” may not necessarily be the first step for additional risk minimisation and furthermore it may not even be necessary if safety communication as described in Module XV is likely to be effective.<br>***CIOMS suggests that ‘education’ as mentioned in Module XVI should be clearly defined and*** | The Module briefly mention safety communication and refers to the dedicated Module XV |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | ***distinguished from 'information'. Module XVI should also cross-refer to Module XV on Risk Communication*** | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
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| 93 | | Comment:<br>Consider cross-reference to CIOMS IX (see general comments above)<br><br>Proposed change (if any): Further practical guidance may be obtained from *CIOMS IX Practical Approaches to risk minimisation for Medicinal Products.* | |
| 333 - 339 | | Comment:<br>The concept of 'undue burden' on the patient or the healthcare system could be mentioned here and a cross-reference made to CIOMS IX<br><br>Proposed change (if any):<br>Undue burden on the patient or the healthcare system should be given consideration in these situations (please refer to *CIOMS IX: Practical Approaches to Risk Minimisation for Medicinal Products*). | |
| 390 – 393<br>599 - 600 | | Comment:<br>Adverse drug reaction frequency and incidence is given here as the outcome measure to be obtained whilst other clinical outcomes are not described. In most practical situations it will not be feasible, practical, or ethical in view of the sometimes far too long timeline or huge expense needed to conduct | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
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| | | studies systematically (eg for a very rare outcome such as aplastic anaemia), therefore indirect clinical outcome measures could be considered. Such safety-related outcomes of interest (SOI) are not mentioned in this module. The reader should be referred to CIOMS IX which includes a description of these SOI. In addition to these considerations a step-wise and proportionate approach may be relevant in some situations such as use of drug utilisation studies alongside routine pharmacovigilance before escalation to an assessment of incidence of adverse drug reactions in a safety study.<br><br>Proposed change (if any):<br>It should be noted that the concept of safety related outcome of interest (SOI) is introduced by CIOMS IX. For further consideration of SOI refer to *CIOMS IX Practical Approaches to Risk Minimisation for Medicinal Products*. | |
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Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from: EFPIA

| Name of organisation or individual |
| --- |
| EFPIA |

*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<br>*(To be completed by the Agency)* | General comment | |
|---|---|---|
| | EFPIA welcomes the opportunity to provide comments on the draft Module XVI of the *Guideline on Good Pharmacovigilance Practices – Risk minimisation measures: selection of tools and effectiveness indicators*. Optimisation of the benefit risk balance is a fundamental and critically important concept fully supported by EFPIA in the interest of public health protection. Therefore, we consider that there is a strong need for a well written, unambiguous guideline which provides a clear structured basis for understanding the objectives behind risk minimisation measures, when additional risk minimisation activities should be proposed, when they are a condition of the marketing authorisation and when they are not, how their effectiveness may be assessed and the expectations of the European regulatory authorities. It also needs to be acknowledged that this is an evolving area of science with no universally agreed standards at the current time.<br><br>As a general observation, we note that in a number of sections, the draft guideline refers to other GVP Modules (IV, V and VII and the EU RMP template, in particular) but gives more detailed, and in some cases, new, instruction than currently contained in those modules/ templates. EFPIA therefore recommend that careful consideration should be made to ensuring that the respective content of these modules is aligned and that they should be updated instead and appropriate cross-references provided in this module only.<br><br>EFPIA fully supports the concepts proposed in this guideline with respect to the assessment of effectiveness of additional risk minimisation measures and agrees that the step wise approach of considering a combination of process and outcome indicators is a logical and appropriate aim. The proportionality which has been | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | applied to the risk minimisation measures themselves also needs to be applied to the assessment measurements in order to avoid placing an undue burden on the healthcare system, prescribers, patients, regulators or industry. It is also important to ensure clarity in a number of areas in the guideline in order to avoid setting unrealistic expectations. and facilitate it`s use as a helpful guidance to industry in implementing appropriate standards for risk minimisation.<br><br>The following points reflect areas of significant concern :<br><br>**1) Additional Risk Minimisation Activities, Risk Selection, Expectations, Condition of Authorisation, Thresholds & Terminology**<br><br>**a) Selecting important risks suitable for additional risk minimisation measures**<br>EFPIA support the concept that additional risk minimisation measures should focus on the most important preventable risks. Therefore this GVP module should emphasise that recognised important risks should be prioritized and that only a minority of risks will need additional minimisation measures so should be chosen judiciously taking into account frequency of occurrence, seriousness, severity, impact on public health and preventability. In selecting the risks considered suitable for additional minimisation activities, the impact of the risk minimisation activities themselves and measurement of effectiveness should be balanced with the burden on the healthcare system, feasibility of assessment, benefit for the patient and, ultimately continued access to a product from which they are deriving benefit.<br>We have noted a lowering of the threshold for what is classified as an important risk over recent years, since the implementation of ICH E2E in | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | 2004, and are anxious to avoid a similar path for selecting important risks amenable to additional risk minimisation measures.<br><br>**b) Unrealistic Expectations and the Practice of Medicine**<br><br>EFPIA is concerned that, as currently written, the guideline will set an unrealistic expectation for Assessors or PV inspectors if it is interpreted that it is always possible to influence attitudes and prescribing behaviour when this may well not be the case for multiple and legitimate medical reasons. This concern is based on broad experience to date whereby there is a tendency to interpret the content of guidelines literally and not necessarily with the spirit or even understanding of the underlying intent in mind.<br><br>We agree that understanding the reasons for not complying with all the provisions of the interventions (whether routine or additional) is important through evaluation of effectiveness at various points of the process but, ultimately, the physician, as the learned intermediary, will be making individual benefit risk decisions which may or may not conform to the advice provided in the SmPC or educational tool. Advice in these tools is based on population level data and the prescriber may well have very good reasons to use the product outside the recommended terms when he/she considers it appropriate for an individual patient or patients, particularly if the risk being minimised is rare and the patient(s) is clearly deriving benefit from the treatment. Some MAHs have evidence of this prescribing behaviour from previous surveys of risk minimisation, namely that clinicians are making these decisions in what they consider to be in the best interests of their patients, notably in oncology and other | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | specialist areas.<br>In these circumstances, EFPIA consider that it is inappropriate and outside the remit of the risk minimisation plan to regulate the practice of medicine or interfere with the doctor-patient relationship. 100% compliance will be unachievable in most situations, so the setting of realistic targets is important and needs to take into account the extent to which MAHs can truly influence process and outcomes. Influencing outcomes is likely to be less “effective” than process when it comes to factors affecting attitude, prescribing behaviour and decision making as these are complex. The extent to which “ educational “ tools, for example, can automatically influence behaviours and how a product is used will be highly variable unless it is patently obvious that not following the guidance is detrimental to patients.<br>Further context and acknowledgement of these challenges therefore need to be added to the guideline and some proposals for amendments are made in the next section of this commentary.<br><br>**c) Condition of Authorisation**<br><br>The guideline is currently somewhat ambiguous and contradictory as to when, and when not, additional risk minimisation measures are considered to be conditions for the safe and effective use of the medicinal product and, hence, of the authorisation by implication.<br>Section XVI.B.2 seems to clearly state that additional risk minimisation activities can ONLY be proposed when they are laid down as conditions for the safe and effective use but then, later, in the introduction to section XVI.C.1, the guideline refers to its application only in relation to centralised products. Section XVI.C.1 then alludes to “*circumstances where additional risk minimisation measures **are*** | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | ***not imposed as a condition*** *of the marketing authorisation that are included in the RMP*, however, omits to give any examples of when this situation might apply.<br>It would appear that, for centrally authorised products, the legal basis determines that all additional risk minimisation are automatically conditions of the authorisation e.g. even when measures have been voluntarily proposed by the MA/MAH and agreed with PRAC for inclusion in the RMP. As an additional risk minimisation tool, it is difficult to see how a DHPC can be practically handled as a "condition of authorisation", even if it is considered to be important "for safe and effective use", when the timeframes for agreeing and distributing such a communication are usually very short.<br>On the other hand, for products licensed under the mutual recognition or decentralised procedures, Article104.3 of Directive 2001/83/EC appears to allow for risk minimisation activities to be included in the RMP but not be classified as a condition of the authorisation. EFPIA assume that this is the situation to which section XVI.C.1 is alluding and have proposed wording accordingly, as well as in the introduction to XVI.C.6 as this is currently silent on products approved through procedures other than centralised<br>EFPIA consider it important for MAAs/MAHs to continue to be able to voluntarily propose additional risk minimisation activities for inclusion which they consider to be in the best interests of patient safety (important for safe use). Assuming agreement with the regulatory authorities, these can be included in the RMP but should not automatically qualify as conditions of the MA.<br>We understand that this flexibility is not afforded to centrally authorised products and concur that every effort should be made to implement any additional risk minimisation measure in accordance with the standards and milestones agreed in the RMP, regardless of the authorisation procedure and whether or not it is a | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | condition of the authorisation. However, there may be genuine or unforeseen reasons out of the MAHs control when an activity does not meet, for example, all the agreed milestones. In these circumstances, EFPIA trust that there will be due consideration of the circumstances and that the MA itself is not unduly jeopardised, especially within the centralised procedure when all additional risk minimisation measure become conditions of the MA by default, even if not strictly imposed.<br><br>d) **Threshold for Proposing Additional Risk Minimisation Activities**<br><br>Although not explicitly stated as such, the approach being taken towards additional risk minimisation measures would indicate that the threshold is being raised for situations when such measures can be proposed by MAs/MAHs or requested by the regulatory authorities/PRAC. If this is indeed the case, it would be helpful if this point is clarified, namely that additional risk minimisation activities will be targeted towards the only the most concerning risks and that the provision applies to both industry and regulatory authorities alike. EFPIA are particularly concerned to maintain consistent standards as it is the experience of many MAHs that there is an increasingly low threshold being set for requesting DHPCs as a communication tool, almost on a “routine” basis, as noted in the specific comments section below. In these circumstances, there is concern that overuse of the DHPC tool will cause it to become devalued or even ineffective as an important communication tool and place an undue burden for all stakeholders if the stipulated additional assessments of effectiveness are then applied. | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | **e) Consistent use of terminology**<br><br>EFPIA assume that the terms “conditions for the safe and effective use” and “conditions of the authorisation” are being used interchangeably. In particular, these terms appear to be being used in their strict regulatory sense, when the main audience of this guideline (usually physicians and scientists working in a pharmacovigilance /risk management environment and not necessarily fully cognisant of all the highly complex regulatory procedures/terminology contained in multiple non- PV guidelines which operate in the EU) may understand differently. For example, “essential for the safe and effective use of the medicinal product”, will not necessarily be interpreted as a regulatory reference to “condition of the authorisation”, but “important for patient safety”.<br>We consider that, in order to promote clarity in a complex procedural system, terminology is consistent and precise within and across the different GVP guideline documents and that it is clear when terms are being used in their strict regulatory sense as opposed to a “general principle”.<br><br>**2) All Assessments of Effectiveness Classified as PASS**<br><br>We agree that the measurement of outcome does qualify as a study, however, measurement of process (e.g. a questionnaire to check mailing of a DHPC to HCPs or awareness/knowledge of the content) cannot be considered as a study. It is important that this separation is clear in this Module as the data generated from assessment of process does not inform how well a risk is minimised.<br>This will have significant implications not only for the MAH but also PRAC/Member State Competent Authorities as the guideline stipulates that evaluation of the risk minimisation measures be undertaken at the individual tool | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | level as well as the programme as a whole. Therefore, if 4 risk minimisation measures are agreed in the RMP, then this will involve 9 PASS (assuming one process and one outcome evaluation per tool plus one for the whole programme). As the risk minimisation measures will be a condition of the MA, then it would appear that the measurement of effectiveness will be imposed and require individual assessment by PRAC, as well as being subject to all PASS provisions in Module VIII. If local amendments are needed, the number of different protocols would be even higher.<br><br>Overall, this is considered to be overly burdensome, with inclusion of process indicators as PASS having no ostensible positive contribution to public health, as well as not being in keeping with the principle of proportionality. EFPIA accept that process indicators will still need to be monitored, results acted upon as appropriate and results presented in the RMPs /PSURs but urge that they do not fall under the definition of PASS for all the reasons highlighted<br><br>**3) What constitutes a Successful Risk Minimisation Measure**<br><br>Although, it is clear that it is not possible to give concrete targets for what constitutes an effective vs. ineffective risk minimisation programme, the draft guideline appears to be silent on this important point. EFPIA accepts that it not possible to be prescriptive and make concrete recommendations that cover every eventuality but mention of the uncertainties and general lack of guidance on what constitutes a successful and effective risk minimisation measure or an acceptable target of effectiveness would be helpful to set realistic expectations. Conducting surveys to strict/auditable requirements would be extremely difficult, especially | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | |
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| | in large patient settings and when biases cannot be reduced by increasing sample size, and would be almost impossible to inspect.<br>Whilst there is an understanding amongst MAHs and Regulators, that this is an evolving area of science, and that better tools and methods of measuring effectiveness may be available in the future, it would be important that this situation is highlighted.<br>In particular, in setting targets for assessment of effectiveness, it is vital that "success" measures are proportionate to the nature and frequency of the risk, the level of uncertainty of the risk, the target audience (e.g. specialists vs. general practitioners) and the extent to which any level of non- compliance has public health implications<br><br>Overall, EFPIA appreciate that this commentary is longer than the actual draft guideline itself but the comments are thorough and made with the constructive intent to assist in ensuring that it becomes a valuable guidance to industry in implementing appropriate standards for risk minimisation and hence promote patient safety . | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
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| Lines 67-69 | | Comment: As noted in the general comments section, it is important to ensure that terminology is used consistently. With respect to additional risk minimisation measures, the rationale is expressed in different ways which, in the current environment of literal interpretation, will likely lead to inconsistent interpretations of when these should be proposed, namely "essential for the safe and effective use", vs. a "condition of the authorisation" vs. "necessary to manage risk and/or improve benefit risk". EFPIA accept that this comment may seem to ignore the fact that the "spirit" of the respective terminologies is essentially the same, but, based on actual experience , this is not how it may be perceived or interpreted in practice e.g. in an inspection situation<br><br>Proposed changes: For some risks, however, routine risk minimisation measures will not be sufficient and additional risk minimisation measures will be necessary, **when essential for the safe and effective use of the medicinal product i.e. in order** to manage **selected important identified** risk**s** and/or improve the **benefit** risk ~~benefit~~ balance of a medicinal product. | |
| LL71-73 | | Comment: As currently written, the scope of assessment of routine risk minimisation could be interpreted as the intent to request systematic measurement of effectiveness for **all** routine measures, notably the SmPC/PIL, even in the absence of associated additional | |

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| | | risk minimisation activities to support the content. These routine measures are considered by industry and regulators alike globally to be the pivotal risk minimisation tools, applied to all products because they are considered to be well established and fulfilling their purpose. The phrase "important for the benefit risk balance of the product" is very broad and has a significant potential for inconsistent interpretation. It is clearly not the intent of this guideline that the SmPC/other routine risk minimisation tools regularly require an evaluation of effectiveness, particularly as this approach is not in keeping with the principle of proportionality and poses a significant burden, including for patients and HCPs. Nevertheless, there are already indications that regulatory assessors are interpreting this provision very conservatively. In order to avoid inconsistency and provide clarity, EFPIA consider that it is necessary to define more precisely what information in the SmPC/PIL would be considered "important to benefit risk". This would need to link to the RMP and, in practice, would almost invariably have associated additional risk minimisation activities anyway.<br><br>Proposed change: **In specific circumstances,** ~~H~~ **h**owever ~~it should be understood that the principles for~~ evaluating the effectiveness ~~of risk minimisation~~ may also ~~be applicable~~ **apply** to ~~the evaluation of~~ routine risk minimisation measures **associated with an important identified risk(s) which are described in the contraindications and/or warnings and precautions sections of the SmPC/PIL and where the SmPC provides guidance for clinical actions beyond routine standards of clinical care for either the risk itself or** | |

