



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2024
EMA/341696/2024

Comments received from public consultation on 'Guideline on good pharmacovigilance practices (GVP) Module XVI Rev 3'

The draft of this module was released for public consultation during the period of 3 February to 28 April 2021. The document 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 and survey tool.

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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<28th of April 2021>

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP)' (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

Agency for Global Health Responsibility

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

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	The “controlled access programmes” should be renamed in “exclusive access programmes” because it avoids confusion with similar terminology while being clear on the issue, that there is no general access to these medicines outside the scope of the programme. XVI.A. Introduction The pivotal legal basis for analyzing and providing further guidance on the RMM criteria are Art. 30 (1) lit (c) and Art. 31(1) IR 520/2012 “(t)he summary of the risk management plan to be made publicly available ... shall include key elements of the risk management plan with a specific focus on risk minimisation activities and, with regard to the	

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Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	safety specification of the medicinal product concerned, important information on potential and identified risks as well as missing information.” From a legal point of view, it would be important to outline that the underlying legal provisions do not differentiate between “routine” and “additional” RMM and consequently, there is no definite legal definition available. In other words, the outline solely reflects the regulatory approach of the EMA but no clear-cut statement is provided in the text that the legal provisions do not distinguish between routine and additional RMM. As such, the strict division between “routine” and “additional” is not based upon law and thus this should be made sufficiently clear. Legally speaking, every identified risk, including important information on potential and identified risks, needs to be governed by an effective risk RMM measure. XVI.B.2. Criteria requiring additional risk minimisation measures The advancement of this section is very promising. Nonetheless, there is still not enough definite guidance on the issue, that every important risk – identified or potential – has to be governed by a RMM.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
78		Comment: Art. 107j(3)lit d Directive 2001/83/EC with regard to the legal provisions stipulating RMM and the assessment of their effectiveness. The provision concerns the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) in case the urgent Union procedure has been initiated, which shall conclude on, <i>inter alia</i>, the implementation of RMM. This provision is especially pivotal in governing emerging safety issues in relation to already effective or new RMM and their effectiveness. A rationale for the non-inclusion cannot be identified and thus, the pertinent provision needs to be amended. Proposed change (if any): include Art. 107j(3)lit d Directive 2001/83/EC	
109-11		Comment: The definition is not enough precise and not reflecting the mandatory legal authority of RMM with regard to safety concerns. It provides the wrong impression that RMM might be only of a "regulatory" dimension. In fact, is a mandatory component of authorization and thus, this should be made more transparent.	

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		Proposed change (if any): RMM are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. In terms of authorization, RMM are mandatory elements of RMP governing safety concerns.	
138		Comment: There is not enough emphasis that important risks shall categorically and automatically be administered by additional RMM, while “regular” risks could also be governed by these interventions next to the routine RMM. Proposed change (if any): Additional RMM shall in any case be administered for any important safety concern, while they are optional for risks defined in the RMP as “not-important”.	
142-154		Comment: The listing order of the criteria should reflect the importance of the objectives at stake and should be easy to use and not be repetitive for the competent authority (especially in the process of authorization) . Therefore, the guidance should give priority to the most important principles in a ready friendly way. Moreover, the outlined criteria for the assessment of risks are confused	

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		with some specific problems of application, therefore some passages should be integrated to the guiding principles through short exemplifications. Moreover, the criteria should not be concerned so much with the “burden of impact” but rather focus on safeguarding patients’ health. The section, as proposed, does unfortunately not give the impression, that the utmost regulatory prerogative is to minimize the health threat by any means available, even if they are “burdensome” in any way or the other, they should prevent severe health hazards and thus, safety has to be the guiding principle. Therefore, a more user-friendly, less repetitive table guided by the objective to reduce important safety concerns through additional RMM should be developed. There is no guidance that the “non-application” of RMM directly violates mandatory legal requirements of pharmacovigilance legislation and constitutes an obstacle for authorization. Proposed change (if any): • The risk has to be evaluated in accordance of the following guiding principles: - seriousness and severity,	

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		- target population (i.e. advice to patients or healthcare professionals), - frequency, - context of use (i.e. excluding patient exposure if contraindicated), - possible impact (i.e. behavioural changes of healthcare professionals and patients), - preventability (i.e. early detection and management of adverse reactions); The RMM tool has to be - risk-proportionate and - effective (i.e practical). Upon these mandatory legal requirements, which are stipulated in the EU pharmacovigilance legislation, any important risk requires additional RMM. Otherwise, a legal infringement is given, resulting, <i>inter alia</i>, in an obstacle for authorization.	
133		Comment: There is no rationale, why the new version versus the current has omitted clear guidance on “veiled” promotional activities in educational material. should be still a strict and rigid ban on promotional interests. The sentence has to be exchanged with the current deliberations, which give a more exact account on the issue of promotional interests which are strictly	

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		forbidden. Otherwise, the transparency and credibility of the regulatory aspects are at stake. Proposed change (if any): 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. Promotional elements, either direct or veiled (e.g. logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.	

Please add more rows if needed.



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21 April 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012)

Comments from:

Name of organisation or individual

APCER Life Sciences

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1. General comments

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<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	Comment: To improve RMM outreach and to increase awareness on RMM availability, suggest including a statement in Package Leaflet (PL) for patients: "This medicine has educational materials with key information which is important to read before taking this medicine. For copies of this educational materials contact your doctor who will provide you the details of materials OR please contact MAH medical information department on <Tel no.>" Rationale: During Valproate Public hearing, it was notified that "Educational material is not currently used by care providers, and information is not systematically issued to patients either."	

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2. Specific comments on text

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6		Comment: EMA is specifically seeking comments on the need and suggestions for possibly replacing the established term 'controlled access programmes' to avoid confusion with the concepts 'access to medicines' and 'controlled substance'. Hence, please find below some suggestions: • Regulated access programme • Authorized access programme • Restricted risk mitigation programme • Constricted accessibility /acquired programme	
98-100		Comment: Some medicines are acting as prophylactic or utilised by healthy people also e.g., Oral contraceptive Pills and some are used for diagnostic purpose. Hence, the term 'patient' can be replaced with "patients/ humans".	
140 – 154		Comment: Suggested text in bold and underlined Proposed change (if any): In determining whether additional RMM are needed and which measures would be most effective, marketing authorisation applicants/holders and competent authorities should: • Select the RMM tools that are expected to be..... • <u>To assess risks which require targeted RMMs, systematic methods may be used like Failure Mode and Effects analysis (FMEA) etc.</u>	

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157-159		Comment: Suggested text in bold and underlined Proposed change (if any): Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination with reference medicinal product holder, <u>unless otherwise specified by NCA</u>	
177 - 179		Comment: This section (XVI.B.3.1. Educational materials) only includes reading materials in different formats to ensure risk minimisation. However, other communication channels also should be included like Specialised training programmes for HCPs e.g., workshops, disseminating risk minimisation information to HCPs through (Continued medical education) CME programmes, professional societies, or symposia.	
184-185		Comment: If user testing for all the educational materials would be required in future, consider clarifying if PIL user testing guide can be used for testing educational materials also. Provide the reference for the same for consistency.	
187-191		Comment: Suggestion below in bold and underline. Up-to-date, objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be provided in more detail or in a different	

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		way than in the SmPC/PL e.g., by the use of tables, flow charts, or illustrations <u>or pictogram/infographics</u> ;	
198 - 200		Comment: Suggested below in bold underline (addition) and bold strikeout (removal) . Proposed change (if any): Statement explaining that this educational material is part of the marketing authorisation <u>and has been approved by the respective competent authority</u>, including the version <u>issue</u> date /number and date of approval. <u>Rationale: Approval details of other competent authorities within the educational materials do not provide significant information.</u>	
224-225		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention 'Description of the tool'. If the requirement mentioned here is specific to size of patient card, suggest adding the below text bold and underlined. Also, if specific examples can be provided. Proposed change (if any): In the description of the tool in the RMP <u>(this is considered an exception to the guidance Module V - Rev 2)</u>, details on the format (e.g., DIN A4 size or larger), its length (e.g., a short or a comprehensive guide) should	

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		be specified <u>based on user requirement specification for risk minimisation e.g., size of patient card which fits in wallet, to ensure utilisation. Other format related specification should be mentioned only in RMM submission package along with dissemination plan for NCA agreement.</u>	
276		Comment: Considering Risk awareness forms are very specific to certain type of risks, couple of examples can help the readers to understand better.	
298-300		Comment: Though initially in the document it is mentioned that aRMMs should be different than promotional materials; however, chances to promotional elements is high in demonstration kits like inhalers or injectors, considering they replicate the real device. An additional clarifying point is required to avoid promotion.	
444-447		Comment: As per the section XVI.B.3.1.b, suggest adding the below text bold and underlined Proposed change (if any): Educational material tools (see XVI.B.3.1.) to inform healthcare professionals and patients about the teratogenic risk and the required actions to minimise this risk (e.g., guidance on the need to use appropriate contraception, on the time period during which pregnancy is to be avoided after	

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		stopping the treatment); <u>to use Healthcare professional checklists for risk minimisation to record pregnancy testing results, support counselling on the need to avoid pregnancy and therefore use of contraception and support advice in the case of becoming pregnant during treatment.</u>	
477-484		Comment: To gather evidence that the implementing steps of additional RMMs have been successful, suggest to include some process indicator parameters in section XVI.B.3.4.b. Centre accreditation systems like documentation of prescriber, dispenser and patient documenting RMM receipt and understanding of information related to safety concern. This data will allow to assess the process indicator parameters for effectiveness evaluation.	
496-503		Comment: Suggest including below statement in section XVI.B.4. Dissemination plans for one time distribution of RMMs to ensure latest information is received by target audience: Proposed change (if any): In case of one time distribution agreed with NCA, MAH should ensure to distribute modified version of the materials informing that previous version is obsolete.	
510-512		Comment: DHPC communication plan template (GVP Annex II) does not allow all parameters for the content and format of dissemination plans to be included (as mentioned in the line	

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		497 to 503) and therefore dissemination plan template with these requirements can be considered to be provided as a separate Appendix to this Module.	
520-521		Comment: Current Module V (Rev 2) and its integrated template does not allow to mention any monitoring parameters to evaluate effectiveness of Routine RMMs (like SmPC or PL or other RMMs like pictograms, pack size etc.). Similarly, effectiveness evaluation guidance for SmPC (e.g., clinical actions beyond routine standards of clinical care) and other routine RMMs is missing in this guidance (Module XVI-Rev 3).	
532-533		Comment: Suggest including the below text (bold and underlined) Proposed changes (if any) Details of how RMM effectiveness will be measured at regular timepoints should be included in the pharmacovigilance plan and <u>Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)</u> of the RMP (see GVP Module V).	
536-543		Comment: These are the general guidelines for timely evaluation of effectiveness of aRMMs.	

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		As per respective therapeutic areas (for eg: oncology, rare disease segment), this may require revision which will help in effective utilization of aRMMs in terms of risk minimization and will reduce the time based burden & unintended outcomes of aRMMs especially if the tracking can be done at shorter durations or on real time basis if possible. Consider adding below sentence in bold and underlined. Proposed Change: <u>Depending on the therapeutic area/ disease segment, timelines may be changed as agreed with NCAs</u>	
574-575		Comment: Guidance is missing where effectiveness evaluation is carried out by means of Routine PV activities (and not defined study protocol). Hence, suggest adding below text (bold and underlined): Proposed change (if any): Measurements and indicators of RMM effectiveness should be defined as part of the study protocol. However, if effectiveness of RMMs are assessed by routine PV activities, then milestones should be defined in RMP Part V.2, which may be agreed with NCAs during the submission of dissemination plans along with measurements and indicators.	
574-575		Comment: As mentioned in XVI.B.6, there is no need to request the MAH of the generic, biosimilar or hybrid product to evaluate	

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		RMM for their product when RMM is fully identical with originator/reference product. In this situation, Dissemination metrics should be agreed with NCA and MAH should be asked to submit the data periodically for NCA's oversight to ensure outreach of materials, (considering that generic products are developed to reach maximum patients at affordable prices after expiry of exclusivity). Suggestion in bold and underlined. Proposed change (if any): Measurements and indicators of RMM effectiveness should be defined as part of the study protocol. <u>MAH of the generic, biosimilar or hybrid product should submit the measurements and process indicators along with the dissemination plan and submit the data periodically to NCA to ensure compliance.</u>	
576-577		Comment: In the Figure XVI.1, white boxes are not clear. Hence, consider providing explanation on what white boxes refer to?	
719-726		Comment: Considering market coverage, generics, biosimilars and hybrids may provide more data in addition to originator. Therefore, these MAHs should submit process indicators along with the dissemination plan and submit the data periodically to NCA to ensure compliance.	
768-769		Comment: As per the GVP Module II, suggest adding following text:	

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		Proposed change (if any): For this purpose, the marketing authorisation holder should keep track and record the dissemination process and outcomes. <u>MAH & QPPV should ensure that the PSMF annex, records the product specific RMMs contained in the RMP or laid down as conditions of the marketing authorisation and the monitoring information is provided as a secondary list.</u>	
889-890		Comment: Ideally, additional RMMs are approved by NCAs after approval of RMP by the Agency. Hence, inclusion of risk awareness forms implementation details in RMP prior to NCA approval will be difficult for centrally authorised products. Consider providing pragmatic approaches to follow.	
902-906		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention effectiveness evaluation results unless it is removed. So, suggest adding the below text in bold and underlined. Proposed changes (if any) The marketing authorisation holder should report the findings of the evaluation when updating the RMP (<u>this is considered an exception to the guidance Module V - Rev 2</u>) and in the periodic safety update report (PSUR) with a view whether the RMM ensure the positive risk-benefit balance of the product or adjustments to the RMM or other regulatory action is needed.	

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935-936		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention a summary evaluation of the outcomes of specific RMM in the EU. So, suggest providing more guidance on this.	

Please add more rows if needed.



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<21-April 2021>

Submission of comments on:
Guideline on good pharmacovigilance practices (GVP). Module
XVI – Risk minimisation measures: selection of tools and
effectiveness indicators (Rev 3) (EMA204715/2012 Rev 3* - Draft for public
consultation)

Comments from:

Name of organisation or individual

Argenx BV

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1. General comments

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2. Specific comments on text

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179-180		Comment: Proposed change (if any): Educational materials may be helpful <u>are</u> useful for encouraging discussions between healthcare professionals and patients in relation to the safety	
205		Comment: Proposed change (if any): TheTypical objectives of such guides include to:	
215		Comment: Proposed change (if any): Additional <u>Other</u> objectives of patient guides may be:	
216-17		Comment: This cannot be considered an objective it is part of the regular healthcare professional checklist before to initiate any new treatment for a patient Proposed change (if any):	
224		Comment: this sentence is not necessary to be provided in the RMP otherwise format are video. Please consider to delete	

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		Proposed change (if any):	
254-6		Comment: Proposed change (if any): Prompt the healthcare professional to inform the patient about the importance of returning unused product and keeping medicines away from children and not sharing the medicine with others, especially for medicines <u>persons</u> with high risks for other persons or the environment;	
843-5		Comment: Proposed change (if any): For those RMM introduced after the initial marketing authorisation, the competent authorities in Member States should ensure prompt consideration and agreement of the RMM with the marketing authorisation holder.	
855-6		Comment Proposed change (if any): In addition to the above, for centrally authorised products, further responsibility for ensuring <u>implementation on timeline agreed</u> of the RMM in Member States maybe be given to national competent authorities by	
		Comment:	

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		Proposed change (if any):	
		Comment:	
		Proposed change (if any):	
		Comment:	
		Proposed change (if any):	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
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<Date of submission 28 04 2021>

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) 4 Module XVI – Risk minimisation measures: selection of tools and 5 effectiveness indicators (Rev 3)'
(EMA/204715/2012 Rev 3* - Draft for public consultation)

Comments from:

Name of organisation or individual

Axian Consulting Ltd. , The Bradfield Centre, 184 Cambridge Science Park, Cambridge, CB4 0GA, UK.

www.axian.consulting

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	We have approximately 20 years of experience in developing and implementing risk management strategies and plans for clients in the pharmaceutical industry. This experience covers both conventional and digital approaches. We are pleased to see various references made to the acceptability of digital/web-based formats for additional risk minimisation measures (aRMMs) in the guidance. However, limited consideration of the benefits of digital aRMMs in terms of availability, interactivity, and ability to collect data is made in the guidance. There is also no consideration of one of the key aspects of digital content management. i.e., the separation of the content from the channel. In a	