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| | | **management of the target population (e.g. when specific genotyping is required prior to prescription of a product)** ~~particularly where important for the risk - benefit balance of the product~~.**, When these circumstances apply for a routine measure and this is associated with additional risk minimisation activities, evaluation of the effectiveness of the relevant sections of the SmPC or PIL (as appropriate) would be expected in conjunction with assessment of the effectiveness of the additional tools.** | |
| LL116-121 | | Comment : It is important for this guideline to recognise that national medical practices and health care standards can influence the tools that need to be used for efficient and feasible risk minimization consistent with the level of minimization agreed at the EU level<br><br>Proposed change: The performance of these measures in healthcare systems requires assessment to ensure that their objectives are fulfilled and that the measures in place are **feasible and** proportionate**,** taking account of the risk-benefit profile of the product**, the respective differences in medical practice and health care systems in the Member States** and the efforts required of healthcare professionals and patients to implement the measures. | |
| Lines 127-128 | | Comment: As highlighted in the general comments section, realistic expectations need to be set in relation to what constitutes "success" in terms of the evaluation of a risk minimisation measure. Practical | |

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| | | considerations should also be taken into account. i.e., physicians do not reply to surveys and the ones that do respond are not necessarily representative.<br>For process indicators, this is relatively more straightforward and more under the control of the MAH e.g. using established market research criteria /standards. Changes in behavioural indicators can be measured but due to the complexity of clinical decision making, less readily amenable to influence by simple educational tools and DHPCs unless it is very clear that there would be detriment to any patient as a result of failure to follow the advice given. This may be particularly so in specialist settings such as oncology, for rare adverse effects/risks and where a patient is clearly deriving benefit from the product.<br>These aspects need to be clarified in the guideline to avoid an unrealistic expectation that all measures will be a 100% effective all the time; it may also not be possible to measure risk reduction as a safety outcome if the frequency of the risk is low.<br><br>Proposed change; The evaluation of effectiveness **is an evolving area of science, with no universally defined or accepted standards as to what constitutes a successful or effective risk minimisation measure or programme. In the context of this guideline, it is not possible to give detailed or specific guidance that applies to all situations. This may need to be determined on a case by case basis, taking into account the seriousness and severity of the risk, its frequency and level of certainty, the condition being treated, the extent to which the risk is** | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
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| | | **manageable/preventable, patient exposure and the target audience. These considerations particularly apply for behavioural change/outcome indicators which are subject to multiple factors including the need for a clinician to make individual benefit risk decisions for their patient(s). In some situations, demonstration of risk reduction may not be feasible if the risk is rare and patient exposure is relatively low. Targets for effectiveness therefore have to be realistic and proportionate but** should facilitate early corrective actions, if needed **and may require modification over time**. | |
| Lines133 - 134 | | Comment: Measures to address specific safety concerns could include those which optimise benefit too.<br><br>Proposed Change: There should be a clear description of how the additional risk minimisation measure proposed will address a specific safety concern **or improve treatment benefit;** | |
| Lines 131-143 | | Comment: As highlighted in the general comments section, these bullet points, in general, give more detailed instruction than currently contained in GVP Module V and the EU-RMP template and it is not intuitively obvious exactly where the information stipulated by these bullet points should be included in the current template. In particular, the way in which the third and fourth bullet points are written is somewhat confusing as they imply that there are | |

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| | | two discreet sections in the current Module V/EU-RMP template called “Implementation Plan” and “Evaluation Plan” when there are not. Furthermore, under the Effectiveness of Risk Minimisation subsection of V.1 in the template, there is no provision at all to include milestones. EFPIA therefore recommend that the two Modules and template are aligned and the template updated for consistency and ease of use in this respect. Due to the interface with Module VIII on PASS, EFPIA also recommend that this module is checked to see if amendments in Module V and Module XVI have an impact in that Module too.<br><br>In order to provide clarity, we recommend that cross reference should be made in bullet points 3&4 to denote which sections in the EU-RMP template to which they apply. Finally, the “Evaluation Plan” section implies that it is always possible to assess effectiveness of health outcome measures such as reduction of risk, when it is not always practical and feasible to do so. In many cases, demonstration of a reduction of health outcome measures will not be possible and would add an unduly high hurdle in what is a new and evolving science. This would particularly apply to risks which are rare and where an evaluation of risk reduction could take many years to build a database large enough to provide a scientifically meaningful data or where existing databases may not have sufficient power to provide robust data.<br><br>Proposed change:<br>• Rationale for additional risk minimisation measure (linked to | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
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| | | specific safety concerns). This section **(V.1 of the EU-RMP template)** should set out…<br>• Description of additional risk minimisation measures(s).This section **(V.1 of the EU-RMP template)** should provide….<br>• Implementation Plan: This section **(V.1 of the EU-RMP template under "Proposed Actions")** should provide….<br>• Evaluation Plan : This section **(V.1 of the EU-RMP template)**should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimisation in process terms and in terms of overall health outcome measures, **where it is practical and feasible to do so** ( e.g. reduction of risk) | |
| Lines 147-148 | | Comment: Changes proposed as per general comment in order to provide more clarity on additional risk minimisation activities in relation to the various approval procedures and to promote consistent standards by both MAs/MAHs and regulatory authorities alike<br><br>Proposed changes: While routine measures are applied to every medicinal product (…), additional risk minimisation activities should only be proposed **or recommended** when they are **deemed essential** ~~laid down as conditions~~ **to ensure** the safe and effective use of the medicinal product**(for more details, see section XVI.C.1**. **T**~~t~~hese **measures** should be science based and developed and provided by suitably qualified people. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
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| | | **In determining if additional risk minimisation activities are needed, important identified risks should be prioritised in terms of frequency, seriousness, severity, impact on public health and preventability. Additional risk minimisation measures should focus on the most important, preventable risks, particularly if there is a need for clinical actions beyond routine standards of clinical care for either the risk itself or management of the target population The burden of risk minimisation should be balanced with the benefit for patients and need for continued access to the drug** ~~and~~ | |
| Lines 156-158 | | Comment: As indicated previously, additional risk minimisation measures may be proposed by industry but also requested by regulatory authorities. In the interests of consistency, it is important that the same standards apply to both parties. EFPIA therefore propose the following amendments.<br><br>Proposed changes: If additional risk minimisation activities are **proposed by MAAs/MAHs or** requested **by regulatory authorities,** the rationale for the request-should be clearly documented **and** should be linked to **a** specific safety concern**(**s**).** ~~and sufficiently detailed in~~ **The** implementation and evaluation plan**s** ~~ning~~ **for these activities should be detailed in the risk management plan.** | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
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| Lines 179-182 | | Comment: EFPIA agrees with the objectives as set forth in this section; however, it needs to be acknowledged that, as all these activities aim to optimise the benefit-risk balance for the medicinal product, it may be appropriate to reference benefits or efficacy data in the materials.<br><br>Proposed change (if any):<br>Any educational material should be clearly focused on defined risk minimisation goals, providing clear and concise messages **and putting the benefit-risk balance into perspective** | |
| Lines 179 - 185 | | Comment: EFPIA agree that educational materials provided for risk minimisation purposes should not contain information of a promotional nature. However, as the aim of any risk minimisation activity is to optimise benefit risk, inclusion of appropriate efficacy/benefit information should not be precluded where appropriate as long as it is presented in a balanced, objective fashion. Given that the current EU-RMP contains a summary of efficacy, including the publically available lay summary, it seems illogical that information consistent with that section cannot be included in educational material, where appropriate. We accept that the emphasis should be on balance and objectivity but material focussing solely on risk may actually have a contrary effect if patients are unduly alarmed and discontinue treatment. Depriving patients of benefit would therefore be an unintended consequence. EFPIA propose that it should be possible to include efficacy or benefit information that is consistent with that included in the RMP | |

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| | | Proposed change: **<u>As the benefit risk balance may need to be placed into perspective in an educational tool, the efficacy/benefit information used should be consistent with that included in section V.B.10.1 RMP Part IV (Summary of Existing Efficacy Data) and the equivalent section of the publically available summary. The information should not be written in a</u>** ~~P~~ **<u>promotional</u>** **<u>fashion i.e.</u>** **promotional** elements, either direct or veiled, should not be included. ~~and t~~ The focus of the educational material…… | |
| Lines 183-185 | | Comment: GVP module XVI suggests that any educational programme should be completely separated from promotional activities (183-185) also that educational tools should be distributed separately from promotional materials as a "stand-alone communication" (300-302). EFPIA accept that, in an ideal world, it is desirable to avoid distribution of educational material and promotional material at the same time but, in practice, this will not always be possible. Educational materials are not promotional but the likelihood is that they will be distributed alongside promotional materials via the sales representatives to physicians (who may distribute them to the patients). Thus, in the current situation, it would be impossible for the MAH to completely separate their distribution from promotional activities. A further consideration is that direct presentation of the material to an HCP does ensure that it reaches its target audience, can be tracked and is likely to be more effective than simply mailing the material. As a means of consistent | |

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| Lines 300-302 | | delivery of educational materials (and one which can be tracked), a direct mailing is the only other practical way of distribution with all the limitations associated with that this mode of communication. The term “stand-alone” communication seems vague, redundant and open to interpretation, especially as it is obvious that any educational tool should be complete in its own right. EFPIA assume that it would not be approved by the regulatory authorities otherwise.<br><br>Proposed change: Any educational ~~programme~~ **materials** should be completely separated from promotional materials ~~activities~~ **(e.g. in separate folders), however they could be presented to the HCP during the same visit. Sales representative involvement in an educational programme should be confined to distribution of materials only.** ~~and c~~ **C**ontact information of physicians or patients gathered….<br><br>Proposed change: Furthermore, educational tools should be ~~distributed~~ **presented** separately from promotional materials **(e.g. in separate folders)** ~~as a stand- alone communication~~ and it should be clearly stated that the tools are **for risk minimisation purposes.** ~~not promotional material.~~ | |
| Lines 195-197 | | Commen: As this section relates to what is provided to HCPs/patients who are not bound by the PV legislation nor are necessarily familiar with the content and terminology, it is important that the wording is clear and understandable in any materials | |

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| | | provided to the target audience Tthe term “mandatory as a condition of the MA” will be meaningless to most HCPs or patients but the significance of a phrase” safe and effective use” would be more likely to be understood and appreciated.<br><br>Proposed Changes: In addition to an introductory statement that the educational material is **essential** ~~mandatory~~ ~~as a condition of the marketing authorisation~~ **to ensure safe and effective use and appropriately manage** ~~in order to further minimise~~ important selected risks… | |
| Lines198-201 | | Comment: This guidance should include recommendations on how to deal with an adverse reaction and ways to optimise benefit risk but it is not the role of industry to educate on the usual practice of medicine. Reference to benefit optimisation is considered to be important, as well as avoiding education on how to manage risks which would be part of usual clinical practice or which the target audience would otherwise be expected to know.<br><br>Proposed change:<br>• Guidance on the management of such risks (to healthcare professionals and patients or carers).**Guidance to healthcare professionals should be focussed on the management of risks specific to the medicinal product and that are outside usual clinical practice or for which the target audience would otherwise not be expected to know**<br>• **Guidance on how to optimise the benefits of the medicinal** | |

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| | | **product** | |
| Lines 220-227 | | Comment: Educational tools targeting patients and/or carers can also be aimed at providing information about the correct use/administration of the product, e.g. in case of home administration as well as early recognition of signs or symptoms of the risk.<br><br>Proposed change: If appropriate, a patient`s educational tool could be used to provide information **on the correct administration of the product or early recognition of signs and symptoms of the risk** and…. | |
| Lines 234 - 259 | | Comment: EFPIA fully support the point made that controlled access programmes have large implications for all stake holders and the stated drivers for considering such a stringent measure. This important point, however, is made at the very end of the section and we consider that it would be more appropriately placed in the first paragraph to complement and clarify when such a measure should be considered. It would also be helpful to add clarification that the threshold for considering a controlled access programme is that access to the product is contingent on one or more of the requirements ( per the bullet points being met)<br>Per the 4th bullet point, such a process for pharmacies to be registered and approved for dispensing certain products may be actually part of the legal status of the product (e.g. dispensed only in hospital pharmacies), hence a “routine” measure. | |

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| | | Proposed Changes : Move wording currently in lines 257-259 to the first paragraph<br>A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measure i.e. legal status. **Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited to those rare circumstances where there is a clear ~~is likely to be driven by~~ therapeutic need for the product based on its demonstrated benefit (e.g. treats a serious disease without alternative therapies, has documented advantage over existing therapies, or treats failures on existing therapies) ~~and~~ the nature of the risk (e.g. risk that is life-threatening) and where these risks are expected to be managed by this intervention. Therefore,** ~~Controlled access~~ **it** should **only** be considered as a tool for minimising a**n** ~~serious~~ **important** risk ~~for a product~~ **with significant public health impact for a product with** clearly demonstrated benefits but ~~which~~ **that** would not **otherwise** be available without ~~additional risk minimisation measure(s) due to the public health impact of the risk~~ **a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure safe use.**<br>Examples of requirements that need to be fulfilled….<br><br>• Specific testing…..criteria | |

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| | | • Prescriber, dispenser and /or…..understanding of information on the serious risk of the product **(e.g .informed consent could be considered);**<br>• Explicit procedures……..e.g. patient registry<br>• Medicines made available for dispensing only to pharmacies ~~who~~ **which** are registered and approved to dispense the product **where this is not actually part of the legal status of the product.** | |
| Lines 270-273 | | Comment: It would be helpful and a good reminder that educational materials could also include information when the male partner is treated<br><br>Proposed change: add to the list of examples: **information when the male partner is treated** | |
| LL281-283 | | Comment: EFPIA support the need to monitor pregnancy outcomes of patients who become pregnant on treatment but a registry is more appropriate to monitor outcomes and/or the effectiveness of the pregnancy prevention programme than as a measure to prevent the pregnancy itself , so the current wording could be confusing. We recommend some clarification as follows :<br><br>Proposed change: The design and implementation of a pregnancy registry (**as a standalone activity or as part of a pregnancy prevention programme)** should also be considered for universal enrolment of patients who become pregnant during treatment or | |

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| | | within an appropriate time from the end of treatment e.g. 3 months. **Use of this systematic tool to collect pregnancy outcome information can be helpful in assessing the effectiveness of the pregnancy prevention programme and/or helpful in facilitating further characterisation of the risk, particularly in the early period post authorisation when human pregnancy data may be very limited and/or when the potential concern may be based on non- clinical data alone.** | |
| Lines 285-289 | | Comment: As there is a separate module on safety Communications (Module XV), EFPIA understand the need to avoid repetition of information and guidance already included elsewhere. We accept that it has been classified as an additional risk minimisation but, as noted in the general comments section, we are very concerned that it is almost being used as a “routine” measure by the Assessors with regular requests to use a DHPC and/or include in the RMP when other forms of communication may well be a more effective alternative. If the volume of DHPCs continues, we are concerned that they will become devalued as an important communication mechanism and place a significant burden on the healthcare system In this respect, we strongly consider that reinforcement of the need for a higher threshold for issuing a DHPC is included in this Module, i.e. when there is a need to take immediate action or change current practice in relation to a medicinal product and a DHPC is the only way in which continued safe use can be assured. It would also be helpful to include a re-emphasis on alternative forms of | |