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	digital world content is stored in a database and the same information can be delivered via multiple tools or channels. This fundamental difference versus a paper-based document means that the resulting digital tools may not fully align with the categories outlined. In terms of effectiveness evaluation, the PASS approach could be enhanced by digital via continuous real-time data collection. This would allow much more rapid evaluation of usage at a granular level i.e., parts of the RM tools that are used, and how, as well as knowledge assessments and potentially deeper behavioural monitoring approaches. Faster evaluation provides more opportunities to continuously improve the delivery of or content of these aRMMs. In our experience of delivering innovative digital risk minimisation (RM) tools (over the past eight years), occasionally, we encounter pushback from NCAs where the content or way of delivering that content takes advantage of digital approaches and as a result differs slightly from the paper-based material. Due to this, potentially valuable additions to the materials (for example optional surveys to allow patients to test their knowledge of key risks) may be omitted from	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	RM tools in certain countries, thereby reducing the materials' utility. In a world that is increasingly digital for everything we do (even more so post COVID) we feel that it is important that any guidance reflects this reality. It should provide all stakeholders with an unambiguous foundation to help them harness the opportunities digital can offer to improve the safe use of medicines. More complete guidance on the use of digital and its potential utility and value to patients and HCPs would give manufacturers and NCAs greater confidence to; utilise and approve these approaches, build experience, and deliver evidence of their effectiveness. Given that understanding and knowledge of digital may not be fully developed in PRAC, the NCAs, nor in the safety departments of many manufacturers, we believe there is need for additional guidance on the use of digital tools to address aRMM's objectives. To inform any future guidance we recommend the formation of a working group consisting of manufacturers (drug safety, PV, QPPVs, Clinical), health authorities and other interested parties to investigate this topic. This could potentially be done	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	under the auspices of a respected organisation (for example, BRACE). The aim would be to produce a perspective which could inform further guidance. We would be happy to convene and help run such a working group.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
125-133		<u>Comment:</u> We agree with the sentiment of the purpose of aRMMs and their non-promotional nature. However, in our experience (~20 years) of delivering RM, to achieve greatest effectiveness, the uptake/usage of aRMMs will be maximised if the aRMMs reflect end-user needs (especially patients). This goes beyond the basic messaging and functionality related to potential and identified risks and missing information. The presentation of key messages tends to use relatively complex language and information is often only presented in one format. Materials which are tailored to a range of learning styles using different formats can help patients better understand the risks and the behaviours that are to be encouraged. Patients prefer to obtain information from a single, trusted, source. In addition to the formal risk minimisation information; they may want to know how the treatment helps them get well, and about support networks that can help them adopt desired behaviours. This broader, routine risk minimisation, information can largely be derived from the label and could be delivered	

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		with the aRMM as it would encourage appropriate product usage and behaviours yet is currently often considered to be promotional. At present it is often delivered through mechanisms such as patient support programmes. We have observed that NCAs often strictly interpret aRMMs as having only to contain language that is specifically present in the labelling. This narrow focus can result in patients not receiving support in a way that is accessible to them or in the context of wider information that supports both safe use and treatment adherence. <u>Proposed change (if any):</u> Information and digital functionality that promote appropriate use and behaviour should not be considered promotional. Effective aRMMs should contain content and useful information to enable the intended users of these materials adopt appropriate (safe) behaviours. Information about the benefits and risks, and, without being promotional, other content to aid the adoption these behaviours should also be allowed.	
138-139		<u>Comment:</u> "Additional RMM(s) should focus on important safety concerns." If applied rigorously, this limits the opportunity to deliver value to HCPs and patients via additional content or functionality and there is a significant risk that the tools will not be deemed useful, are not used, and, therefore, will not help minimise risk.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		<u>Proposed change (if any)</u> : "The core safety content of additional aRMMs should concentrate on important safety concerns." In addition, consideration needs to be given to factors that will motivate usage and drive behaviour. These factors should be determined through user research and or co-creation activities. Where this evidence is available, it should be considered in the selection and design of aRMMs.	
155 - 159		<u>Comment</u>: There is a risk that multiple versions of the same content will continue to be implemented for generic drugs. Multiple versions of aRMMs are likely to lead to confusion and potential error for HCPs about which materials need to be read or passed on to patients/caregivers. Prescribers of a generic drug (e.g., isotretinoin), may not know which version of the PPP (Pregnancy Prevention Plan/Programme) materials should be given to the patient for the specific generic the patient will receive. <u>Proposed change (if any)</u>: A single core set of aRMMs, ideally available from a single web resource (e.g., EMA site), for generic drugs.	
161-164		<u>Comment</u> :	

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		Digital provides the opportunity for treating content differently with advanced content management and distribution through multiple channels, personalisation of content according to the user preference as well as rapid evaluation of usage patterns and understanding of knowledge. <u>Proposed change</u> Acknowledge that digital can provide unique ways of managing and delivering content which is different from paper-based tools and it can be more customer centric. Digital aRMM approaches may therefore differ from some categories of aRMMs listed in this document. Furthermore, guidance should highlight that effectiveness can be evaluated more rapidly digitally.	
182-185		<u>Comment:</u> Use of user-testing is encouraged. Materials that are co-created with users are often more useful for the user as well as more usable. Should the results of this type of research be included in submission materials? <u>Proposed change (if any):</u> Guidance should acknowledge the importance of aRMM usefulness (utility) as well as usability. It should also reference co-creation to improve both usefulness and usability.	

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433-456		<u>Comment:</u> In addition to the above comment on generics, PPPs for generics may be better managed with a single set of resources (consent forms, pregnancy advice, pregnancy follow-up forms) from a single source per country. This would also enable more effective and complete metrics collection. There is a risk that an AE in a patient on a generic drug (product X) is reported back to the wrong MAH as product Y. Pregnancy prevention/teratogenicity management programmes could easily be implemented as a single (multiple drug, multiple generic) resource, potentially linked to a pan-EU PPP registry. Similar approaches could also be adopted for other generic drugs with other side-effect profiles, wherein the EMA could lead a single, core source of information and material which could be localised for each country. Guidance on generic PPPs and other “risk issue” risk minimisation single sources from the EMA is required. <u>Proposed change (if any):</u> N/A	
500-501		<u>Comment:</u> The guidance briefly mentions more modern 'electronic' delivery of RM guidance but does not consider	

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		the benefits of digital delivery in terms of the availability of the information (historically, a significant issue for paper-based material), version control (the latest version is the only one available; as there are risks with paper and PDF of receiving or using out-of-date information), the ability to tailor content to user's needs, and the ability to monitor RMM use in real-time. <u>Proposed change (if any)</u>: Future guidance should consider the advantages of the digital delivery of content and the potential inherent in designing materials to take advantage of all the potential benefits of digital. In time, this may lead to a digital-first approach to the design of more effective aRMMs, with paper-based material as a back-up for the limited number of users who prefer it.	
507-508		<u>Comment</u>: "Periodic provision... competent authority level at time of implementation..." aRMMs need to be available whenever a patient is at risk. Sending out tranches of aRMMs, especially by post, at launch and potentially one or two years after is unlikely to be adequate. Different NCAs have different opinions on the operational details of, or audience for, dissemination plans. This leads to varying RM approaches across countries. Whilst the need for the implementation to reflect local healthcare	

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		structures is accepted, it may be helpful for the EMA to agree on the dissemination periodicity and core target recipients to make aRMMs available more consistently across markets. We have experience of certain countries not allowing patient materials to be provided due to the local assessor's belief that only HCPs should deliver all the information. In the digital era, patients often actively seek out medical information. Should they do this, they may access health information, including medicines and their benefits/risks, online from various sources, not all of which may be trustworthy. It is our opinion that MAHs should not ignore this real-world risk. Adhering to outdated methods of disseminating important information potentially increases patients' chances of accessing inaccurate information about product benefit/risk, thereby potentially putting patients at risk, and failing to meet their needs. <u>Proposed change (if any):</u> N/A (see above)	
522		<u>Comment:</u> "Any study measuring the effectiveness of RMM is a PASS." One of the benefits of digital aRMMs is the ability to automatically collect utilisation data. For	

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		example, it would be possible to measure the impact on RMM utilisation of different approaches to communicate about their availability. It is also possible to include embedded feedback surveys for users, typically asking questions of the same type that are used in PASS, thereby providing information on the usefulness/utility and behavioural impact of the tools. These approaches may be incompatible with the current definition of 'PASS' as a study in the current version of the guidance. Usage of prototype aRMM during clinical studies may provide a useful means to evaluate their effectiveness pre-launch Assessing the impact on outcomes of aRMMs is still challenging due the lack of a direct comparator <u>Proposed change (if any):</u> Include a recognition that in the use of digital methods, aspects of effectiveness may be able to be measured through the collection of real-time data. Acknowledge that pre-launch evaluation of aRMMs in clinical development may be a useful additional approach	

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		Provide more guidance on methods for outcome assessment	
531-543		<u>Comment:</u> "Regular evaluation." We support the suggested approach to effectiveness evaluation, which proposes a consistent timetable and more frequent review. This is to be applauded as a more rigorous approach to provide feedback on and hence the opportunity for continuous improvement of the tools. However, the continuing use of PASS surveys to obtain this effectiveness data is concerning as such studies are often slow to recruit and have limitations in their operation which can lead to difficult to interpret and limited results. The current approach described in the guidance seems to be based on aRMMs as paper-based materials sent out to the intended users, with collection of simple distribution process measures which offer no insight into effectiveness, evaluated at some point in time after using methodologies (e.g., surveys) that are recognised to suffer from significant biases. Given that the guidance is open to the use of digital approaches for risk minimisation, we feel that there is an opportunity to further describe the opportunities of regular reviews of real-time metrics from digital tools as a part of	

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		the effectiveness measurement mix. Digital approaches can provide a wide range of granular evaluation metrics in real time and would support more frequent effectiveness review at lower cost per 'study', thus improving industry adherence to guidance. <u>Proposed change (if any):</u> We feel that a greater focus on the potential for the role of digital delivery mechanisms in effectiveness measurement should be considered and covered in the guidance.	
568		<u>Comment:</u> Delivery of aRMMs (often captured as numbers of materials posted out) is flawed as a core measure of effectiveness. It answers the question 'were the tools sent out' but whether they were they received by the intended audience and used is not available from these process measures. <u>Proposed change (if any):</u> Strengthen the expectations of what constitutes a suitable measure of effectiveness at each of the assessment points. Clarify that process measures alone are inadequate to meet this periodic assessment need.	
627 - 663		<u>Comment:</u> Digital tools which are designed to elicit behavioural changes can provide a more proactive and	

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		dynamic approach to support appropriate behaviours than paper (e.g., applications can provide reminders to take risk-related tests). Behaviours could be observed using digital aRMMs in real-time and can include: 1. Did an HCP demonstrate a patient RM tool to a patient? 2. Did an HCP complete a patient screen? 3. Did a patient complete a compliance diary? 4. Did an HCP record an essential lab result? <u>Proposed change (if any):</u> Consideration should be given to inclusion of more dynamic assessments, particularly of behavioural objectives, that could be delivered through digital vs traditional paper.	
669-703		<u>Comment:</u> aRMMs are often implemented at product launch (post-MAA); hence, changes in health outcomes cannot be ascribed to the presence or absence of risk communications. Lines 677-680 acknowledge this. The following section (687-703) discusses changes in the incidence of ADRs linked to RMM changes. Attempts to assess these effects would likely be subject to many confounding factors. Attempts to determine health outcomes' results would be challenging, including identifying suitable control groups and comparators.	

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		<u>Proposed change (if any)</u> : Should this section be deleted or amended to reflect the known difficulties?	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 27,2021

Submission of comments on ' GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012)

Comments from:

Name of organisation or individual

Baxter

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	NA	

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
155-159		Comment: With respect to the recommendation for new generic/biosimilar/hybrid applicants to maintain additional RMM consistent with the reference medicinal product, in many cases the safety concern associated with historical additional RMM for the reference product no longer meets the definition of an important risk under GVP Module V Rev 2. Proposed change: 1) Consider adding specific recommendations for additional RMM requirements for generic/biosimilar/hybrid Applicants when the safety concern profile/additional RMM of the reference product were established under GVP Module V Rev 1 definitions. 2) Consider adding recommendations for innovators/originators with respect to maintaining RMPs and additional RMM in line with current GVP guidances, as they are the driver for other MAHs.	
226-229		Comment: The content in lines 155-159 states that additional RMM should be consistent across MAHs of common active substances when possible.	

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		Proposed change: Consider including a recommendation for generic/biosimilar/hybrid applicants for handling of terminology when the RMP/additional RMM details of the reference medicinal product are outdated with respect to the current GVP requirements.	
157-159		Comment: Statement "Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product." Proposed change: Remove dissemination. The dissemination may need to be different depending on product distribution model. Electronic dissemination should be prioritized where possible.	
502-509		Comment: There should be allowances for aRMM dissemination to hospital pharmacies. Aim to reduce overall burden on healthcare system. Proposed change: Add hospital pharmacy as e.g. (Row 503)	

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		Add option to point to a website where aRMM documents are maintained and directly accessible to patients and HCPs as needed.	
828		Comment: Alignment between generic, hybrid or biosimilar products is desirable. Proposed change: Publish key elements of aRMM to be implemented for all concerned products on EMA/CMDh website, to ensure consistent, accurate and up to date messaging.	



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI - Risk minimization measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/419982/2019)

Comments from:

Name of organisation or individual

Bayer AG, Pharmaceuticals

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).



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	The EMA's efforts to provide guidance on good pharmacovigilance practices in risk minimisation measures are supported and we welcome the opportunity to participate in the current stakeholder consultation process. While most of the recommendations and guidance seem reasonable, in evaluating the document we identified some topics that requires additional information, while others require clarification regarding their rationale for inclusion as follows: The definitions of some educational materials (e.g. risk awareness forms, patient cards) are not clear enough, making difficult to interpret the situations when one or the other (or both) are needed.	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	While the benefits of developing risk awareness forms is well perceived, the lack of a template/guidance regarding the basic information to include in these forms could create differences in the level of information that the patients/HCP's could receive, creating confusion and expectations issues. Also, the guidance draft would benefit for clarification of the role of the patient diaries for safety data collection, as some content could be interpreted as contradictory. While the proper use of the already limited space in the patient cards is clear, it is still not recommended to not include the information on how to report adverse reactions in this tool. This could only eliminate another channel to collect relevant information for the benefit-risk profile of medicinal products Also, it is recommended for module XVI to address in more details the use of applications for portable devices as tools to support educational risk minimisation and patient follow up. This should include guidance on how the MedSafety-2 App may be used, but also provide guidance to make such apps to qualify for a system to operate additional risk	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	minimisation and collection of data for measuring the effectiveness of risk minimisations measures.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Line 19		Comment: The section mentioned here "XVI.B.5.4." does not exist in the document – suggest amending to XVI.B.5.3. Proposed change (if any): "Changes to XVI.B.5.3 to give more guidance on risk minimisation evaluation parameters (e.g. implementation, ...)"	
Line 133		Comment: Additional clarification/granularity need to be provided on what is considered under promotional elements to be separated from additional RMM. Proposed change (if any): Please provide more clarification/granularity on what kind of information is considered under promotional elements to be separated from additional RMM (e.g. introduction of categories according to which promotional elements could be identified like company or product branding etc.)	
Line 150-151		Comment: Please consider adding some additional considerations that could be linked to healthcare professionals and patients' behaviours during treatment. Proposed change (if any):	

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		Consider the intended behavioral changes of healthcare professionals and patients during each step of the treatment process (the medication route/dose, correct administration, possible lack of adherence due to difficulties in administration, not understanding the instructions for use etc); and	
152, 301		Comment: Suggest consistent use of the term RMM or additional RMM, this seems to be intermittently used. The abbreviation aRMM is used once for additional RMM suggest writing out as done throughout document. 152: Select the RMM tools that are expected to be 301: In These demonstration kits would typically be supplemented with other aRMM. Proposed change (if any): 152: Select the additional RMM tools that are expected to be 301: These demonstration kits would typically be supplemented with other additional RMM	
Line 153		Comment: Please consider changing the order of words to improve readability.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): risk-proportionate and effective in minimising the risk in timely manner;	
Line 157		Comment: The guidance states "Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product (see XVI.C.1.1.1.).", in order to avoid the situation where a MAH must follow a specific RMM just because a prior product in the class did this, we would like to propose to add here the following guidance "where the RMM is still the most appropriate way to address any remaining risks". Proposed change (if any): "Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product (see XVI.C.1.1.1.) where the RMM is still the most appropriate way to address any remaining risks."	
Lines 163 - 169		Comment:	

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		Considering the increased use of digital tools in healthcare instead of the paper/physical ones, appropriate guidance is required regarding the situations/cases where each of the options should be used. Proposed change (if any) Certain RMM tools (e.g. Risk awareness forms) are supposed to be received by patient from physician as a paper version, and risks discussed alongside. In the “all going digital” trend, more precise guidance should be provided about publishing different RMM tools online. This should include information on the proper set-up of on-line/digital RMM tools and situations where the digital version is preferred/could be used instead of the paper ones.	
Line 165		Comment: In the way the information is stated, it could be interpreted as both electronic and paper based materials are required. Also, from a sustainability point of view, we recommend to replace the words “in addition” by “alternatively”. Proposed change (if any):	

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		"As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered alternatively to paper-based materials."	
Lines 166-170		Comment: As Controlled-access programs are primarily intended for controlling access to the medicine but usually include an educational component, the larger-scope concept of Additional Risk Minimisation Measures (aRMM) makes sense, however, it is recommended to rename the categories as: 1.) Educational methods, 2.) Access-control methods, 3.) Pregnancy prevention programmes methods, 4.) DHCP communication methods. This could facilitate the adoption of this categorization for non-EU jurisdictions that use the EU-GVP as reference or source of inspiration. Proposed change (if any): Additional RMM can be categorised into the following categories: • Educational methods;	