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| | | communication, as well as the wording in Module XV in relation to measuring effectivess in order to promote consistency and proportionality.<br><br>Proposed change: A direct healthcare professional communication (DHCP).…….(see Module XV).<br>**A DHPC should be disseminated in the following situations when there is a need to take immediate action or change prescribing behaviour in relation to a medicinal product:**<br>**• suspension, withdrawal or revocation of a marketing authorisation for safety reasons;**<br>**• an important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;**<br>**• a restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.**<br><br>**Other situations where dissemination of a DHPC should be considered are included in Module XV but should be proposed or requested when considered necessary for the continued safe and effective use of a medicinal product. In order to avoid placing an undue burden on the healthcare system and undermining the value of a DHPC as an important safety communication, careful consideration of alternative forms of communication should be made in circumstances which require more active communication than simply amending the SmPC/PIL but for which there is not an urgent need to take** | |

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| | | **action or change prescribing behaviour.**<br>**The marketing authorisation holder should be responsible for evaluating the dissemination of the DHPCs they prepare and should inform the competent authorities of the outcome and of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination).**<br>**Appropriate action should be taken as needed to correct the situation or prevent similar problems in the future.** | |
| Lines 305-308 | | Comment: This paragraph includes reference to the term "risk minimisation programme" which is not defined anywhere to our knowledge. EFPIA recommend that more clarity is provided as to whether this means the combination of activities per safety concern or the entire risk minimisation plan in place for all the safety concerns. As the latter approach does not seem logical (the activities for some concerns may be effective whilst another may not be and hence it would be difficult to meaningfully assess overall effectivess. We therefore assume that the former is intended (i.e. by concern). In practice, the two may actually be synonymous as, in most cases, additional risk minimisation would usually only involve one safety concern.<br><br>Proposed change: The evaluation should be performed for ~~the~~ **each** risk minimisation tool~~s~~ individually and for the risk minimisation programme as a whole **for each safety concern.** | |

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| Lines 309-311 | | Comment: The paragraph on effectiveness is very comprehensive and, as noted in the general comments section, raises concerns that assessing effectiveness for some tools may become more burdensome than the actual risk and minimisation tool applied. In addition, as written, it implies that both process and outcome measures can be applied universally to every risk requiring additional risk minimisation measures which may not be the case. As noted previously, it may not always be feasible or practical to measure outcomes, and there may well be good reasons for not achieving 100% “success” in modifying prescribing behaviour when prescribers are making individual patient benefit risk decisions. Overall, significant challenges remain in acquiring accurate and reliable data that differentiate the extent to which behaviour and outcomes have been influenced by a particular tool. Failure to acknowledge these very real, practical issues will only create unrealistic expectations. This section of the guideline therefore needs to emphasise consideration of the burden on patient and HCP, the need for a proportionate approach and feasibility as significant blocks to achieving the “counsel of perfection” described.<br><br>Proposed change: The evaluation should **aim to** address different aspects of risk minimisation, **wherever practical and feasible, notably,** the process itself (i.e. to what extent , the programme has been implemented as planned),its impact on knowledge and behavioural changes in the target ~~population~~ **audience ( i.e. the** | |

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| | | **outcome of the measure(s) in effecting behavioural change),** and **other** outcome **indicators** ( i.e. to what extent the predefined objectives of risk minimisation were met, in the short and long term). **In designing an evaluation plan, due consideration needs to be made toward what aspects of process and outcomes can be realistically measured in order to avoid the generation of inaccurate/misleading data or placing an undue burden on the healthcare system e.g. it may not be possible to measure a reduction of a risk which is rare and unpredictable).** The time of assessing each aspect of the intervention, **as well as setting of realistic metrics on which the effectiveness of the tool is judged,** should also be carefully **considered and** planned within the RMP prior to initiation. | |
| Lines 318-326 | | Comment: With respect to process and outcome indicators, EFPIA agree with the broad categorisation which is helpful. We, however, disagree that knowledge/behavioural/attitude modification is a process indicator per se. Factors impacting behavioural change are complex and go far beyond simple process. As a result, we consider that knowledge and behavioural change belong either under outcome indicators i.e. behavioural change on the part of the prescriber or patient is an outcome of the risk minimisation measure) or as a separate category. This position takes into account that the risk minimisation process cannot be compartmentalised into discrete and non- interacting parts. Knowledge alone without linking to practical behaviour change in the same study will have limited interpretability | |

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| | | and may require mixed methods research to draw relevant conclusions.<br><br>EFPIA`s preference is to retain two categories rather than create a separate category for behavioural indicators.<br><br>Proposed change: These process indicators should provide insight into what extent the programme has been executed as planned ~~and whether the intended impacts on behaviour have been observed.~~ Implementation metrics……to the desired control of specified risks. Outcome indicators provide an overall measure of **whether the intended impacts on behaviour have been observed and, as a result,** the level of risk control that has been achieved with a risk minimisation measure. | |
| Lines 333-335 | | Comment: It is entirely possible that a risk minimisation measure is found to add no value to the overall risk minimisation programme and hence can be removed altogether. MAHs have experience of this situation and modified the plan accordingly in agreement with PRAC.<br><br>Proposed change: '… or lacking a clear focus and could be reduced, or simplified ( e.g. by decreasing the number of tools, **eliminating activities found to be non- contributory to risk minimisation,** or frequency of intervention) | |
| Lines 336-339 | | Comment: Unintended consequences based on their nature would | |

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| | | not have been included as evaluation end points, thus cannot be credibly assessed on a priori basis~~.~~ EFPIA assume this would be undertaken in a post hoc manner once the evaluation of effectiveness is completed. It is also unclear what is meant by unintended consequences, therefore, it would be helpful to add some clarifying text.<br><br>Proposed change (if any): In addition to assessing… it is also important to ~~assess~~ **monitor** **if** ~~of~~ the risk minimization…either in the short and/or long term. **Unintended consequences may include undue burden on the healthcare system, product discontinuation when benefit risk may well be positive, reduced access to the medicine or assessment of a risk minimisation activity which is subsequently shown to be non- contributory to the risk minimisation plan.** | |
| Lines 340-343 | | Comment: As noted before, EFPIA does not consider assessment of the effectiveness of process indicators to be a study or as having a safety end point (i.e. it is not a PASS) as it is merely measuring implementation metrics. We agree that measurement of an outcome qualifies as a study, but simple measurement of a process (e.g. a questionnaire to check delivery of DHCP letter to the HCPs) does not qualify. It is important for all stakeholders that this separation is clearly mentioned in the GVP module, otherwise, the MAH may be completely overwhelmed by the administrative workload of running activities inappropriately classified as PASS e.g. recording them in the ENCePP database when the data generated do not inform on how | |

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| | | well a risk is managed, but simply on how the process has been set up and implemented. The non- value added burden of taking this definition literally for both PRAC and the healthcare system as a whole has already been highlighted.<br><br>Proposed change: …Therefore, **if a study is conducted to assess behavioural or safety outcome indicators,** the detailed guidance…..provided in Module VIII should be followed. **Any risk minimization measure that measures process indicators (e.g. distribution of the tools, reaching the target population, awareness of the tool) should not be considered as a study**. The ENCePP…….. | |
| Lines 353-354 | | Comment: The sentence "These metrics should focus on the appropriateness of the tool for the target audience (adequate language, pictures etc.)" seems inappropriate in the context of measuring the effectiveness of "process indicators" of risk minimisation. EFPIA consider that it would not be possible to objectively measure "appropriateness of the tool" in the parameters described and obtain meaningful results. We therefore recommend that these points should be moved to "design considerations" in section XVI B.2.1.1, i.e. prior to the implementation of the tools. Appropriateness of the tool can really only be addressed through outcome measures such as understanding/assessment of knowledge. In practice, it is very difficult to demonstrate that materials e.g. sent through a mailing or sent by email were actually delivered e.g. to | |

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| | | patients as these may be delivered by the HCP so the target audience is not known by the MAH.<br><br>Proposed changes: These metrics should focus on ~~the appropriateness of the tool for the target audience( e.g. adequate language, pictures, diagrams, or other graphical support) or~~ assess**ing** whether the materials were **delivered to the target audience or whether they were** actually received by the target audience, i**f it is possible to assess receipt.** | |
| Lines 363-365 | | Comment: Reference to tailoring a knowledge survey to monitor attitude and knowledge is confusing, as it could be interpreted that surveys of knowledge should involve assessment of attitude by means of psychometric measures. EFPIA is not convinced that this was what was intended as this is clearly disproportionate. We therefore assume that surveys of knowledge could be guided or informed by other activities using psychometric measures.<br><br>Proposed changes: Such an approach may be guided ~~tailored~~ **by the results of other activities which have** ~~to the~~ monitor**ed** ~~ing~~ of attitude and knowledge…. | |
| Line 366 | | Comment: As indicated before, EFPIA do not consider assessment of process measures, including clinical knowledge to be a study warranting classification as a PASS<br><br>Proposed change: Appropriate attention should be given to the | |

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| | | ~~research~~ **survey** objectives, **survey** ~~study~~ design, sample size……. | |
| Lines 370 - 388 | | Comment: As noted before, EFPIA consider that indicators that are associated with behavioural changes are not appropriately classified as process (implementation) indicators. We therefore recommend that this section is moved to XVI.B.4.2.<br><br>Proposed change: Delete the whole section and move to XVI.B.4.2 | |
| Lines 373-374 | | Comment: EFPIA agree that use of electronic records and record linkage could be considered as a valuable tool for conducting drug utilisation studies. As written, however, use of the word “should” could be interpreted as this methodology being the first choice in all cases when this may be neither feasible nor appropriate. We therefore propose the following modification.<br><br>Proposed change: Drug utilisation studies by means of secondary use of electronic records ~~should~~ **can** be considered as a valuable ~~tool~~ **option** to quantify clinical actions, if representative of the target population **and where adequate databases exist.** | |
| Lines 381-385 | | Comment: When proposing to conduct drug utilisation studies “across European countries”, consideration should be given to the feasibility related to the population exposure size in smaller markets. It is better to perform robust studies in a limited number of countries | |

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| | | where there is the highest exposure than trying to involve all EU countries with uninterpretable results in small populations. In addition drug utilisation needs to take into account medical practices and health care standards that are not homogenous throughout EU.<br><br>Proposed change: … interpretation of drug utilisation studies across European countries, **including relative exposure in the Member States and their national health care systems**, the legal status of the medicine and how it is prescribed and dispensed, since prescriptions patterns may reflect not only the product information and any risk minimisation intervention, but also national guidelines, aspects related to health care services, **local medical practices** and reimbursement constraints.…. | |
| Lines 390 - 397 | | Comment: As indicated previously, EFPIA consider that assessment of behavioural indicators is more appropriately classified under outcome indicators. In addition, it is not always possible to estimate risk reduction following a minimisation measure, especially if the absolute risk is low so this needs to be acknowledged in this section. The current wording seems to imply that a pre-post design will be possible in most situations.<br><br>Proposed change: The ultimate measures of success of a risk minimisation programme are the **prescribing behavioural changes (clinical action) and** safety outcomes i.e. the frequency…( i.e. non | |

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| | | interventional setting) **and both these** ~~those~~ safety outcomes should be the outcome indicator(s).<br>• **Behavioural Changes/Clinical Actions (Insert lines 371-388 here)**<br>• **Safety Outcomes**<br>~~Such an~~ The evaluation of safety outcomes should involve the comparison…<br>Under any approach….guide the assessment of the final outcome of interest. **When practical and feasible,** ~~C~~ **c**omparisons of frequency before and after the implementation of the risk minimisation measures (i.e. pre-post design) should be considered. | |
| Lines 398-404 | | Comment: EFPIA acknowledges that use of a predefined reference value may be a good alternative when no pre-post design is possible; however, this approach poses a methodological complication that over time patient care evolves and also the target population may become subjected to risk minimization measures of various types in long term. The guideline needs to reflect this limitation. In addition, we propose that comparison with CT data can also be considered as an alternative reference.<br><br>Proposed change: When a pre-post design is not feasible (e.g. ……), the comparison of an outcome frequency indicator obtained **from clinical trials or** post-intervention against a general population, would be acceptable (i.e. observed over expected analysis) and should take into account **the impact of** any stimulated reporting**,** | |

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| | | **<u>changes in patient care and/or risk minimisation measures over time</u>** | |
| Lines405-419 | | Comment: The only accepted safety outcome indicators seem to be the frequency and severity of adverse reactions in relation to patient exposure. However, assessing the ADR frequency requires interventional or observational studies, which may not always be feasible. EFPIA agrees that spontaneous reporting rates are a poor estimate of the frequency of adverse events but this does not mean that spontaneous reporting rates are totally useless to assess a safety outcome. In fact, even if only a fraction of all ADRs associated with a product are usually reported, an increase or no change in the reporting rate might speak against the effectiveness of a risk minimisation measure, while a decrease could support its effectiveness (taking into account all potential biases...). So, in the absence of studies to assess the ADR frequency, it should be possible to consider the reporting rate as a possible alternative, though less robust outcome indicator. EFPIA propose that this concept is included in order to avoid unrealistic expectations in this regard.<br><br>Proposed change : ): **Methods to measure the effectiveness of risk minimisation should be proportionate to the risks being minimised, as such use of spontaneous reporting rates may be acceptable in the context of routine risk minimisation.** Spontaneous reporting rates (...) should ~~not~~ be considered with caution ~~as an acceptable estimate of the~~ **<u>when estimating</u>** the | |

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| | | frequency of adverse events in the treated population, **but may be used** ~~except~~ in ~~very~~ specific circumstances, ~~for instance~~ **such as** when **the adverse reaction with the product is rare or where** there is negligible background incidence of an adverse event …. The reporting rates should also be considered as possible outcome indicators, even if they have less value than the ADR frequency. | |
| Lines 420-427 | | Comment: EFPIA understands and supports the overall principle that there should be a coordinated approach by the MAHs of generics for additional risk minimisation measures in place for the innovator product containing the same active substance. The practicalities of actually implementing this approach, however, should not be underestimated for a number of reasons:<br>• The MAH of the innovator product will not know who all the generic MAHs are, so both coordination and oversight will need to be by the regulatory authorities<br>• This guideline, as well as Module V, places considerable constraints e.g. avoiding the use of company logos or trademarks on risk minimisation materials such as educational tools, so it is difficult to see how in practice it will be feasible to assess the effectiveness of such tools for each individual product unless they are clearly differentiated in some way<br>• On the other hand, a collective assessment for all products would be very complex, not least, because a financial model for this undertaking e.g. based on market share in an | |

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|---|---|---|---|
| | | individual country, would be almost impossible to devise<br><br>EFPIA questions the value of assessing the effectiveness of risk minimisation tools used by generics if the content is the same as that of the innovator and the tools of the innovator have already been shown to be effective. The most important point, in these circumstances, is that the Competent Authority ensures that the MAH of the generic product uses the same tools and content already known to be effective.<br><br>Proposed changes: If several products, including medicinal products authorised according to art.10(1) or 10(3) (…….) of the same active substance are available in a market, there should be a consistent approach in the use of additional risk minimisation measures **coordinated and** overseen by the national competent authorities **(XVI.C.1.1.2). It is the responsibility of the MAH of the generic product to ensure that the tools they implement are consistent with those for the reference product, particularly when the tools have already been assessed as effective.** When a coordinated action for a class of products is needed, a harmonised approach should be agreed, if appropriate **and feasible.** Under these circumstances, ~~advanced planning~~ **careful consideration will be needed in order to determine the most practical method of evaluating the effectivess of the risk minimisation measures implemented by multiple MAH. This may need to be judged on a case by case basis e.g. further evaluation may not be necessary when the** | |

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|---|---|---|---|
| | | **same tools that have already been assessed as effective are used by the MAH of the generic product.** | |
| Lines 441-442 | | Comment: MAHs can track how many hardcopy tools are distributed and delivered to the targeted hospitals and pharmacies and possibly HCPs. However, it may be impossible to track receipt by patients, as normally tools are currently provided to patients by HCPs. Requesting recording of receipt by patients would , in most circumstances, place an unnecessary burden on HCPs. In addition, it may not be possible to track receipt of materials from an open access web-site<br><br>Proposed changes: To this purpose, the marketing authorisation holders are encouraged to keep track of the ~~recipients~~ **receipt** of any risk minimisation materials, **when this is possible.** | |
| Lines 446- 460 | | Comment: As noted in the general comments section, the introduction to section XVI.C only refers to additional risk minimisation under the centralised procedure but remains silent on these activities for products approved under the mutual recognition and decentralised procedures. EFPIA considers that it is important to clarify how risk minimisation activities for products authorised through procedures other than the centralised procedure will be managed in the EU regulatory network. As indicated in the general comments section, we consider that it is important for MAAs/MAHs to be able to voluntarily propose additional risk minimisation | |

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|---|---|---|---|
| | | activities for inclusion in the RMP. Assuming that these measures are agreed with the competent authorities, they can be included in the RMP but do not automatically qualify as conditions of the MA. We understand that this option is not afforded to centrally authorised products.<br><br>Proposed changes: Add text after line 460 :<br>**For products authorised under the mutual recognition and decentralised procedure, additional risk minimisation activities may be included in the risk management plan or laid down as conditions of the marketing authorisation. MAAs or MAHs may voluntarily propose additional risk minimisation activities that they consider are important for safe and effective use and inclusion in the RMP. Following agreement with the competent authorities, such activities can be included in the RMP but would not automatically be considered as conditions of the MA.** | |
| Lines 469 - 471 | | Comment: It is unclear in which circumstances key elements of a risk minimisation strategy are specific for only “some Member States”. EFPIA are concerned that this statement could lead to multiple requests from national competent authorities to deviate from the plan agreed at an EU level (“gold plating”). EFPIA considers therefore that the circumstances leading to such additional local measures be clarified with concrete examples in order to promote consistency and avoid inconsistent interpretation. | |

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|---|---|---|---|
| | | Proposed changes: In **rare** circumstances where some key elements of the risk minimisation strategy are specific for only some Member States, **the reasons should be justified by either the MAH or Competent Authority e.g. when products are only authorised in some markets or when the activity is specifically linked to the healthcare system in that country.** ~~or~~ Where additional risk minimisation measures are not imposed as a condition of marketing authorisation(**e.g. where voluntarily proposed by the MAH/MAA and agreed with the competent authorities)**), these measures are included in the EU RMP. | |
| Lines 545 - 549 | | Comment: As noted before, EFPIA agree that joint studies are the ideal aim in order to minimise burden on the healthcare system but the logistical challenges of such an undertaking cannot be underestimated, particularly if multiple companies and Member States are involved. This aspect should be acknowledged as a single standard approach will almost certainly not be possible in every case and, hence need to be determined based on individual circumstances relevant to the benefit risk assessment, taking into account the risk, number of MAHs involved and number of EU member States in which a joint study needs to be conducted.<br><br>Proposed changes: For generic products, the effectiveness of risk minimisation measures should be assessed by the marketing authorisation holders in close cooperation with the competent | |

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|---|---|---|---|
| | | authorities. **In circumstances in which many MAHs are involved and/or when assessment involves multiple Member States, the logistics of any coordinated efforts needs to be carefully considered in order to reach a practical solution.** Where formal studies are justified, joint studies are strongly encouraged, **wherever possible and feasible,** in order to minimise the burden on the healthcare systems. | |
| Lines 558 - 560 | | Comment: Per Module VII C.5.6, evaluation of broad global experience will be reflected in the body of the report (VII Section B.16.5) as this is submitted to global agencies. This section of the report reflects findings with relevance across multiple regions globally.<br><br>Proposed changes: The applicant or marketing authorisation holder should report in the Periodic Safety Update Report (PSUR), results of the assessment of the effectiveness of risk minimisation (see VII.B.5.16.5 **for findings of global relevance and the Annex VII.C.5.6 for EU specific evaluation)** | |
| | | | |
| Lines 570 - 612 | | Comments: this section reflects general comments above, as it is a good example of where more detail, as well as additional requirements, are stipulated than contained in the original Module VII (in particular). Given that the PSUR is a global document, the | |

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|---|---|---|---|
| | | content of VII.B.16.5 needs to reflect global considerations and EU specific guidance needs to be reflected in the EU specific appendix (VII.C.5.6)<br><br>Proposed changes: When referring to the PSUR, this should reflect that it is contained in the appendix VII.C.5.6 and not VII.B.16.5<br>Detail should either be deleted from this section and cross referenced to the relevant section in Module VII or the detail should be the same as in the equivalent sections of Module V and VII.<br>Line 580 should reference the EU appendix ( VII.C.5.6)<br>Lines 584- 585 should stipulate that analysis of process and outcome indicators should occur where feasible and appropriate ( per earlier comments)<br>Lines 588- 600 delete from this section and move to VII.C.5.6<br>Lines 599 – 600: Outcome indicators: (ie…..)should ~~normally~~ be the key end point when assessing the **effectiveness** ~~attainment~~ of risk minimisation measures ~~objectives,~~ **when these parameters are feasible to evaluate** | |
| Lines 604-612 | | Comment: again, this appears to be a situation when more detailed guidance is provided in this Module vs. Module 5. In addition, lines 607 – 608 indicate that where modules of the RMP have been updated, the impacted modules should be clearly highlighted in the cover letter. As this information is contained in Part 1 of the EU RMP template, it is unnecessary to repeat again in the cover letter.<br><br>Proposed changes:: Delete lines 607- 609 | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | |
|---|---|---|---|
| | | Move the remaining wording to Module V and VI , as appropriate or ensure that the wording, if retained here, is reflected in the other modules. | |
| Appendix 1 | | Comment: It is stated that surveys are “cross-sectional studies involving primary data collection from individual participants”, the term “study” is used several times and collection of biological samples are included among other methods. This may cause confusion between observational studies in patients treated with the product (to assess safety outcomes....), to be considered as PASS, and pure surveys to assess process outcomes (e.g. physician knowledge), which are not PASS.<br><br>Proposed change: The term “study” should not be used when referring to surveys conducted to assess process outcomes or a clarification should be added to avoid confusion with observational studies in patients. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2013

# Submission of comments on 'GVP Risk minimisation measures - selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| EGA - EUROPEAN GENERIC MEDICINES ASSOCIATION |
| [redacted] |

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

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

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# 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)<br>*(To be completed by the Agency)* |
|---|---|---|
| | The EGA welcomes this opportunity to comment on this GVP proposal incorporating new elements coming from the new pharmacovigilance legislation.<br><br>Although we fully understand and support the intention of the proposed module, the EGA members have a few comments. | |
| | The document has some examples, but we think a more practical document would suit better the purposes and the interests of all stakeholders. | N/A |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 68, 72, 101, 118, 121, 124, 173, 256, 560, 568, 575, | | The terms "benefit-risk balance" and "benefit-risk profile" are not used consistently throughout the Module.<br><br>"~~Risk-benefit balance~~" and "~~risk-benefit profile~~" should be amended to "**benefit-risk balance**" and "**benefit-risk profile**". | |
| 94 | | Amend typo "~~meassure~~" to "**measure**". | |
| 111-113 | | In the sentence "Technology advances, such as interactive web-based tools may gain prominence in the future in addition to the paper-based (...)", we think there should be harmonisation among the National Competent Authorities (NCAs), as some NCAs are accepting interactive web-based tools, while others are not accepting and therefore, there should be discrepancies in the way a risk minimisation activity is implemented across Europe. | |
| 183 - 185 | | Educational material can never be completely separated from promotional activities. It should mean that a sales rep is not allowed to tell a HCP that there is educational material and should not be allowed to hand that out. This is jeopardizing the safety of the patient.<br><br>Strongly suggest to rephrase: | |

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|---|---|---|---|
| | | Any educational ~~programme~~ **material** should be completely separated from promotional ~~activities~~ **material** and ....<br>**Activities following from educational program (other than brochures/leaflets) should be separated from promotional activities.** | |
| 189 | | Can you please clarify "unambiguous statement(s)" by providing examples, even if in an additional document or annex. | |
| 285-287 | | "A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by ~~a~~ **one or more** marketing authorisation holder**/s** or ..."<br><br>Rationale: Often different MAHs hold MAs for the same active substance. It should be clarified that for DHPCs a harmonised approach is desirable. | |
| 315-316 | | Please provide examples on these indicators, as the document should be more practical and not so subjective. | |
| 334 | | Amend typo "~~minimsation~~"to **"minimisation"**. | |
| 340 - 342 | | Further guidance on what exactly constitutes a PASS study as in the PV fee proposed ruling the EMA charges 43000 euro for a PASS assessment. The work involved in the assessment of a | |

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|---|---|---|---|
| | | survey to measure effectiveness of risk minimisation involves much less work than the assessment of a complex pharmacoepidemiology study with complex statistics. | |
| 354 | | Amend typo "~~adeguate~~" to "**adequate**". | |
| 385 | | Amend typo "~~reimbursment~~" to "**reimbursement**". | |
| 386 - 387 | | Although pre-existing resources and data may exist they may not be accessible for industry or at an unreasonable price and high effort. Surveys should therefore not be positioned here as a "second rate" to but as a practical solution. | |
| 395 | | Not all evaluations of risk minimisation are studies so the statement that those measurements should be obtained in the contact of a PASS is incorrect.<br><br>Should be rephrased as follows:<br>Such an evaluation should involve.... or cumulative incidence of an adverse reaction, obtained **for example** in the context of post-authorisation safety studies. | |
| 397 - 398 | | It is unclear how these frequencies can be obtained particularly when in 405 - 406 the use of spontaneous reporting information is disqualified. Further guidance would be appreciated. | |

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|---|---|---|---|
| 423 - 424 | | This should not only be overseen by national CAs but facilitated and enforced by them. | |
| 429 - 432 | | As some RMPs or risk minimisation measures are imposed by the authorities, or can be changed nationally by the authorities, the responsibility as described in this section cannot only lie with the MAH and EU QPPV but is shared with the authorities. | |
| 541 - 542 | | This requires a more proactive role of the competent authorities. Making documentation publicly available would enable companies to harmonise the risk minimisation. | |
| 541-544 | | When generic medicinal products are requested to implement/develop risk minimisation activities, a global approach should be used, to avoid multiple studies to be conducted. Even if generics' MAHs coordinate as a group, at least, 2 studies with the same objectives and the same population will be conducted. Duplication of costs and resources should be avoided. The Agency and NCAs should encourage a coordination approach among all MAHs involved. | |
| 545 - 549 | | If it is intended a generic product should join an ongoing prospective cohort study as conducted by the innovator line 545 should be changed:<br><br>For ~~generic products~~ **products available as brand as well** | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **as hybrid/generic**, the…. | |
| 636 - 638 | | Making publicly available should not be a recommendation but a "shall" This links in with some of the comments above. | |
| | | | |
| | | | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

UEMS-D/V

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

No comments – well done

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Comment: no<br><br>Proposed change (if any): | |
| | | Comment: no<br><br>Proposed change (if any): | |
| | | Comment: no<br><br>Proposed change (if any): | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<13/07/2013>

# Submission of comments on 'GVP module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (EMA/204715/2012)

## Comments from:

Dr Jürgen Beckmann, Germany

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# 1. General comments

| Stakeholder number<br><br>*(To be completed by the Agency)* | General comment | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

1. It should explicitly be made clear that additional measures should only under exceptional circumstances be introduced. Otherwise, health care professionals (HCPs) and patients will be flooded and possibly annoyed by materials and molested by phone calls of advisors, interviewers and monitors.
The fact that much advice is devoted to generics one can conclude that too many drugs, i.e. more than just new and extraordinary risky medicines are targeted.

2. It is unclear under which circumstances additional measures which, in medical terms, substantially exceed the safeguards outlined in the SmPC may be necessary. Too few examples are given, so that almost everything is left to the reader's phantasy.
The question therefore arises what kind of measures conceivably may be necessary to exceed what is advised in SmPCs and – if they seem really important – could and should not be remedied by improving the SmPCs.
What is clear, however, is that that those measures to which is given much emphasis in the guideline, i.e. tools aiming at improving the compliance of HCPs and patients with what is recommended in the SmPCs, are difficult to distinguish a) from materials used in teaching general medicine and b) advertising.
Not difficult to anticipate a scenario where lots of company representatives are competing in storming surgeries and hospitals with brochures and posters to be displayed in waiting rooms and corridors about how best to use drugs X or Y in order to achieve maximum safety (and effectiveness, of course…).

3. The requirement that those materials should not be for advertising does not prevent this kind of competition, and it seems naïve not to consider formally "neutral" information as advertising.
For material to have an advertising effect it is not necessary to use terms like "excellent" or "you should use X and will be healthy again within two days".
Indeed there is already a huge advertising effect induced by indisputably correct and formally neutral statements like "This drug X belongs to a completely new class of substances and was recently approved by the European Commission for the use against disease Y on the basis of studies showing its superiority over older drugs like Z. In order to achieve optimum benefit-risk you should use it as early as possible after being diagnosed with Y."

Also diary forms or booklets for chemical or physical data, such as blood sugar, body weight or blood pressure, with company logos, have will clearly have advertising effects, and company representatives will fiercely compete in bringing them to their target populations (HCPs and patients).

4 The proposed methodology considering the effectiveness evaluation of risk reducing measures shows several weaknesses:

a) The typical pre-post comparison is insufficiently addressed. At the time when a new drug is marketed for the first time it will be almost impossible to assess the effectiveness of specific safeguards which were introduced from the beginning. Only if risk reducing measures are started later it may be possible to assess their impact on the basis of pre-post comparisons.

One of the options for this presented as sometimes and cautiously applicable is the comparison of spontaneous ADR reporting rates. This should, however, for practical reasons be considered as lacking any value for the assessment of risk lowering actions under all circumstances. The reason for this is the considerable influence that those measures themselves will have on reporting behavior (e.g. risk awareness or over-confidence in the drug or the feeling of guilt).

b) Any survey would meet almost insurmountable problems in terms of participation bias, e.g. good doctors may either be particularly willing to engage themselves for the best of their patients or – on the contrary – refuse to participate due to too many patients and too little time to spend.

c) An important effect which would escape capturing by a study sponsored by a specific company would be the channeling to alternative medicines marketed by other companies. If those other drugs were even more dangerous the study result could show an improved safety profile with regard to the investigated medicine whereas the patients' risk had actually increased.

5. The descriptions of the fundamental tools are mostly non-specific and trivial and could likewise be used as general advice for how to teach geography to school children. HCPs might be angered by this. Also there are many redundancies and tautologies.

6. The term "risk minimisation" is a misnomer and should be replaced by "risk reduction" or "risk lowering", because the "minimum" is an ideal and extreme the value of which can in principle not be known, so that "minimisation" is always an unproven and unjustified claim (with the exception that the drug is withdrawn).

7. The term "benefit-risk" should consistently be used and not (as in the later part of the document) be replaced by "risk-benefit".