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		• Direct healthcare professional communication methods (DHPCs); • Pregnancy prevention programmes methods (PPPs); • Access-control methods.	
Line 196		Comment: The proper use of the SmPC is essential for routine risk reduction within medicinal products. Nevertheless, the benefit of this document could be overlooked due HCP's work overload and time constraints. Reinforcing the adequate and timely use of the SmPC through the proposed guidance will benefit the adequate use of medicinal products and contribute to minimize their risks. Proposed change (if any): For materials intended for HCP, to include a note on the importance to read carefully the SmPC and a link to it. (Please note this is already a requirement to the MAH by NCA (i.e. Spain).	
Line 198		Comment: It is recommended to reinforce the interrelation between the educational material to be provided to the HCP's and	

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		the existence of a Risk Management Plan, as these plans success is linked to the adequate awareness and participation of them. Proposed changed (if any): Statement explaining that this educational material is part of the marketing authorisation (including the Risk Management Plan) and has been approved by the respective competent authority, including the version date/number and date of approval.	
Lines 222-223		Comment: Having in mind that post-authorisation studies and registries are not considered RMM, reminding HCP's about such activities through RMM guides would lead to a potential increase in the RM material update frequency (with the subsequent additional burden for healthcare professionals and local health authorities) for reasons that will be potentially not safety relevant. Proposed change (if any): Do not include information about post-authorisation studies and registries into RMM which are not having an	

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		impact on the safety content and risk minimization of the materials (see below)	
Line 254		Comment: Being the HCP's checklist a tool aimed to list actions to support the prescriber/dispenser to identify circumstances that would increase or reduce the risk of a medicinal product, its completeness is essential to aim for this goal. An effective and open conversation between the HCP/dispenser should be promoted through the checklist to support the main objective of this risk minimisation tool. Proposed change (if any): Please consider adding the following bullet point: • Prompt the HCP to encourage the patient to ask possible doubts about the treatment to ensure the correct administration of the product to minimize errors and to guarantee adherence to treatment.	
Lines 262-265 Lines 277-281		Comment: Risk awareness forms are meant to support documenting that the patient has been made aware of the risk(s) during a discussion with a physician and that he/she understands the risk and actions to take. Nevertheless, the guidance	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		do not specify who is responsible to keep these forms (that could contain personal data from patients) neither who is responsible to oversight that privacy data rules are applied during the use and life cycle of the proposed forms. Proposed change (if any): Having in mind the data privacy regulations and the multiple stakeholders involved, guidance should be provided regarding roles and responsibilities for data storage and data privacy during the use of the proposed forms (who keeps the form, should the HCP and the patient keep a copy of the risk awareness form after the conversation between them ends)	
Lines 265-266		Comment: While the scope of the Risk Awareness forms is clear, the documentation process of such forms will benefit of additional information, as it is not clear if one copy of the form should also be kept in the patient record or if any need or "signature" from the patient/carer/guardian is required. Proposed change (if any): Please provide additional information on the expected documentation process for the Risk awareness forms.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 261-266 Lines 339-341		Comment: The difference between the proposed definitions of Risk Awareness Form and Patient Card is not clear enough, especially for stand-alone patient cards which are not integral part of medicinal product packaging and which are disseminated by HCP Proposed change (if any): Make a clearer distinction between content and consequent need for either or both of the aforementioned tools (e.g. both RMM tools, same medicinal product)	
Line 276		Comment: More clarity is needed on what is covered under the concept of "very particular risks" for the application of Risk awareness forms. Proposed change (if any): Please provide a definition of what is or need to be considered as "very particular risk" in the context of Risk Awareness forms use.	
Lines 282-284		Comment: It is recommended to EMA/NCA's to provide/develop a Risk Awareness Form template, indicating the basic information to be included. Otherwise the patients/HCP's	

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		could receive different level of information/details from each MAH due the lack of harmonization. Proposed change (if any): EMA/NCA to develop and provide a Risk Awareness Form template.	
Line 306		Comment: It is not completely clear how the reporting of concerns regarding demonstration kits should take place, including if the demonstration kits should be handled as a medicinal product or as a device component. Proposed change (if any): Please consider provide more guidance/details on how the reporting of concerns regarding demonstration kits should take place, including examples. Also, please clarify if the concerns regarding demonstration kits should be reported as an Adverse Event or a Product Technical Complaint.	
Lines 311-321		Comment: The description and activities described for patient diaries for risk minimization is very similar to those for patient disease and patient support management programs. Also, considering the kind of information that could be collected	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		in the diaries, patient inform consent form and/or data privacy rules would need to be considered. Proposed change (if any): Please include a clear differentiation between the description and activities proposed for patient diaries for risk minimisation and those that applies for patient disease and patient support management programs, including specific guidance for the use of patient inform consent and/or data privacy rules when applies.	
Lines 322-323 Lines 328-329		Comment: The draft guidance states that the objective of a patient diary includes the recording of "signs and symptoms indicating a possible adverse reaction". Nevertheless, the draft guidance also states that patient diaries for risk minimisation are not primarily meant to be used as a data collection tool by marketing authorisation holders for e.g. PASS. This could create confusion during interpretation and application of the guidance. Proposed change (if any): Please include a clearer explanation/differentiation of the role/use/no use of the patient diaries for safety data collection.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
328-332		Comment: As it is clearly stated that patient diaries are not categorised as educational material for risk minimisation and should not be proposed as part of the RMP, it is recommended to not intermingle the advice for PASS in the document. Also, it is recommended to add clarity on the proper setting these patient diaries need to be used. Proposed change (if any): Information for healthcare professionals regarding a patient diary should remind a healthcare professional who suspects an adverse reaction on the basis of the patient's entries in the diary to report this by using the usual spontaneous reporting systems.	
Lines 352-353		Comment: It is stated that for consistency reasons no other term than "patient card" is to be used. However, this statement is in conflict with current EMA's QRD template v10.2 where the term "Patient Alert Card" is used. Proposed change (if any): Please review the topic to ensure terminology consistency between the proposed updated guidance and the current EMA QRD template.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 382-387		Comment: Being aware of the need to effectively use the limited space in a patient card, it is still not recommended to not include the information on how to report adverse reactions. While the patient card should facilitate the HCP-patient discussion about risks, it also should give the patient the possibility to report AE by himself/herself. This is of relevance in situations where AE reported need to be granted but the availability of the prescriber HCP availability is not granted (e.g. holidays, traveling) Proposed change (if any): To respect the limitation in space and the risk minimisation purpose of the card, it is recommended to not include in a patient card information on the black triangle if applicable to the product (see GVP Module X) (this is considered an exception to the guidance on the black triangle and explanatory statements provided in the GVP XVI - Addendum I and in GVP Module X and this does not affect the obligation to include the relevant text about additional monitoring in other documents such as the SmPC and the PL).	
Lines 457 - 465		Comment:	