## 2. Specific comments on text

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|---|---|---|---|
| | | Comment:<br><br>Proposed change (if any): | |
| | | Comment:<br><br>Proposed change (if any): | |
| | | Comment:<br><br>Proposed change (if any): | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1st August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Pharmacovigilance department CBG-MEB (Medicines Evaluation Board – The Netherlands) |

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | How, when and in which format an evaluation plan should be submitted is addressed only marginally. It should be clarified that protocols need to be submitted according to the format of a PASS study. Incorporation of a summary or a paragraph describing what would be expected could be very helpful. | |
| | The discussion on EU level and national implementation of the risk minimisation measures is not clearly reflected. | |
| | The part on measuring the effectiveness:<br>Nothing is stated about the timing and frequency of the evaluations. This should be laid down in the study protocol but there is no guidance in the GVP. As this raises a lot of discussion during the procedures, it is important to achieve a consistent approach. MAHs sometimes want to evaluate very frequent using a survey, which might then be used as a tool to "market their drug". In this context, a standard time planning would also be nice. In the US there is the 3, 12 and 18 months evaluation. This could be added to this GVP and MAH should provide adequate justification if they want to deviate from this. | |
| | Outcome measures (process or final indicators) are difficult to assess since potential effects of the RMM | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | itself can often not be excluded.<br><br>The GVP document could benefit from adding (i.e. in ANNEX) some (hypothetical) examples (e.g. measuring effectiveness of DHPC, PPP, surgeon training etc). | |
| | Guidance on planning of the evaluation in term of timing and frequency, performing it and submitting the results is not discussed at all and important to be included in the GVP. This addition benefits both MAHs and regulators. | |
| | Please align with GVP Module X 'Additional Monitoring' stating that the MAH should include information on the status of additional monitoring in any material to be distributed to healthcare professionals and | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 68 | | Comment:Regarding ".. will be necessary to **manage** risk and/or improve the B-R.. " . Not only 'manage', also 'minimise' the risk.<br><br>Proposed change (if any):<br>Add 'minimise' | |
| 66 | | Comment: Regarding " the majority of the safety concerns may be .."<br><br>Proposed change (if any):<br>please add 'a medicinal product' here:<br>"the majority of the safety concerns **of a medicinal product** may be .." | |
| 131 | | Comment: Tt is stated that "the rationale for additional risk minimisation measures should include *defined objectives*". It is suggested to use these objectives also to verify the effectiveness of the measures (are the desired effects reached?).<br>However, the GVP does not describe that these " defined objectives" should be used as outcome measures in the evaluation of effectiveness or should be mentioned in the protocol etc. This would facilitate the evaluation in later stage. So please make sure the objectives are laid down at correct | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | places. | |
| 138 | | Regarding the implementation plan: The actual implementation of RMM occurs at national level, and could vary between countries. It may be confusing that MAHs need to submit an implementation plan with detailed proposals at EU level as well. How should such EU plan be assessed ? Does it make sense to ask for a “general” implementation plan?. Also it is unclear what should be included in this plan. | |
| 149 | | It is stated that only “science based” additional risk minimisation measures should be proposed. This is impossible. Please remove this from the GVP. | |
| 156 | | It is stated that “If additional risk minimisation measures are *requested*”…<br>These are not always *requested*.<br>Please change this into “ necessary” | |
| 168 | | Regarding “.. providing clear and concise messages”<br><br>Please add “**preferably leading to actions of the target group”** to this sentence | |
| 201 | | It is stated that educational tools could provide “guidance on how and where to report adverse reaction of special interest”. This should be changed in “reporting adverse reactions” in general, not only the AEs of special interest. If applicable, adverse reactions of special interest could be specified. | |
| 243 | | Please add the following example of controlled access:<br>- Prescription is restricted to those Health Care | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Professionals that participated in an educational program | |
| 259 | | Please add a statement that controlled access programmes need to be carefully agreed with clinical practice at national level. Differences in prescription practices, reimbursement etc do exist. Please refer to section XVI.B.3 implementation of RMMs. | |
| 278 | | “monitoring of the programme performance” sounds like the mandatory evaluation of effectiveness. This is not an objective of the PPP itself. Please remove this or rephrase. | |
| 290-303 | | Implementation of RMM. Please elaborate more on this topic, for example “What are the responsibilities of the MAH to implement?’. Please emphasize the EU and national implantation! The information on distribution is provided but too limited to get clear idea’s what is expected (how often should that be distributed?).<br>Suggest a minimum. | |
| 298-303 | | Submission of promotional material by MAH’s is outside the scope of national competent authorities (NCAs). The way it is worded now in line 298/299 can be interpreted in a way that promotional material will also be reviewed by NCA. The same with the last lines (302/303) in this paragraph: distribution systems of promotional material is outside the scope of NCAs. It is suggested to reword these phrases. Please note that line 300-302 [Furthermore … material.] is very clearly stated. | |
| 306 | | It is stated that if intervention is not effective, the MAH should explain why. It might be impossible to explain why an | |

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|---|---|---|---|
| | | intervention was not successful; this can only be suggested by the MAH. | |
| 311 | | As mentioned in a previous comment, please state somewhere that the RMMs need to be evaluated using the pre-defined objectives; these objectives should be considered as outcome measures. Furthermore, please **provide guidance on how to define adequate pre-defined objectives and outcome measures i.e. knowledge level, behaviour, occurrence of AEs**. Also it should be clarified where in the RMP and study protocol this should be laid down. This is the basis for a consequent and adequate evaluation and well-defined RMMs! | |
| 319 | | Sentence "whether the intended impacts on behaviour have been observed". It is not only behaviour that's impacted, also knowledge.<br>Please add "**and knowledge".** | |
| 345-349 | | Please make it more explicit that process and outcome indicators are complementary to each other **and both should be used in an evaluation.** | |
| 334 | typo | Typo 'minisation'; change to minimisation | |
| 345 | | Please clarify in this paragraph whether an evaluation that only considers process indicators can be acceptable. Similar comment on Section XVI B.4.2 on outcome indicators. | |
| Appendix I | | Very useful! | |
| 300-400 | | Please emphasize the need for careful consideration of the methodology to be used. The products with RMMs are complicated, often used in hospital and often use less standard care. Consider this in the type of data to be collected | |

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|---|---|---|---|
| | | or database to be used. This is an important aspect leading to challenges in evaluation of RMMs, and is worth addressing in the GVP. | |
| 389-419 | | Regarding evaluation of RMMs; it is not clear at which level this should be performed. EU wide? Or some EU countries? As the implementation of the RMMs differs between all EU MSs, results of the effectiveness can not be extrapolated. The way in which data will be collected, target groups to be included in the evaluation studies may differ across EU Member States. Which approach should be taken by the MAH? This is not addressed at all. Often not all MSs are included in the evaluation. Is this acceptable? Is there a minimum to be set? | |
| 420-427 | | When additional RMM have been agreed for an innovator/reference product these in principle also apply for generic products. However the practical implementation may be more complex since multiple different MAHs are involved. *I.e.* there may be legal obstructions for the Regulatory Authority to share the already agreed (but proprietary) innovator's RM materials with the generic companies.<br><br>In terms of consistency and efficiency/speed of the review/implementation process this should be considered especially since there often are multiple generic products/MAHs. | |
| 526 | | “Clearly define objectives?” Where should this laid down? Suggest to introduce this earlier in the GVP, it should be very | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | clear for MAHs and regulators. | |
| 538 | | Somewhere in the GVP, please add a section on "consequences of the evaluation of RMMs". | |
| 570 (section XVI.C.2 | | It is stated that results of the assessment of the effectiveness of RMM should be included in the RMP.<br>However, the RMP is a planning tool, so in stead of saying what 'the focus' should be, the wording could be more precise stating that only conclusions and new milestones should be listed in the RMP. | |
| | | | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20th June 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Mundipharma Research |

*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<br>*(To be completed by the Agency)* | General comment | COMPANY COMMENT |
|---|---|---|
| | | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | COMPANY COMMENT) |
|---|---|---|---|
| LL146-148 | | Comment: this paragraph reads as if additional risk minimisation can only be imposed and not entered into voluntarily by the MAH if they feel it is needed.<br><br>Proposed change (if any): while routine measures are applied to every medicinal product... additional risk minimisation activities should only be proposed when they are deemed necessary for the safe and effective use of the medicinal product. | |
| LL405-419 | | Comment: This section should be clarified to state that routine PVG to monitor effectiveness of routine risk minimisation is acceptable in order to avoid disproportional expectations for monitoring effectiveness as is suggested in LL599.<br><br>Proposed change (if any): First sentence inserted as follows and the beginning of line 405 adjusted. Methods to measure the effectiveness of risk minimisation should be proportionate to the risks being minimised, as such the use of spontaneous reporting rates may be acceptable in the context of routine risk minimisation. Spontaneous reporting rates (...) should be considered with caution when estimating the frequency of adverse events in the treated population... | |
| LL441-442 | | Comment: For open access web-based materials it is not possible to track recipients unless log-in details are required. As online resources are continually updated it would not seem necessary to do so and reduce uptake of the materials. Therefore this text should be updated to specify that such tracking is not necessary for online tools. | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | COMPANY COMMENT) |
|---|---|---|---|
| | | Proposed change (if any):LL442 ...recipients of any risk minimisation tools, other than those which are only accessible in the current version e.g. web-based materials. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Pfizer Inc |

*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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | Overall, this draft guidance document is clear and logical. We agree with EMA's assessment that this is an emerging regulatory science and that strong science is needed to develop and rationalize routine and non-routine risk minimization measures (RMM). We also agree that non-routine RMM should be clearly identified as such to distinguish from many other types of health and safety information that physicians, pharmacists, patients, caregivers, and other stakeholders receive. | |
| | To be successful, a risk management plan should engage all healthcare stakeholders, including patients, regulators, and marketing authorisation holders (MAHs). When additional RMM beyond routine pharmacovigilance are required, the overall burden on the healthcare system should be considered. As a matter of practicality, the least burdensome measures that accomplish the goal of minimising the specific risk should be implemented. Thus, the concept of "undue burden" should be inserted into the module as a recommended consideration when planning and implementing additional risk minimisation | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | interventions. | |
| | While Pfizer supports the application of effectiveness metrics to assess additional RMM, the rationale for extending such measurements to routine risk minimisation is not clear. Pfizer recommends that the application of effectiveness metrics be restricted to additional RMM, under ordinary circumstances. Further, the Agency should clarify, with examples, when effectiveness assessments of routine RMM might be contemplated. | |
| | Endpoints for assessing the effectiveness of non-routine risk minimisation interventions should be feasible to apply and relevant from a time perspective. Thus, while overall outcomes are important, e.g., death as a consequence of liver failure, there may be “softer” measurements that are actionable, i.e., safety-related outcomes of interest, such as periodic monitoring of liver function test results or granulocyte counts, that could be applied on an interim basis to facilitate early detection of risk and permit dose adjustments (or discontinuation). Mention of safety-related outcomes of interest with alternative endpoints should be made in the module. | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | Also, a step-wise approach could be considered, if appropriate for the medicinal product and the risk involved. | |
| | Additional detail on the practical implementation of non-routine RMM and their evaluation would be desirable. For example, it would be helpful to have information about:<br>• *Under what specific circumstances* either the MAH or EMA should consider implementing non-routine RMM;<br>• *Which additional* RMM tools (e.g., education, controlled access programmes, or other tools) might be appropriate under which circumstances;<br>• *Which* evaluation techniques for non-routine RMM might be appropriate under what circumstances; and<br>• *What might be appropriate timing or frequency* for application of non-routine tools and evaluation techniques in a typical program | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | The role of individual Member States in approving local variations to non-routine RMM and their evaluation programs should be clarified vis-a-vis the Pharmacovigilance Risk Assessment Committee (PRAC). As written, it appears that MAHs could be required to develop vastly different versions for each of the Member States (beyond translations or minor adjustments for local practice) of a non-routine RMM and evaluation programs to accommodate local medical practice. This variation could be a significant barrier to effective implementation and interpretation of the effectiveness of non-routine RMM because varying RMM programs could necessitate different operational, logistical, scientific, and effectiveness measures. This is likely to be a significant resource burden, be unduly complicated to implement, and the introduction of confounders into disparate data would likely to lead to uninterpretable measures of the program's effectiveness as a whole. | |
| | Responsibility for routine and non-routine RMM programs for generic drugs with multiple MAHs is not clear – while sharing is "encouraged", it is not clear whether existing | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | generic products would be subject to the same RMM programs as a new applicant for the same generic. Suggest clarifying. | |
| | The role and value of social/behavioral sciences in the creation of effective evidence-based non-routine RMMs and their evaluation could be strengthened and further clarified by the Agency. For example, additional guidance on the use of qualitative research methods to evaluate the effectiveness of risk communication to both healthcare professionals (HCPs) and patients would be helpful. This is useful to identify variations in the effectiveness of non-routine RMM across cultures and socio-demographic categories of patients (e.g., gender, socioeconomic status, health literacy levels, and age). Equally important is to understand the most effective evidence-based communication modalities for HCPs. Qualitative research methods can inform the development and assessment of such modalities (e.g., Dear Healthcare Professional Letters, treatment protocols, and checklists that can be tailored for patients and incorporated into an electronic medical record or electronic prescribing system). Additional methodologies, such as shared-treatment decision- | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | making by HCPs and patients, could be used to evaluate the effectiveness of risk messaging and could also provide a basis for effective counseling to the patient along with informed consent that describes proper use conditions for the product, possible risks, and measures to mitigate risks. In addition, such methods could frame a structure for the HCP to instruct the patient on the safe and appropriate use of the product(s). | |
| | Specific proposed changes are highlighted with **bold underlined** text. | |

**2. Specific comments on text**

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 70-73 | | Comment: The intended meaning of this statement is unclear because it implies that an MAH should regularly apply metrics to routine RMM without a rationale for doing so: "However, it should be understood that the principles for evaluating the effectiveness of risk minimisation measures may also be applicable to the evaluation of routine risk minimisation measures, particularly where important for the risk-benefit balance of the product."<br><br>Proposed change:<br><br>Revise line 70 "However, it should be understood that, **in certain limited instances**, the principles for evaluating the effectiveness of risk minimisation measures may also be applicable to .... balance of the product. **The application of effectiveness metrics would ordinarily be applied only to additional risk minimisation measures and not to routine risk minimisation measures.** | |
| 93 | | Comment: The Report of CIOMS Working Group IX is being prepared with much practical insight and it would be a useful companion to this GVP module. This CIOMS report is already referenced in the text for section IV of the EU RMP template (EMA/718034/2012, as corrected).<br><br>Proposed change:<br><br>Revise line 94: "... European regulatory network. **Further practical guidance may be obtained from the Report of CIOMS Working Group IX, Practical Approaches to Risk Minimisation for Medicinal Products**." | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 109 | | Comment: When additional RMM beyond routine pharmacovigilance are required, the overall burden on the healthcare system should be considered. As a practical matter, the least burdensome measures that accomplish the goal of minimising the specific risk should be selected. Thus, the concept of "undue burden" should be inserted into the module as a recommended consideration when planning and implementing additional risk minimisation interventions.<br><br>Proposed change:<br><br>Revise line 109: "... measures will be necessary. **When planning and implementing additional risk minimisation measures, consideration should be given to the potential additional burden on the overall healthcare system and its individual components. The least burdensome measures that accomplish the goal of minimising the specific risk should be selected. This includes measurements of tool effectiveness**." | |
| 131-133 | | Comment: Rationale and objectives for non-routine RMM are combined in the same section, which makes the guidance confusing. This text apparently is intended to complement the subsection of Part V (risk minimisation measures) of the EU RMP template (EMA/718034/2012, corrected 10 April 2013) that focuses on "Additional risk minimisation measure(s)." Guidance provided in the template indicates that this subsection of the template may be repeated. Thus, it would be logical to separate the rationale for any additional measures, i.e., non-routine RMM, from the objectives, i.e., outcomes, of each specific measure. | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change:<br>Revise line 131 and separate into two bullets:<br>"● **When a non-routine risk minimisation measure(s) is needed to ensure that a product's benefits outweigh its risks, a rationale should be provided** ~~**Rationale**~~ for the~~**se**~~ additional risk minimisation measure**(s). Each additional risk minimisation measure should be** ~~(~~linked to **a** specific safety concern**(**s). **:** This section should set out the rationale for the proposed additional risk minimisation measure(s);<br>"~~● which should include defined objective(s) for e~~Each of the additional risk minimisation measures proposed~~. There~~ should ~~be~~ **have** a **defined objective(s) and a** clear description of how the additional risk minimisation measure**(s)** proposed will address a specific safety concern;" | |
| 183-185 | | Comment: Clarity on the distribution of educational materials is needed. The guidance states "Any educational programme should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes should not be used for promotional activities." To maximise effectiveness of non-routine RMM, it would seem appropriate to use established and available networks to distribute educational materials in addition to any specialised distribution channels that may be needed. For example, the MAH's field sales staff could be used to distribute educational materials to HCPs as long as promotional materials are not distributed/discussed during the same visit. Note that field sales staff currently distribute routine RMM, e.g., SmPCs, to HCPs. | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change:<br>Revise line 185: "... promotional activities. **However, there may be instances when the MAH's field staff, including sales staff), for example, could participate in distribution of educational materials to health care providers as long as there is a strict separation of activities, i.e., promotional materials cannot be distributed or discussed during the same visit as educational materials for a non-routine risk minimisation programme are distributed**." | |
| 195-197,<br>202-203 | | Comment: "In addition to an introductory statement that the educational material is *mandatory* as a condition of the marketing authorisation in order to further minimise important ..."(Italics added.) This complements guidance provided in Module V.B.9.2., but a description of the notification process is lacking. When and how will the MAH be notified that the educational tools (or other non-routine RMM) are mandated by the HA?<br>Proposed change:<br>In section XVI.C.1., provide additional description of the timing, process, and procedure for notification to the applicant or marketing authorisation holder that non-routine RMM will be required. | |
| 213-218 | | Comment: More guidance is needed in Module XVI on the format/design of educational tools. Module V.B.11.2 (p.42) states the following:<br>"For public health reasons, applicants/marketing authorisation holders for the same active substance may be required by the | |

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|---|---|---|---|
| | | competent authority to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorisation applicants/holder are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material<br><br>Further extensive guidance on additional risk minimisation measures is provided in Module XVI."<br><br>We recommend that language similar or identical to that in Module V be provided. Please also clarify the use of product brand colours in educational materials if only one applicant or marketing authorisation holder is involved.<br><br>Proposed changes:<br><br>(a) Revise line 218: "Other formats may be preferable, depending on the scope of the tool. **When there is a single applicant or marketing authorization holder, product brand colours may be included in educational materials to strengthen the association of the risk minimisation measure with the risks of the particular product. This may necessitate modification when generics enter the market**."<br><br>(b) Insert new paragraph after line 218 : "**For public health reasons, applicants or marketing authorisation holders for the same active substance may be required by the competent authority to have educational material with as similar as possible layout, content, colour and** | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, the applicant(s) and marketing authorization holder(s) are strongly encouraged to avoid the use of company logos or other trademarked or patented material in educational material."** | |
| 247-250 | | Comment: Inclusion of specific requirements of EU Member States on practical aspects of implementation by MAHs would be helpful.<br>Proposed change:<br>Add information on national requirements, perhaps in tabular form. | |
| 284 | | Comment: A Direct Healthcare Professional Communication (DHPC) represents a way to inform HCPs of the availability of educational materials, or other non-routine RMM. Usually, a DHPC is not a letter to the HCP that contains the actual additional risk minimisation measures (e.g., educational programme and tools), but rather only a means of notifying HCPs that these measures exist and explaining where they can be found.<br>Proposed change:<br>Revise line 289: "... a medicinal product (see Module XV). **Ordinarily, a DHPC is a means of notifying healthcare professionals that an additional risk minimisation** | |

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|---|---|---|---|
| | | **measure(s) exists for a product and provides summary information on the concerned risk(s) and a description of the non-routine measure(s) intended to minimise that risk(s). DHPCs can also provide instructions on how to obtain additional information. DHPCs should not be used to reply to enquiries to healthcare professionals, nor are they intended to be comprehensive educational material.**" | |
| 290 | | Comment: This section is silent on controlled access programmes, including distinction at the national level, which should be included.<br>Proposed change:<br>Add information on EU Member State requirements. | |
| 307-308 | | Comment: It may not be feasible to completely adhere to the following guidance in all instances: "The evaluation should be performed for the risk minimisation tools individually and for the risk minimisation programme as a whole." For example, implementation of an HCP Checklist and a Patient Alert Card will not permit a simultaneous evaluation of their relative effect in reducing the incidence of an AE post-intervention. Similarly, the individual contribution of an information brochure or a poster for clinics in enhancing HCP's knowledge about a particular risk cannot be ascertained. Guidance should accommodate such circumstances.<br>Proposed change:<br>"The evaluation should be performed for the risk minimisation tools individually **(when feasible)** and for the risk | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | minimisation programme as a whole." | |
| 329-335 | | Comment: It may be a challenge to precisely classify the findings into the indicated categories (no changes, modify existing activities, add activities) in certain studies, particularly those that evaluate the effectiveness of additional risk minimisation activities. An additional possibility would be to eliminate non-routine measures entirely if all objectives have been achieved in a sustainable manner. It would be helpful to have further guidance on this, e.g., what are some of the indicators that could be used to classify the assessment findings into the appropriate categories?<br><br>Proposed change:<br><br>Revise line 335: "... decreasing the number of tools or frequency of intervention). **In some instances, findings may support the elimination of non-routine measures entirely if all objectives have been achieved in a sustainable manner. Thus, results of effectiveness findings may be stratified into these categories:**<br><br>**"• No changes indicated;**<br><br>**"• Consider modifying existing activities;**<br><br>**"• Consider adding activities;**<br><br>**"• Consider full reliance on routine pharmacovigilance only.**<br><br>**"The following are examples of indicators that could be used to facilitate categorisation of effectiveness findings and, therefore, guide decision-making regarding possible adjustments to individual tools, or** | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **to the risk minimisation programme as a whole: (a) A survey conducted at 18-months following programme launch indicates that 100% of prescribers recall a specific risk and how to mitigate it (non-routine measure may not need to be changed); (b) A survey conducted at 36-months following programme launch indicates that 100% of prescribers recall a specific risk, but only 5% recall the measures that are in place to mitigate the risk (may need to increase efforts or modify educational programme regarding non-routine minimisation tools); (c)** *insert additional examples* **When evaluating possible adjustments to a non-routine activity, consideration should be given to choosing effective tools that minimise the burden on the healthcare system**." | |
| 336-339 | | Comment: This statement regarding unintended negative consequences is not clear.<br><br>One interpretation could be that the additional RMMs may (unintentionally) have a negative impact on the prescription/use of the product if the prescribers/patients do not fully understand the risk communication message/educational program: prescribers may be reluctant to prescribe the drug and instead use a less effective drug; patients may be reluctant to take the drug because of the associated risks (or request for an alternative drug), which in turn could affect the health outcomes.<br><br>Further, it will be helpful to have guidance on how unintended (negative) impact of risk minimisation intervention can be | |

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|---|---|---|---|
| | | assessed (e.g., Knowledge, Attitude, Behaviour (KAB) surveys could include questions to assess whether the non-routine risk minimisation activities will impact physicians' prescribing behaviour in a negative way (e.g. physicians may be less likely to prescribe the drug, denying access to patients who may benefit from the medication). Similar questions could be included in patient surveys to assess if patients may be reluctant to take the drug after receiving additional information about the associated risks.<br><br>Proposed change:<br><br>Revise line 339: "... long term. **The method(s) used to evaluate unintended consequences of non-routine risk minimisation activities may vary from programme to programme, and may encompass Knowledge, Attitude, Behaviour (KAB) surveys (patients, prescribers, dispensers, etc.) or other types of social science surveys, or pharmacoepidemiologic studies or other relevant assessments**." | |
| 340-341 | | Comment: Clarity on expectations regarding the timeline for a protocol evaluating the effectiveness of proposed non-routine RMM (i.e., post-authorisation safety study (PASS) protocol) is needed. It is not clear when a PASS protocol would need to be submitted to the Agency for review. It is to be noted that a PASS protocol cannot be fully developed until the proposed non-routine risk minimisation tools and the implementation plan are finalized (i.e, endorsed by the PRAC and CHMP).<br><br>Proposed change:<br><br>Revise line 343: "... should be considered as appropriate. **A protocol for a post-authorisation safety study designed** | |

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|---|---|---|---|
| | | **to measure effectiveness of risk management measures should be proposed to the Agency for review after the overall risk management plan is endorsed. Typical timing for submission of such a protocol would be within 90-days of the endorsement of the risk management plan.**" | |
| 358 | | Comment: Assessing the effectiveness of the SmPC is given as an example of assessing effectiveness of an informational tool. The SmPC is a routine risk minimisation tool, which is not the focus of Module XVI.<br>Proposed change:<br>Revise line 358: " ... information provision (for example, via ~~the SmPC~~ **an educational programme with a goal of preventing drug exposure during pregnancy**) ... " | |
| 361-363 | | Comment: Although it is reasonable to assume that the number and timing of the assessment surveys may vary by target population or by the risk being mitigated, it would be helpful if the Agency could advise on expectations regarding the number and timing of assessment surveys for a typical program.<br>Proposed change:<br>Revise line 363: "...over time. **The interval between surveys should take into account the time required for launch of non-routine activities as well penetration into the healthcare system. Thus, for example, a typical program might schedule a survey at 18-months and 36-months after the programme is launched, with additional survey(s) conducted only if necessary.** | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **Another programme might have different timing.** Such an approach may be tailored ..." | |
| 365 | | Comment: A random sample may not be feasible in all surveys, e.g., in case of limited number of potential survey subjects and/or expected low response rate, all subjects would need to be invited to participate in the survey.<br>Suggest modifying the statement to accommodate such situations.<br>Proposed change:<br>Revise line 365: "**Whenever feasible, a** randomised sample and an adequate sample size should be selected." | |
| 390-419<br>599-600 | | Comment: ADR frequency and incidence are given as the outcome measure to be obtained, but other clinical outcomes are not referenced. From both practical and ethical perspectives, this is not feasible, particularly for rare events or outcomes. The Module is silent on safety-related outcomes of interest, which may be more appropriate than a long-term systematic study. This would also permit a step-wise approach that could be tailored to the risk.<br>There also may be other situations when the frequency and/or severity of adverse reactions (even for a relatively old product) could not be assessed in a real world setting because of reasons such as 1) lack of appropriate database(s) that adequately captures patient-level data in the EU, 2) inadequate number of patients with drug exposure data for meaningful analyses, particularly for rare safety endpoints/outcomes, and 3) compilation of patient-level data/setting up a drug registry would not be feasible. In such | |

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|---|---|---|---|
| | | situations, assessment of 'process indicators' may be the only a viable option, the protocol (and study report) can include justification/discussion on not assessing an outcome indicator.<br><br>Furthermore, there may be situations where due to efficacy or nature of the disease, patients accept the risk of an adverse event based on a thorough understanding and acceptance of the risks and benefits; in such cases the rate of adverse events (i.e., outcome indicator) would be expected to be unchanged, but the non-routine RMM should be considered successful if effective benefit-risk (B-R) discussions and decisions are undertaken.<br><br>Proposed changes:<br><br>(a) Insert new paragraph after line 404: "... appropriately justified.<br><br>"**The concepts of safety-related outcomes of interest and step-wise assessments may be considered in appropriate circumstances. Refer to the Report of CIOMS Working Group IX, Practical Approaches to Risk Minimisation for Medicinal Products**."<br><br>(b) Revise line 392: "... and**, where feasible,** those safety outcomes should be the outcome indicator(s)."<br><br>(c) Revise line 395: "... obtained in the context of post-authorisation safety studies. **When it is not feasible to assess safety outcomes using real world data, assessment of process indicators may be a substitute. In such situations, the protocol (and study report) should include the rationale for not assessing an outcome indicator.** Under any | |

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|---|---|---|---|
| | | approach, scientific rigour ..."<br>(d) Revise line 600: "... endpoint when assessing the attainment of risk minimisation measures objectives. **If alternative safety-related outcomes of interest are selected, it may be relevant to use endpoints other than frequency or severity of adverse reactions**." | |
| 451-453<br>489 | | Comment: Guidance on the requirements for additional risk minimisation measures at the Member State level is lacking, particularly requirements related to controlled access.<br>Proposed change:<br>Provide guidance on the requirements for additional risk minimisation measures at the Member State level, particularly requirements related to controlled access. | |
| 571-572 | | Comment: Results of a study evaluating the effectiveness of additional RMM may not available several weeks/months after implementation of additional RMM. Suggest modifying the statement to include "when available".<br>Proposed change:<br>Revise line 571: "PSUR and RMP updates should include a summary evaluation of the outcome of specific risk minimisation measures implemented to mitigate important risks in the EU**, when available**." | |
| 571-587 | | Comment: In case of multiple communications with the Agency with regards to development and finalization of non- | |

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|---|---|---|---|
| | | routine RMM implementation plan or educational tools, it is not clear whether an updated RMP should be submitted with every communication, i.e., should an updated RMP be submitted to the Agency each time the Agency makes comments on a particular section?<br><br>Proposed change:<br><br>Revise line 572: "... mitigate important risks in the EU. **In line with V.C.5., the time schedule for "routine" updates will normally be provided as a condition of the marketing authorisation or as otherwise notified. Every minor change, e.g., clarification, to effectiveness assessments in the RMP does not automatically trigger an update, but an updated RMP should be submitted if there is a significant change in the planned effectiveness assessments or read-outs that could have an important impact on the additional risk minimisation measures or the benefit-risk profile of one or more medicinal products included in the RMP. Examples of an important impact include: (a) A planned survey will be expanded from HCPs to include patients and, as a consequence, the read-out will be postponed by 6-months; (b)** *insert additional examples.* In the RMP, the focus ..." | |
| 705-706 | | Comment: Individual level characteristics from non-responders (either HCPs or patients) may not be available in all surveys. Suggest modifying the statement to include "when possible".<br><br>Proposed changes:<br><br>(a) Revise line 705: "Data on no response or incomplete | |

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|---|---|---|---|
| | | response**, when possible**."<br>(b) Revise line 706: "Comparison of responders and non-responders characteristics**, when possible**." | |
| 718 - 728 | | Comment: Section XVI.App1.4. in the Appendix is entitled "Ethics, privacy, and overall study feasibility", but there is no mention at all of privacy considerations in this section (or any other section of the guidelines). It would be useful for privacy issues to be addressed in the Guideline.<br><br>Proposed changes:<br>(a) Revise line 719: "Ethical **and data privacy** requirements are not harmonised across EU Member States, with notable differences in national (or regional) processes."<br>(b) Insert table with national requirements for ethical and privacy requirements that relate to considerations and possible constraints in determining study feasibility. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

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

*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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators. | |
| | The draft Module XVI provides already some examples of risk minimisation tools, however, more examples especially regarding the evaluation of the effectiveness of risk minimisation measures would be helpful. | |
| | According to Module XV safety communication and measuring their effectiveness i.e received by target audience, knowledge and behaviour which is related also to Module XVI measuring effectiveness of a DHPC or educational materials with process indicators such surveys should not fall under the definition of a PASS. If a survey on process indicators is classified as PASS all quality checks of a DHPC or educational material distribution like receipt, failures, knowledge and behaviour change would require a PRAC assessment, such a quality control cannot really follow the guidance on PASS protocols and reports (Module VIII) as the intention for this module was different and has not considered a quality check of distribution for DHPCs or educational materials. This is also demonstrated by the | |