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		As the term “Controlled access programme” could be linked to formal controlled distribution measures, we recommend to use the alternative term “Focused access programme” which may be further specified as “Focused access and follow-up programme” if follow-up measures are added to focused access measures. Proposed change (if any): XVI.B.457 3.4. Focused access programmes A focused access programme is a tool or set of tools that seeks to control access to a medicinal product beyond the level of control applied to medicinal products by means of routine RMM (see 460 XVI.A.). It may restrict the time period of validity of a prescription or the maximum amount to be prescribed in a single prescription, or require a visual reminder as part of the labelling of the outer packaging. Focused access programmes should be considered and applied only in exceptional situations of an important safety concern with a severe impact on the patient or the (unborn) child exposed in utero, or a significant public health impact, taking into account the nature of the risk and the likelihood that this risk cannot be managed by other RMM.	
Lines 468 - 484		Comment:	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		While the additional guidance on controlled access tools is welcome, additional clarification is required on the roles and responsibilities of the involved parties/stakeholders within these tools. This is of special relevance considering the limited influence MAH's can have on medicine dispensing systems or prescription controls. Proposed change (if any): Please provide additional clarification/information on the roles and responsibilities of involved parties/stakeholders on: • Controlled prescription and supply systems. • Centre accreditation systems.	
Line 475		Comment: There is a typo in "For products that need to be prepared for a specific patient (i.e. advanced therapy medicinal products (ATMPs),...", please correct. Proposed change: "... specific patient (e.g. advanced therapy medicinal products (ATMPs))",	
Line 495		Comment:	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		It is not completely clear which aspects should be covered in the agreement (e.g. form/ way of how to dispense/distribute the involved medicinal product) Proposed change (if any): Please provide clarification on the agreement scope, including if this should consider the form/ way how to dispense/distribute the medicinal product, including roles and responsibilities.	
Line 643		Comment: The wording proposed for the bullet point is not completely clear and would benefit of the addition of the information already provided in lines 652-654 Proposed change (if any): Quantification of enablers or barriers for intended behavioural changes (e.g. healthcare environment factors, availability of resources and processes, access to alternative treatment, healthcare professionals' and patients' perception of a regulatory action and related attitudes).	
Lines 722 – 726		Comment:	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Please consider to add a line break before "For example" to make it clearer that with this sentence "new" content is introduced not related to the previous sentence. Proposed change (if any): "...This applies under the assumption that the RMM evaluation strategy requested for the reference product will be able to gather sufficient data. For example, if the introduction of a generic, biosimilar or hybrid product(s) reduces exposure to the reference product, the ..."	
Lines 775 - 778		Comment: Lines 775 -778 apply to CP products and EU procedures resulting into an EC decision but is not applicable for all kinds of marketing authorisations i.e. not applicable for MRP/DCP and NP marketing authorisations. Therefore the wording/terminology need to be revisited. Proposed change (if any): The Annex IID for a centrally authorised product outlines the key elements of any additional RMM imposed on the marketing authorisation as a condition for the safe and effective use of a medicinal product.	
Line 783-784		Comment:	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		As the GVP Module XVI Addendum I applies only for Educational material and not for any kinds of aRMMs, the wording/terminology need to be revisited. Proposed change: "... some RMM may need to be implemented differently at the level in Member States in accordance with feasibility, and the educational material dissemination by the marketing authorisation holder requires additional agreement with the competent authorities of Member States (see GVP Module XVI - Addendum I)."	
Line 793		Comment: Line 793 uses the term Reference and Concerned Member States. These terms are only applicable for MRP and DCP products. However, line 790 mentions "purely national procedure". It is recommended to update the wording to ensure consistency. Proposed change: "... agreed by the competent authorities in the Member States."	
Line 818		Comment: What are "key elements of the "necessary regulatory actions"? It is recommended to delete "key elements of". Proposed change:	

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		"The PRAC should evaluate the need for RMM and their outcome, including additional RMM, and make recommendations regarding the necessary regulatory action to the Committee"	
Line 820 + Line 838		Comment: What is meant with the term "nationally authorised products referred to PRAC"? Involvement of PRAC because CMD asked for advice within in regular procedure e.g. EU variation or is a referral procedure meant? The guidance would benefit from additional clarification in this regard. Proposed change (if any): Please specify.	
Lines 843 - 849		Comment: These lines use the term "RMM" but it ends with a reference to GVP Module XVI - Addendum I. However, this addendum applies "only" to educational material and not to the other RMMs as described/defined in sections XVI.B.3.2 – B.3.4. Looks like the term "RMM" is not used in a consistent way. Proposed change (if any): Either the term "RMM" needs to be replaced by "educational material" or the reference to GVP Module XVI – Addendum needs to be deleted.	
889		Comment: There is a typo in the text, please correct.	

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		Proposed change (if any): to the other, a therefore detailed description	
Lines 895 - 898		Comment: The information regarding distribution of additional RMM could vary depending on the MAH tracking tools in places and the agreements/requirements within the competent authorities in Members States. This could generate variability of expectations during inspections, as a basic set of information/parameters on RMM distribution is not currently provided/specified in the guidance. Proposed change (if any): Please specify the basic information regarding distribution of additional RMM to be provided by MAH.	
Lines 906-908		Comment: Not all information that may impact the benefit-risk balance of a medicinal product qualifies as a "emerging safety issue". Only if the criteria for an ESI (in accordance to GVP module IX "Signal management) are met this should be reported as an ESI. Otherwise the appropriate regulatory procedure should be used e.g a labelling variation. Proposed change:	

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		"If the marketing authorisation holder becomes aware of information regarding RMM that may impact the benefit-risk balance of the medicinal product, this should be reported as an emerging safety issue if the definition is met (see XI.A.1.1)."	
Lines 922 - 932		Comment: As the contributions of the patients and healthcare professionals are essential to develop and optimize RMM tools, the Agency, its Committees and competent authorities in member states should ensure that all the involved stakeholders (i.e. MAH's) can participate and have access of their engagement activities and subsequent obtained information to ensure that all perspectives are considered during the process. Also, it will be important to specify at which point in time this engagement should take place and by which means (surveys, panels, etc.). Proposed change (if any): Where possible, it is encouraged that the Agency, its Committees and competent authorities in Member States, as applicable, engage with healthcare professionals and patient representatives for obtaining their contributions and discussing:	

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		• Current awareness, understanding and management of the potential risks of the medicine; • Effectiveness, appropriateness and feasibility of having additional RMM in place; • Most efficient risk minimisation tools and appropriate and feasible dissemination processes in relation to target audience(s) and channels; • Support for healthcare professional and patient organisations by means of e.g. clinical guidelines, patient guides made available by healthcare systems or patient organisations, articles in scientific journals and conferences; and • Other practical suggestions for improvement. MAH's should be invited to participate during engagement activities leaded by the Agency, its Committees and competent authorities in Member States when relevant for the safety profile of their products. The information obtained from these activities will be made accessible to any stakeholder that could contribute to a proper development and optimization of current and future RMM tools. The engagement activities should start during and the following format for interactions are recommended:	

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		• Surveys (add additional recommendations) • Panels (add additional recommendations) • Add additional formats and recommendations.	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<23 April 2021>

Submission of comments on 'Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

German Pharmaceutical Industry Association/Bundesverband der Pharmazeutischen Industrie e.V.

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).



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	Wherever possible, examples should be given, to better understand and illustrate the topic/issue. Despite increasing the volume of the document examples might be very useful tool to improve understanding.	

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
General comment		While it is very much appreciated by pharmaceutical industry to receive detailed guidance on the different PV topics from regulators, there are aspects where successful implementation and therefore an improvement for patients' safety cannot be achieved by the collaboration between competent authorities and pharmaceutical industry solely. This is particularly true when it comes to risk minimisation. HCPs play an integral role in whether a risk minimisation activity will achieve the desired result or not and current available data suggests that there is room for improvement. Question: What plans do EMA and the other competent authorities have to induce stronger engagement and commitment of healthcare professionals in terms of their adherence to risk minimisation activities?	
23-24		Comment: Reference to sub-chapter XVI B.5.4: this number does not exist; chapter 5 ends with 5.3. Please check.	

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74-76		Comment: Objectives of risk minimisation are not only achieved by risk minimisation measures required by competent authorities. Each MAH also acts self-responsibly if and when required. Proposed change (if any): Please consider changing the wording of this sentence to reflect that risk minimisation is not only achieved by regulatory action but also by MAHs who act responsible out of their own initiative.	
148-149; 154		Comment: This might be difficult to measure. The burden to patients, HCP and costs should be considered in relation to the setup/request of such measures, comparable to line 154.	
154		Comment: the wording „not too burdensome“ is not very succinct. Can this be explained better? Proposed change (if any): Can you please consider adding some examples for measures which are justified as well as examples, which are regarded as too burdensome?	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
162-165		Comment: Paper-based materials should no longer be considered state- of-the-art when it comes to the dissemination of information and should thus be limited to the absolute minimum. Nowadays there are means that are, apart from environmental considerations, more efficacious, more easily distributed and more accepted than hard copies. Ultimately new or updated information can be made available and accessed much more rapidly. Certainly it depends on the situation which means of communication (one or both) should be considered. But electronic means should at least be considered a real alternative to paper based materials instead of merely an 'add-on'. Proposed change (if any): Please consider changing the wording of the sentence to allow for dissemination of relevant information by electronic means in addition to or instead of paper-based materials. Please consider changing the wording: As digital technology advances, the potential of electronic dissemination ... should be considered an alternative to/ or replace paper-based materials.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
171 ff., section XVI.B.3.1		Comment: Whilst it is clear and acknowledged that the focus of educational material is to provide safety-relevant information, it may be prudent, particularly for materials targeting the patient population, to also provide information why it is important that the medicinal product is used by the patient as intended and prescribed by the physician. Experience has shown that there are situations where patients become uncertain regarding the risks of a product just because of the mere existence of educational material and therefore do not take that medicine. Such effect is a burden to the healthcare system and may have severe consequences for a patient with a severe or even life-threatening disease. Therefore, it should be considered to include some re-assurance that despite of the introduction of a risk management tool the benefits of such a product outweigh the risks and that the prescriber has considered the patients individual situation when they decided to prescribe the drug. Proposed change (if any): Please consider adding wording to explain that on a case-by-case basis educational material may contain some carefully phrased information about the benefit of the treatment in order to prevent therapy non-compliance by patients out of the fear of its risks. This proposed change may also be applicable to GVP XVI Addendum I.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
231-259		Comment: The intention and usefulness of such HCP checklist is well explained. However, merely completing the checklist seems not to be sufficient. Proposed change (if any): Please consider adding that the HCP should document/ file/ save the completed checklist (e.g. in patient's record).	
265-266		Comment: The format of risk awareness forms should be tailored to the target population. Nowadays, there are quite a lot of people, particularly younger generations, that prefer electronic means over paper. A hard copy may not be the most accepted tool and therefore not be used as intended. Also, electronic means usually provide better options for repeating the messages to be given and – if required – their acknowledgement. Hence, a hard copy or print out should not in every case be required but there should be freedom to agree on the most suitable format. See also comment on lines 162-165 Proposed change (if any): Please consider changing the wording to allow for other formats of risk awareness forms. Perhaps also consider using a different term, i.e. instead of "risk awareness form" use "risk awareness information".	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
422-425		Comment: A collaboration of MAHs is absolutely reasonable and appreciated. But how is this going to be organized: who is accountable for kicking off the process/ organising the process? Can this be the regulators? Is a platform needed? What are your expectations in this regard? Can you name an accountable party to take over the leadership?	
422-425		Comment: In the interest of HCP and patients this paragraph should not only apply to patient cards but to all educational material. Proposed change (if any): If agreed, move paragraph to explain the collaborative approach to section XVI.B.3.1.	
576		Comment: Figure XVI.1 is not very clear- where can I see the use of the 'concerned medicinal product' versus the use of 'other medicinal products'? Are 'other' MPs the white boxes? Can this be explained better in the figure's subtext?	
691-692		Comment: If advice contained in RMM has become standard healthcare, the RMM should be discontinued to avoid unnecessary burden to the HCP/patients/companies. Proposed change (if any): Please consider to strengthen the wording from "may conclude to discontinue" to "discontinuation of RMM is required".	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
713-733		Comment: how is this “consistent approach to planning the evaluation of RMM” supposed to be achieved? Who is accountable/ kicks off/ leads the discussion? Can the regulators provide the platform and take over the leadership?	
719-726		Comment: Not only the status of a product (originator or generic), but also the market share (number of prescriptions, sales) should be considered when determining the responsible party to evaluate RMM for their product. A high number of sales= results in more data available for evaluation. Proposed change (if any): add market share/prescription number/number of sales as criteria for responsibility for RMMs Again who signs responsible for coordinating this? Can this be the regulators?	
751		Comment: If advice contained in RMM has become standard healthcare, the RMM should be discontinued to avoid unnecessary burden to the HCP/patients/companies. See comment for line 691 as well Proposed change (if any): Please consider changing the wording: risk is appropriately mitigated and the additional RMM could (→ should) be discontinued.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
772- 773		Comment: For some products the authorised product information changes rather frequently and within a relatively short time frame. If such changes relate to printed RMM it should be considered by regulators that it takes some time to update, print and disseminate the material. Proposed change (if any): Is it appropriately reflected/ explained that competent authorities in the Member States align their implementation of an update to the product information and associated RMM thus providing the basis for the MAH to ensure the RMM can in fact be consistent with the current product information?	
779-789		Comment: The additional agreement on national level for centrally authorised products contradicts the approach of a centralised approach. Can/ should national level approaches be limited to a minimum? Can national authorities be requested to provide a comprehensive justification in case of request for different approaches/requests? Proposed change (if any): Please consider strengthening of wording in case of different/additional local requirements for RMMs related to centrally authorised products.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
779-793		Comment: As there is detailed guidance available a more common approach towards risk minimisation measures and their implementation should be possible by competent authorities in the EEA. Whilst it is appreciated that different health systems in the different Member States may require some country-specific adaptations there are still differences seen in the implementation which cannot be explained by that. Question: What plans do EMA and the other competent authorities have to achieve more harmonisation amongst the relevant competent authorities when it comes to the implementation of additional risk minimisation activities for a product authorised in more than one EU member state?	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
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25th April 2021

Submission of comments on Guideline on good pharmacovigilance practices (GVP): Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3) (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

UK Chartered Institute of Ergonomics and Human Factors (CIEHF) Pharmaceutical Human Factors Sector Group.



EUROPEAN MEDICINES AGENCY
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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	Whilst Risk Minimisation Measures (RMM) are the subject of this Module; this Module makes no reference to the Human Factors/Usability Engineering (HF/UE) risk management and usability engineering processes conducted, preauthorisation, on products' risk control measures especially for a drug-device (in particular the risk control measure, <i>information for safety</i> such as, labelling, Instructions for Use (IFU), packaging, and training). In addition, the role of HF/UE in the products' life-cycle and its continuous improvement, postauthorisation, also appears to be overlooked. The Medical Device Regulation (MDR) will come into force in May 2021. This new regulation places a greater emphasis on the role of HF/UE in post market surveillance. Whilst medical devices are out of scope for this Module, which is concerned with medicinal products, the user interface aspects of labelling,	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	Instructions for Use (IFU), packaging, and training, will require HF/UE input for Notified Bodies (NB) and Competent Authorities.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Comment: The term <i>use error</i>¹ does not appear in this Module, even though the subject matter is largely aimed in some way at the mitigation or elimination of <i>use error</i>. Although concerned with medicinal products, much of the RMM discussed in this Module, are actually related to user interface design. In HF/UE: labelling, IFU, packaging, and training, are all considered part of the user interface and referred to as <i>information for safety</i>^{1 and 2}. Information for safety is a risk control measure, as defined by ISO14971:2019², To conform to EU regulations, harmonised standards, such as IEC62366-1:2015+A1:2020¹ and ISO14971:2019², should be followed by pharmaceutical companies. To comply with IEC62366-1:2015+A1:2020, an extensive <i>Usability Engineering Process (UEP)</i>¹ will be followed, which will generate a <i>Usability Engineering File (UEF)</i>¹. This UEF will contain documentation of the use related risk analysis performed, and the usability evaluations conducted. Proposed change (if any): This Module would benefit from recognising the role played by HF/UE in developing <i>Information for safety</i>¹ i.e.	

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		packaging/labelling/IFU/training; and incorporate some of HF/UE's risk-based processes. For example, section XVI.B.3.1 Educational Materials, just states, "<i>Educational materials may have different target audiences, e.g. healthcare professionals or patients</i>". There is no explicit connection made between the products' target audience and the fact that the UEP undertaken by the pharmaceutical company will have already established and defined the target audience, as <i>intended users</i>¹; and that definitions and characteristics of the <i>intended users</i> will be documented in the <i>Intended Use</i>¹ document and the <i>Use Specification</i>¹. 1. IEC62366-1:2015+A1:2020 Medical devices. Part 1: Application of usability engineering to medical devices 2. ISO 14971:2019 Medical devices - Application of risk management to medical devices	
		Comment: A medicinal product will form the drug constituent part of a drug-device combination product. Whilst the device constituent part is out of the scope of this Module, it does refer to dummy or demonstrator injectors and inhalers in section XVI.B.3.1.d. Demonstration kits. It is becoming more common that Demonstrator kits are developed with the involvement of HF/UE. Whilst	

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		demonstrator injectors and inhalers are not medical devices, and from a risk perspective do not have any harms associated with their use; the development, use, and effectiveness of demonstrators are determined by HF/UE processes and evaluations. Proposed change (if any): Include a reference that any data concerned with <i>user errors</i> associated with a demonstrator is fed back into the product's HF/UE risk management (uFMEA); to inform any design changes required to the user interface.	
		Comment: The Module recognises that RMM is an iterative process of evaluation, correction and re-evaluation of RMM. However, there is no recognition that this iterative process for <i>information for safety</i> begins with the HF/UE work undertaken during the product development, and that the HF/UE process should be updated with any new use related data generated in an evaluation, correction, and re-evaluation iteration. Proposed change (if any): References should be added throughout that any subsequent new data that is generated in post market surveillance related to RMMs or the user interface should be fed back into the HF/UE risk management work.	

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		Comment: There is a strong trend that therapies are being moved away from clinical settings to self-administration at home. With this move new drug devices are being developed with on-body injection devices, smart packaging, and digital connectivity to help with convenience and adherence. This is especially important in oncology. With this move, medicinal products are going to be more dependent on safe and effective <i>information for safety</i> developed for <i>intended users</i>. This Module appears only to recognise new digital technologies as a means of disseminating information. It does not appear that new digital technologies have been considered as intrinsic solutions to act as RMMs. Proposed change (if any): A section should be added recognising the development of digital technologies as RMMs, and that HF/UE has a role in developing the user interface of digital technologies.	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3) (EMA/204715/2012 Rev 3)

Comments from:

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.