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|---|---|---|
| | Appendix 1 Key elements of survey methodology which are not in line with Module VIII and would not be needed if it would relate also to process indicators.<br>Only effectiveness measures targeting the outcome indicator as criterion should be considered a PASS. Otherwise the burden for the pharmaceutical industry would not be in relation to the intention of this module. This would also be in accordance to line 599 to 600 stating that the outcome indicators are key for the effectiveness assessment of additional risk minimisation measures. | |
| | It should be clearly differentiated within the Module XVI if “additional” risk minimisation measures are meant or also “routine” risk minimisation measures. At the moment it is mixed within the module and not clearly differentiated. For example concerning the effectiveness measurement (in process or outcome indicators) now all Non-interventional studies (NIS) would classify as a PASS as also the SmPC (contraindications/warnings) as routine risk minimisation measures are captured in this section. All NIS are focusing of the safe use of the product including following the SmPC or drug utilizations studies i.e amount of “off-label use” which would also investigate the wording in the SmPC related to indication or dose adjustments due to renal impairment. There would be no situation in which a NIS would not be a PASS. Please specify that this is only related to | |

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | “additional” risk minimisation measures investigating outcome indicators. | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 113 | | Comment:<br>Paper based information is also the SmPC and the PL and the educational materials are targeting focused additional information.<br><br>Proposed change (if any):<br>Delete: paper-based information<br>Should read:<br>…gain performance in the future in addition to the paper based **additional** educational materials | |
| 129 | | Comment:<br>The “risk minimisation plan” is not a part of the RMP it is a subpart in Module V and even no longer on the guidance on format of the RMP Part V<br><br>Proposed change (if any):<br>**The risk minimisation measures** an integral part of the RMP, should therefore give appropriate consideration to the following parts: | |
| 139 - 140 | | Comment:<br>Implementation plan is newly introduced in this context and not part of Module V nor in Guidance on Format for Module V of the RMP<br><br>Proposed change (if any): | |

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|---|---|---|---|
| | | **The section Proposed actions/components** should provide a detailed proposal…… | |
| 141 - 143 | | Comment:<br>Evaluation plan is newly introduced in this context and not part of Module V nor in Guidance on Format for Module V of the RMP.<br><br>Proposed change (if any):<br>**Planned dates for assessment:** This section should provide….. | |
| 156-158 | | Comment:<br>Request is not defined in the module<br><br>Proposed change (if any):<br>If additional risk minimisation activities are **suggested, the rationale should** be clearly documented, should be linked to a specific safety concern and sufficiently detailed in the RMP part risk minimisation measures. | |
| 159 | | Comment:<br>Distinguish between routine and additional risk minimisation measures<br><br>Proposed change (if any):<br>XVI.B. describes **additional** risk minimisation measures that should be considered in addition to the routine measures, including: | |

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|---|---|---|---|
| 170 | | Comment:<br>Risk is sometimes used instead of Safety concerns as the RMP represents only important risks and not all risks<br><br>Proposed change (if any):<br>.and patients towards minimising **safety concerns**. | |
| 172 | | Comment:<br>Important risk is selected here instead of safety concerns as this would not capture i.e. important missing information.<br><br>Proposed change (if any):<br>..and that applying this measure is considered important for minimising **safety concerns**/or for… | |
| 174 | | Comment:<br>Safety concerns is missing in the sentence<br><br>Proposed change (if any):<br>.., can address more than on **safety** concern and .. | |
| 175 | | Comment:<br>Materials are mentioned but defined<br><br>Proposed change (if any):<br>Ideally, **additional educational materials**… | |
| 181-182 | | Comment:<br>Risk is sometimes used instead of Safety concerns as the RMP represents only important risks and not all risks | |

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|---|---|---|---|
| | | Proposed change (if any):<br>..the **safety concern**(s) related to the product and the management of those **safety concern**(s) requiring additional risk minimisation. | |
| 190 | | Comment:<br>Risk is sometimes used instead of Safety concerns as the RMP represents only important risks and not all risks<br><br>Proposed change (if any):<br>..regarding the **safety concern** to be addressed with the proposed tool, the nature of such **safety concern**(s) and the specific.. | |
| 198-199 | | Comment:<br><br>Proposed change (if any):<br>.., in order to minimise **selected important** risks | |
| 216 | | Comment:<br><br>Proposed change (if any):<br>..awareness of specific **safety concerns** with focus on the early recognition | |
| 230 | | Comment:<br><br>Proposed change (if any):<br>..therapy and its **safety concerns** (e.g. potential… | |
| 239 | | Comment: | |

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|---|---|---|---|
| | | Proposed change (if any):<br>..measure(s) due to the public health impact of the **safety concern**. | |
| 234-259 | | Comment:<br>Please clarify that a controlled access programme as a risk minimisation measures even if organized data collection does not fall under the definition of a PSP (patient support programme) and spontaneous reporting should be followed<br><br>Proposed change (if any): | |
| 261-267 | | Comment:<br>Please clarify that a Pregnancy Prevention Programme with a controlled access programme as a risk minimisation measures even if organized data collection does not fall under the definition of a PSP (patient support programme) and spontaneous reporting should be followed.<br><br>Proposed change (if any): | |
| 277 | | Comment:<br>Supply should only be limited to the population at risk i.e. woman of childbearing potential<br><br>Proposed change (if any):<br>Prescription limited to a maximum of 30 days supply **for the** | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | **population at risk** | |
| 278 | | Comment:<br>Monitoring of the programme performance would qualify as an effectiveness study and therefore as a PASS<br><br>Proposed change (if any):<br>Monitoring of the programme performance **i.e pharmacy self audits, and compliance measuring to the programme i.e pregnancy test results checks do not qualify for an effectiveness measure and therefore PASS as these are only process indicators** | |
| 281-283 | | Comment:<br>This section does not really fall under a Pregnancy Prevention Programme as it is a pregnancy registry focusing on the outcome of an exposed pregnancy and would qualify as a PASS<br><br>Proposed change (if any): | |
| 284-289 | | Comment:<br>Additionally to the reference to GVP Module XV – Safety communication - we suggest to provide also reference to Annex II – Templates: Direct Healthcare Professional Communication (DHPC)<br>Proposed change (if any): | |
| 290 | | Comment: | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Routine and additional risk minimisation measures are mixed<br><br>Proposed change (if any):<br>XVIB3 Implementation of **additional** risk minimisation measures | |
| 304 | | Comment:<br>Routine and additional risk minimisation measures are mixed<br><br>Proposed change (if any):<br>XVIB4 Effectiveness of **additional** risk minimisation measures | |
| 306 | | Comment:<br>Typo succesful<br>Proposed change (if any):<br>succes**s**ful | |
| 307 | | Comment:<br><br>Proposed change (if any):<br>..The evaluation be performed for the **additional** risk minimisation tools.. | |
| 316 | | Comment:<br>See general comment<br><br>Proposed change (if any):<br>Outcome indicators **measurement would qualify for a PASS** | |
| 320 | | Comment:<br>Implementation metrics… | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change (if any):<br>Please provide examples for implementation metrics. | |
| 324 | | Comment:<br><br>Proposed change (if any):<br>..specified **safety concerns** | |
| 325-328 | | Comment:<br>It should be clarified that outcome indicator as an objective qualifies for a PASS.<br><br>Proposed change (if any): | |
| 340 | | Comment:<br>The concept of in process and outcome indicators is not clearly defined and should be clearly defined or distinguished as a process indicator is not measuring effectiveness it is only a process or quality check.<br><br>Proposed change (if any):<br>The legislation defines “any study…measuring the effectivness of risk **miminisation** measures” as a post-authorisation safety study. **Only studies measuring the effectiveness via outcome indicators of risk minimisation measures are considered to fall under this definition.** | |
| 354 | | Comment:<br>Typo | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change (if any):<br>..(e.g. ade**q**uate language.. | |
| 373-374 | | Comment:<br>Electronic records are not always available<br><br>Proposed change (if any):<br>Drug utilisation studies by means of secondary use of (e.g. electronic) records should be considered as a valuable tool to quantify clinical actions, if representative of the target population. | |
| 414 | | Comment:<br>Typo<br><br>Proposed change (if any):<br>..in response to a safety **concern** detected… | |
| 429 | | Comment:<br><br>Proposed change (if any):<br>..developing and implementing **additional** risk minimisation measures | |
| 471 | | Comment:<br><br>Proposed change (if any):<br>..not imposed as a condition for marketing authorisation these **shall be** in the RMP | |
| 479 | | Comment: | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | The outcome is defined as outcome indicator in the RMP<br><br>Proposed change (if any):<br>..of the outcome **indicator** of risk minimisation measures which comprise additional.. | |
| 484 | | Comment:<br>The outcome is defined as outcome indicator in the RMP<br><br>Proposed change (if any):<br>..should evaluate the outcome **indicator** of **additional** risk minimisation measures,.. | |
| 488 | | Comment:<br><br>Proposed change (if any):<br>…the effectiveness of risk minimisation measures **focused on outcome indicators.** | |
| 552 | | Comment:<br><br>Proposed change (if any):<br>..shall monitor the outcome **indicator** of **additional** risk minimisation measures | |
| 559 | | Comment:<br><br>Proposed change (if any):<br>**…**of the effectiveness of **additional** risk minimisation measures.. | |
| 568-569 | | Comment: | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change (if any):<br>..consideration to any **additional** risk minimisation measures.. | |
| 576 | | Comment:<br><br>Proposed change (if any):<br>..of the most recent **additional** risk minimisation measure(s)… | |
| 609-612 | | Comment:<br>Please clarify if for a variation application only the proposed changes must be captured in the PSUR and an updated RMP must not be submitted and can be submitted with the next routine submission with the changes captured.<br><br>Proposed change (if any): | |
| 643 | | Comment:<br>Typo<br><br>Proposed change (if any):<br>…data collection **from** individual participants. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| **Italian Society for Applied Pharmacological Sciences - Pharmacovigilance Working Group** |

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

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

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## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 52-54 | | Comment: to identify the risk/s. On which basis<br><br>Proposed change (if any): | |
| 67 | | Comment: what does it mean "sufficient" ?<br><br>Proposed change (if any): | |
| 82-83 | | Comment: is it really possible to monitor, i.e. to identify the correct minimization measure? I think it is only possible to place hypotheses about minimization.<br><br>Proposed change (if any): | |
| 89 | | Comment: additional to what?<br><br>Proposed change (if any): | |
| 101-104 | | Comment: it might be indicated a timeline to assess the benefit-risk balance, i.e. every 3, 6 12 months after the identification of a new risk or a new signal ?<br><br>Proposed change (if any): | |
| 110-111 | | Comment: what is it meant by "tools" ? It might be a good | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | idea to list those developed up to now.<br><br>Proposed change (if any): | |
| 119-120<br>122-123 | | Comment: additional to what?<br><br>Proposed change (if any): | |
| 151-152 | | Comment: why should it be excluded: a possible mistake, abuse or misuse is always possible.<br><br>Proposed change (if any): | |
| 154 | | Comment: this is a relevant item: LASA drugs should be prevented.<br><br>Proposed change (if any): | |
| 159-160 | | Comment: the "routine measures" haven't been clearly defined as yet.<br><br>Proposed change (if any): | |
| 173-174 | | Comment: minimization should also take care of different "understanding" or cultural capacities ?<br><br>Proposed change (if any): | |

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|---|---|---|---|
| | | | |
| 262-263 | | Comment: what does it mean: "to minimize pregnancy exposure" in this cases? There is only one way: avoidance of treatment.<br><br>Proposed change (if any): | |
| 277 | | Comment: why a 30 days period?<br><br>Proposed change (if any): | |
| 306 | | Comment: what about to add an example of a successful intervention ?<br><br>Proposed change (if any): | |
| 541<br>604 | | Comment:<br><br>Proposed change (if any): generics (in place of generic products) | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05.08.2013

# Submission of comments on draft guideline on good pharmacovigilance practice module XVI

## Comments from:

| Name of organisation or individual |
| --- |
| F.Hoffmann – la Roche |

*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<br>*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)<br>*(To be completed by the Agency)* |
|---|---|---|
| | | |

## 2. Specific comments on text

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|---|---|---|---|
| Lines 71-73 | | Comment: As RMPs should only include risks that are important for the risk-benefit balance of a product, does this indeed mean that all routine minimization measures must be evaluated?<br><br>Proposed change (if any): | |
| Line 72 | | Comment: As currently written in Line 72, is the EMA truly imparting the concept of an additional categorization of an important safety concern beyond what is described in GVP V?<br><br>Proposed change (if any): | |
| Lines 71-73 | | Comment: If routine risk minimization activities are indeed within the scope of measurement of effectiveness, further guidance should be provided to MAHs to consider and to minimize variability across assessors and rapporteurs for this endeavour.<br><br>Proposed change (if any): Additional written guidance as stated above. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| Lines 141-143 | | Comment: Additional guidance should be provided in determining what is an acceptable evaluation plan. It is anticipated that MAHs would develop an evaluation plan to include select territories as appropriate and it needs to be acknowledged that not all EU territories may be reflected in the evaluation of effectiveness.<br><br>Proposed change (if any): Additional written guidance as stated above. | |
| Line 156-158 | | Comment: The current sentence is ambiguous in its intent based on the information provided in the beginning of this section. Is the intention here to describe when MAHs propose additional risk minimisation activities thus prompting the rationale for the request? Or is this to be interpreted when the Health Authorities makes the request?<br><br>Proposed change (if any): Please provide additional clarity. | |
| Lines 179-185 | | Comment: Specific guidance is warranted to prevent misalignment in the interpretation of this concept between HAs and MAHs in areas such as the level of accepted rigor, the accepted burden of proof in demonstrating such a partition, etc.<br><br>Proposed change (if any): Additional written guidance as stated above. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| Lines 195-196 | | Comment: It is anticipated that such an introductory statement is to be applied only to new educational materials. However, if this is not the case and this statement is to be applied to existing educational materials, this must be made absolutely clear with additional implementation guidance for the MAHs.<br><br>Proposed change (if any): Please see above. | |
| Line 201 | | Comment: This aspect appears to be a PV activity and not strictly an additional risk minimization measure. This should be acknowledged and described accordingly.<br><br>Proposed change (if any): Clarification as suggested from above. | |
| Lines 237-239 | | Comment: The expected threshold for meeting this criterion appears to be rather vague and may predispose general inconsistencies from one medicinal product to the next based on the individual discussions between the HAs and various MAHs.<br><br>Proposed change (if any): | |
| Lines 237-239 | | Comment: The current wording of this sentence should be reconsidered. While the benefits may still be achieved, they may still be outweighed by the important safety concern in | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | question.<br><br>Proposed change (if any): Please see above. | |
| Lines 307-308 | | Comment: By programme, is it correct to interpret the entire Risk Minimization Plan or simply the collection of risk minimization activities for the specific important safety concern? Greater clarity is requested concerning this sentence.<br><br>Proposed change (if any): Additional clarification needed. | |
| Lines 333-335 | | Comment: It remains unclear concerning the EMA's standard in determining the reasonable degree of substantiation provided by the MAH in successfully proposing such an action. Please provide additional guidance in this respect.<br><br>Proposed change (if any): Please see above. | |
| Lines 337-338 | | Comment: As unintended consequences would not have been initially conceived and thus included as evaluation endpoints, how could this credibly be assessed on a priori basis? Or is it the expectation of the EMA that this would be done in a post hoc manner once the evaluation of effectiveness is completed? If so, please clarify accordingly in the current sentence.<br><br>Proposed change (if any): Please see above. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | | |
| Line 356 | | Comment: There is still no guidance on the matter of the accepted standard or threshold for determining “success”. Please provide any additional guidance in this regard.<br><br>Proposed change (if any): Please see above. | |
| Lines 371-374 | | Comment: Target populations are likely to be the population of an entire country or several countries. Nationwide databases are available only in a limited number of countries. In many countries they do not exist.<br><br>Proposed change (if any): Exclude “if representative of target population”. A study conducted according to ENCePP guideline should include discussion on data source choice and related limitations. | |
| Line 390 | | Comment: As similarly commented for line 356, there is still silence on the matter of the accepted standard or threshold for determining “success”. Please provide any additional guidance in this regard.<br><br>Proposed change (if any): Please see above. | |
| Lines 541-551 | | Comment: Risk minimisation is described for generic products but risk minimisation for biosimilar products is not mentioned in this draft guideline. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | Proposed change (if any): Please clarify if biosimilars are also in scope of the discussion provided for generics. | |
| Appendix I | | Comment: The authors attempt to provide an overview of key points on design and conduct of surveys. This is difficult to do within two pages.<br><br>Proposed change (if any): It may be more helpful to explicitly guide the reader to reference ENCePP. | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 August, 2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| [redacted] RTI Health Solutions |

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# 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|

We applaud the Agency for developing such a thoughtful set of recommendations regarding risk minimization tools and effectiveness indicators. In general we support and concur with the guidance. We appreciate the opportunity to provide selected general and specific comments.

We reviewed this draft guidance based on our experience in the design and conduct of pharmacoepidemiology studies and experience evaluating risk minimisation programs [1-7]. Our experience in evaluating results from patient and physician surveys has demonstrated the utility of these evaluations: in some cases results are being used to improve the nature and content of educational programs; in other cases, these studies demonstrate that the Risk Minimisation Measures are working well.

**General comments:**

Regarding "Section XVI.B.2. Risk minimisation measure," we note the absence of any recommendations for testing risk minimisation tools in advance of implementing them. We strongly recommend the pre-testing of educational material through cognitive interviews with members of the intended audience prior to the distribution of such materials. Pretesting can identify important aspects of content, format, and word choice that will influence the ultimate utility of the material.

We are pleased that Section XVI.B.4 focuses on both process and outcome measures as evaluation targets. It is very important to measure both, even though it may not always be possible to draw a clear causal link between the process of providing specific education to providers and patients and observed behaviours and clinical outcomes. For example, we know from interviewing patients and physicians that there are some patients who elect NOT to read or use educational materials even if those materials are developed to be extremely relevant and user-friendly as they prefer to just do as their physician says and not be "worried" by all the possible side effects. In addition, some physicians may choose to counsel and monitor patients in a manner that differs from the recommended behaviours based on the unique circumstances of their individual patients. Therefore, it is important not to set unreasonable expectations regarding the desired process and outcome measures. It is also important to set indicators that are within the MAH control.

We also wish to draw attention to the fact that methods to evaluate prescribing and monitoring behaviour using drug utilization studies (DUS) can also include the use of chart abstraction in addition to electronic data sources (lines 372-376).

Regarding the selection of sampling frames for the conduct of physician and patient surveys of knowledge and behaviour, we wish to point out the difficulty of obtaining appropriate and comprehensive physician and patient lists as a starting point. Such lists are generally not available, or may have restrictions on their use. Nevertheless, use of advocacy groups or patient support groups can be considered to be inherently biased through self-selection, and should be avoided.

We note the absence of any specific guidance on adverse event reporting from these risk minimisation evaluations, particularly from cross-sectional surveys about knowledge and behaviour. In our work with multiple pharmaceutical sponsors of these types of studies, we have observed considerable confusion around the reporting obligations in these studies. In general, we believe these studies do not represent the most appropriate way of eliciting adverse event data. Moreover, adding adverse event reporting requirements to these studies can influence the study design and response rates in a manner that may result in lower or biased participation. We believe the study sponsors may benefit from some explicit guidance about the reporting expectations.

The guidance recommends that a representative sample of the target population be selected and notes that representativeness is important for the generalizability of the survey results. However, it should be noted that in some circumstances it is important to oversample certain segments of the population (i.e. ethnic/race, age, patients of lower socioeconomic status) to assure that the distribution of respondents adequately represents the important subgroups that are of concern. Proportional representation from a strict random selection process may exclude such groups. Therefore we recommend using the terminology "diverse" sample that includes representatives from each segment of interest in the target population as opposed to "representative sample". In addition it is mentioned that a randomised sample should be selected (i.e. line 365, 669). Although we agree that a random sample from a full list of available prescribers or patients would be ideal, randomisation of the list is only effective if the original list is unbiased and if the response rate is high. It might be helpful to enumerate factors that may influence response rates including use of incentives for completing surveys, the number of questionnaires the specific physician or patient group is asked to complete, the importance and relevance of the potential adverse event to the respondent, and the length and complexity of the questionnaire

We have focused our detailed comments below on Appendix 1: Key Aspects of Survey Methodology

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 643 | | Comment: Surveys are not always cross-sectional but can be longitudinal. Moreover, for consonance with standard survey definitions, we suggest including in the definition the fact that surveys involve collecting data from a sample for purposes of characterizing the larger population. Also note this definition is different than definition provided in 361-363 "A survey generally includes a core of standard questions administered through telephone contact, in-person interview, or self-administered through postal/electronic communication, which are repeated over time."<br><br>Proposed change: "Surveys are systematic methods of collecting primary data directly from a sample of participants from a larger population, conducted in order to characterize the large population and may be cross-sectional (one-time only) or longitudinal (repeated over time)." | |
| 652 | | Comment: The expression "health conscious patients" may be overly narrow.<br><br>Proposed change: change "more health conscious patients" to "more motivated or educated individuals" | |
| 663-664 | | Comment: Technically, bias can be removed if the sample frame is increased to 100% of the population and the | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | response rate is 100%. The key point here should be that bias cannot be eliminated ONLY by increasing the sampling frame, sample size and response rate. Bias CAN be minimized by selecting the optimal sampling frame, and also assuring the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g., by oversampling a small but important subgroup).<br><br>Proposed change: Change wording to: "Bias cannot be eliminated only by increasing the sample frame, sample size and response rate. Bias can be minimized by selecting the optimal sampling frame, taking into account age, sex, geographical distribution and additional characteristics of the study population. Bias can also be minimized by assuring the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g., by oversampling a small but important subgroup). " | |
| 666-670 | | Comment: The existing sentence refers to the sample, not to the sampling frame. In addition, we generally refer to random selection of participants rather than "randomization."<br><br>Proposed change: Replace existing sentence with the following: "For example, in designing the strategy for randomly selecting the sample from the sampling frame for a physician survey, consider whether a general random sample would be sufficient or if the sample should be stratified by key | |

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|---|---|---|---|
| | | characteristics such as specialty, type of practice (e.g., primary care, specialist ward, academic institution). | |
| 686 | | Comment: The choice of the data collection approach should be guided by the data to be collected, not the inclusion and exclusion criteria.<br><br>Proposed change (if any): Replace "...and the inclusion and exclusion criteria of the study" with "...and the data to be collected." | |
| 713-717 | | Comment: these examples for stratification seem to be specific for prescriber surveys.<br><br>Proposed change: Either add examples of stratification for patients (i.e. age, sex, receipt of educational materials) or clarify that the list is an example for prescriber surveys. | |
| 721-728 | | Comment: We agree with the importance of conducting feasibility assessments prior to study implementation for many evaluation studies. The section currently applies primarily to studies that gather data from patients using a clinical site-based approach.<br><br>Proposed change: Clarify that these key elements are examples for feasibility assessment and relate to site-based patient assessment studies. Add statement that key elements of a feasibility assessment may be different for other study designs and for physician assessments. | |
| 719-728 | | Comment: Indeed there are many notable differences in | |

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|---|---|---|---|
| | | national and regional ethics and privacy processes and requirements. Two key differences that could be mentioned in the guidance are 1) differences in whether survey participants can be offered financial incentives or reimbursement for participation, and 2) privacy considerations in allowing contact with physicians based on a prescriber list that is held by a pharmaceutical company. For example, a company-held list of all physicians prescribing a medication or receiving risk minimisation educational material may be the most appropriate sampling frame for a study. However, if privacy rules require the company to obtain physician consent prior to release their contact information before being invited to participate in a survey, the consent process may introduce an important bias.<br><br>Proposed change: Add the following statements: "National (or regional) differences may exist regarding the appropriateness of providing incentives to survey participants." "There may also be privacy considerations in allowing contact with physicians based on a prescriber list that is held by a pharmaceutical company." | |

1. Tennis P, Toback SL, Andrews EB, McQuay LJ, Ambrose CS. A US postmarketing evaluation of the frequency and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years: 2009-2010 season. Vaccine 2012;30(42):6099-102.

2. Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine. 2011;29(31):4947-52.

3. Miller DP, Bennett L, Hollis KA, Tennis P, Cook SF, Andrews E. A patient follow-up survey programme for alosetron: assessing compliance to and effectiveness of the risk management programme. Alimentary Pharmaco Therap. 2006;24(5):869-78.

4. Tennis P, Andrews E, Hickman P, Miller D, Hollis K, Cook S. The relationship between dosing of alosetron and discontinuation patterns reported by patients participating in a follow-up programme. Aliment Pharmacol Ther. 2007;25:317-22.

5. Hollis K, Calingaert B, Price M, Andrews EB, Moy L, Kooijmans M, Cristiano L, Bozic C. Tysabri TOUCH Prescriber Program Risk Management Program (RiskMAP) surveys. Pharmacoepidemiol Drug Saf. 2010;19(Suppl 1):S59-60.

6. Hollis K, Zografos L, Price M, Gilsenan A, Andrews EB, Calingaert B. A comparison of factors influencing patient knowledge: results across selected REMS surveys. Pharmacoepidemiol Drug Saf. 2011;20(Suppl 1):S213-4.

7. Gilsenan A, Hollis K, Zografos L, Calingaert B, Andrews EB. Examination of respondent bias and patient characteristics in multiple REMS assessment surveys. Pharmacoepidemiol Drug Saf. 2011;20(Suppl 1):S208.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2013.07.12

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| SciencePharma |

*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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | Is it necessary to assess the effectiveness of routine risk minimisation measures? If yes, what methodology should be used? | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| 541-542 | | How will MAH of generic product know what risk minimisation measures were employed by MAH of a reference product? Is there any possibility to ask competent authorities for insight to Risk Management Plan prepared by MAH of reference product? | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05/08/2013

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Takeda |

*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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
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| | | |

## 2. Specific comments on text

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|---|---|---|---|
| Line 70-73 | | Comment: Clarity is needed on whether the Agency will be routinely requesting assessment of effectiveness of the SmPC and/or PIL. If not then clarity is needed on the situations when such assessment may be requested<br><br>Proposed change (if any): | |
| Line 115 | | Comment: include carers in the list of impacted stakeholders<br><br>Proposed change (if any): | |
| Line 138-143 | | Comment: Will the Risk management Plan template going to be updated in line with this guidance? Is there an expectation that such headers are presented in the RMP? | |
| Line 149 | | Comment: Clarity is needed on the term “suitably qualified person”<br><br>Proposed change (if any): | |
| Line 172 | | Comment:<br>Proposed change: ……this measure is considered important for minimising an important risk, alerting patients/carers/prescribers to the early symptoms of a risk and/or……. | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| Line 173 | | Comment:<br><br>Proposed change (if any): In the context of an educational programme, the materials……. | |
| Line 178-182 | | Comment: this assumes that there are specific risks. What about theoretical risks?<br><br>Proposed change (if any): | |
| Line 183: | | Comment: This may need further clarification as it could be interpreted that there should be no mixing with commercial activities, which taken strictly speaking would excludes the Rep network to provide the information and assess its impact. It is understood that Risk minimisation measures should not be promotional, but logistically it would be difficult to ensure appropriate distribution without collaboration with Commercial arms of the business. | |
| Line 197 | | Comment: “should” instead of “could” | |
| Line 220-221 | | Comment: Language is clumsy<br><br>Proposed change (if any):….the awareness of patients or their carers of the early signs and symptoms of the specific adverse….. | |
| Line 233 | | Comment: Portability is not quite the right concept. We want these to be easy to carry anywhere and hence able to be fitted | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | in a wallet.<br><br>Proposed change (if any): | |
| Line 238 | | Comment: “would” is incorrect, this should be “should”<br><br>Proposed change (if any): demonstrated benefits but which should not be available without….. | |
| Line 251-253 | | Comment: Are these 3 lines not already part of the 3rd bullet?<br><br>Proposed Change: | |
| Line 297-303 | | Comment: Surely it is helpful for the prescriber and patient to be able to easily identify material and the product it links to? This would suggest that layout and “branding” may be similar.<br><br>Proposed Change: | |
| Line 318-319 | | Comment: The requirement for understanding whether the intended impacts on behaviour have been observed is difficult in the context of measures such as patient alert cards. Clear guidance should be provided by the Agency on what is expected in this situation.<br><br>Proposed Change: | |
| Line 325-328 | | Comment: There are many examples of situation where putting emphasis on a particular issue may raise the reporting rate of this issue. So if your incidence increases, is it because there is | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | more awareness about it (which is good), or because our RMP measures are failing? Can the Agency provide further guidance in terms of interpretation of such data? | |
| Line 320: | | Comment: Measuring impact on behavior is a very difficult endeavor for all Risk minimisation activities. Further guidance from the Agency in terms of practical expectations would be greatly beneficial. | |
| Line 338 | | Proposed Change: consequences relevant to the public health question under consideration or other unintended consequences | |
| Line 352 - 354 | | Comment: This section discusses collection of metrics to assess distribution, but also appropriateness. Can further clarification be provided as to what metrics in this context would be appropriate to assess the appropriateness of the tool for the target audience | |
| Line 398-404 | | Comment: With currently available data sources it may not be possible to achieve this aim. Examples are drugs that are hospital use only.<br><br>Proposed Change: | |
| Line 424 - 427 | | Comment: When a coordinated action for a class of products is needed can the Agency provide further guidance as to whose responsibility is it to coordinate RMP action across several manufacturers? | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | | |
| Line 442 | | Comment: Please define what is meant by recipients of risk minimisation tools? At what level will this information be requested? Eg patient level, pharmacy level, wholesaler level<br><br>Proposed Change: | |
| Line 469-471 | | Comment: Phraseology is somewhat complex, making the reading confusing, please consider simplifying | |
| Line 550 | | Comment: Available secondary use data are limited by the primary reason for collection. In many instances the specific drug dispensed may not be recorded as many health systems only require the substance level<br><br>Proposed Change: | |
| Lines 565-569: | | Comment: Can the Agency provide comment/clarification as to how they engaging HCP & patients cooperation to optimize the effect of risk minimisation measures | |
| Line 570-579 | | Comment: A comment on the likely frequency of such evaluation, or a statement that the frequency will be determined by PRAC should be included<br><br>Proposed Change: | |
| Line 604 | | Comment:<br>Proposed change: In general, generic products are exempt | |

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| | | from routine PSUR reporting in the EU. | |
| | | | |
| | | | |
| | | | |

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

# Submission of comments on 'GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators' (EMA/204715/2012)

## Comments from:

| Name of organisation or individual |
| --- |
| Uppsala Monitoring Centre - WHO collaborating Centre for International Drug Monitoring |

*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<br>*(To be completed by the Agency)* | General comment | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|
| | The Guideline broadly reflects what is already regulatory practice | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
|---|---|---|---|
| Lines 305-7 | | Comment:if an intervention, which was justified in the first place, was not successful, then corrective action is always necessary (not as in the text "...it is necessary to establish whether corrective actions are necessary...")<br><br>Proposed change (if any):...*corrective action must be evaluated and taken...* | |
| Lines 447-50 | | Comment:if risk minimization measures recommended by PRAC/CHMP are considered conditions for safe and effective use, they should also be considered conditions for marketing authorization<br><br>Proposed change (if any): | |
| | | Comment:<br><br>Proposed change (if any): | |

Please add more rows if needed.