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

#	Stakeholder number	General comment (if any)	Outcome (if applicable)
	<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
1		It is understood that aRMM programmes may require adaptation to local healthcare settings in agreement with competent authorities. The effectiveness of an agreed aRMM will depend on the level of complexity, burden on a health care system and additional country-specific expectations. Therefore, guidance on harmonization of aRMM programmes to the extent possible across the EU Member States - similar as for routine RMMs provided in SmPCs and PLs - will contribute to the success of a aRMM programme and should be considered by EMA. Harmonization across EU MS would also support a streamlined approach for the methods of effectiveness evaluation in all EU Member States."	
2		It is acknowledged that the updated draft Guideline provides more detailed guidance on many aspects of risk minimization measures and their effectiveness measurements. However, selected sections of the draft guideline are overly detailed, leading to overlap and possibly confusion (e.g. in Section XVI.B.3.1 the different categories overlap and are in	

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			<i>(To be completed by the Agency)</i>
		practice combined). Inducing an undue administrative burden may influence treatment decisions by HCPs.	
3		Could a LOGO be mandated across the whole EEA to be added to the materials which are aRMMs (like "blue Hand" in Germany) so they are immediately recognized to help HCP and Patients recognize the risk minimisation materials from other form of information? To improve the awareness of the HCPs/Patients the involvement of NCAs as a key player in the communication campaigns should be reinforced.	
4		The Guideline includes very little information regarding digital resources. B.3 (Line 161 - 165) mentions digital but only in the form of electronic dissemination, possible digital solutions and approaches to delivering digital risk management are not mentioned. Access to digital information is almost ubiquitous in today's society and Regulatory Guidance on operating with regards to Risk Management within this space is of great importance. With the ever increasing digitalisation of healthcare systems globally, the need for innovative new digital RM solutions continues to grow in importance and relevance. There are also environmental advantages to reducing the use of physical/paper based materials. Therefore, given the advances in digital health tools and options, the revision should reflect the acceptance of these options as aRMM.	
5		There is considerable emphasis throughout this draft GVP Module update on the potential burden of RMMs on the patients, HCP and the healthcare system. It would be helpful if similar recognition is made about the potential burden of the RMMs effectiveness evaluations	

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		at each step of the RMMs implementation process on these parties. Therefore, the quantity and scope of aRM and their effectiveness evaluation should be carefully considered with this in mind.	
6		In several sections of this draft GVP Module update, the scope of requirements would benefit from being refocused on the topic itself, i.e., on those Risk Minimisation Measures addressing specific important risks as detailed in the RMP of a specific medicinal product. Also, the requirements for measuring the effectiveness of routine and ARMM should be made more clear. There is considerable vagueness on when specific effectiveness measurement is required (through a PASS) and when routine PV can be considered adequate as RM effectiveness measurement for both routine and ARMM (e.g. in Section XVI.B.5 'RMM' is used when in practice almost exclusively 'ARMM' is to be in scope.) Proposal: Include that the all required effectiveness measurements are defined in the RMP.	
7		It is appreciated that the agency has provided combined experience gathered since the introduction of Module XVI. The provision of detail and examples should be carefully considered and focused to ensure compliance with key regulatory requirements. An appendix similar to Addendum II containing the types of risk minimisation tools and the methodology supporting them would help streamline the main module.	
8		The Effectiveness Evaluation section is overly detailed with methodology information and is difficult to understand because of the academic focus which seems beyond the scope for this	

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		guidance. We recommend this section emphasize the purpose of effectiveness evaluations and provide a high-level description about more commonly used evaluations (drug utilization studies, knowledge, attitude, behavior surveys, outcomes evaluations).	

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Lines 83 - 85		Comment: "Monitoring and amending RMM, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to exceed the risks by the greatest achievable margin." Additional guidance is needed for expectation of when amending of aRMMs would be required.	
120-132		Comment: Consider adding an additional paragraph regarding the format of an aRMM once a particular aRMM has been selected. Having the right information is of little use if it does not reach the intended audience (HCPs, patients etc.) because it has been set up in a format/media which is not suitable for the target population. Proposed change (if any): paragraph on the importance of the format/media for aRMM – including digital/electronic options.	
127-132		Comment: long sentence; suggest to have bullet points: Proposed change: update the sentence <i>'Each safety concern needs to be considered individually, and the selection of RMM should take into account the seriousness of the identified or potential risk, the severity of the adverse reaction(s), the possible impact of the risk and the RMM on the patient, the preventability and the clinical actions required to minimise the risk as well as the indication, the route of administration, the target population and the healthcare setting for the use of the product'</i> to:	

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		Each safety concern needs to be considered individually, and the selection of RMM should take into account: - the seriousness of the identified or potential risk, - the severity of the adverse reaction(s), - the possible impact of the risk and the RMM on the patient,: - the preventability and of the risk, - the clinical actions if any required to minimise the risk as well as - the potential need for a long-term follow-up of the patient - the indication and medical condition (eg. life threatening disease), - the duration of treatment (acute, chronic) - the route of administration, - the target population (HCP, patient) and, - the healthcare setting for the use of the product	
128, 138 & 463		Comment: The text refers to aRMM being considered for safety concerns, but as per the definitions in GVP V, aRMM are usually only considered for important identified risks, not important potential risks and missing information. Proposed change (if any): Additional RMM should focus on important identified risks	
133		Comment: Could you please elaborate a little bit more/be more specific? - As digital technology advances, would that be acceptable to include aRMM in a website or a mobile Apps where other type of information is available (e.g. information about the disease, the use of the drug, etc...)? - In current practices, promotional activities may include face to face communication by company rep with HCPs/prescribers. This is an opportunity to present aRMM also. Is that acceptable? Further clarifications on what can be done, or what should not be done would be helpful.	

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133		Comment: It could be helpful to provide a definition or further guidance on what constitutes promotional activities in the EEA. If this is not available, the sentence 'as per national/local regulations' could be added. Promotional activities doesn't have a clear definition and it has very broad interpretation. Proposed change (if any): Promotional elements, either direct or veiled (e.g. logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation. 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.	
144-147		Comment: Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products, section 5.1.3. – Risk Minimisation Plan – lists<i>"restricted access to medicinal products based on genotype or phenotype testing..."</i> as additional risk minimisation measures Proposed change (if any): Amend the paragraph with these information and reference to the guideline mentioned above	
148-149		Comment: The authors speaks to assessing the 'potential for effectiveness of the additional RMM'. However, there may be situations where the intervention has been tested or utilised in clinical trials in which case that evidence should be considered. However, even if the tool was effective in a clinical trial or controlled setting, consideration for its use in a real world setting should be considered.	

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		Proposed change: To add: Assess the evidence for the effectiveness of the additional RMM in other settings including clinical trials and the potential for effectiveness in real world used"	
142-154		Comment: list of considerations for determining if aRMM would be most effective should be updated. Proposed change: • Consider the target population, the medical condition, the frequency, seriousness, severity of the safety concern, context of use, possible impact and preventability of the risk for which the additional RMM is meant to be developed. • Consider the need for advice to healthcare professionals for appropriate patient selection and excluding patient exposure where the use of the medicinal product is contraindicated, • Consider patient monitoring during treatment to prevent adverse reactions or early detection and management of adverse reactions • Assess the potential for effectiveness of the additional RMM, • the burden the RMM may impose on the system and possible unintended effects; • Consider the intended behavioural changes of healthcare professionals and patients during each step of the treatment process; and • Select the RMM tools that are expected to be: – risk-proportionate and effective in timely manner in minimizing the risk; – practical, user friendly for patients and not too burdensome for patients or the healthcare system.	
154		Comment: We would like to reinforce that both criteria need to be addressed here: not too burdensome and proportionate to the level of risk too Proposed change (if any): Select the RMM tools that are expected to be: • risk-proportionate and effective in timely manner in minimising the risk; and • Practical and not too burdensome for patients or the healthcare system.	

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155-159		Comment: Comment: Consideration is made for consistent approach to developing materials for the same active substance. However, there could be an argument for co-developing additional RMM for the same class of drugs so that tools had the same look and feel. Effectiveness would likely be much higher if drugs in a similar class used similar tools. Example of this exist in the US with Class wide REMS. Who is expected to drive this consistent approach across products? The innovator MAH or the EMA/NCA? Proposed change (if any): Please clarify and/or cross-refer to XVI.B.6 (line 717: <i>XVI.B.6. Coordination of effectiveness evaluation across medicinal products containing the same active substance</i>) if that is relevant to this point.	
160		Comment: It should be mentionned in this section that some educational materials such as patient card or publications are not to be considered as additional RMM because they are not linked to an important safety concern; eg patient card for the Covid vaccine which contains name of the vaccine, a QR code, batch information ect.	
165		Comment: '... in addition to paper-based materials.' Should this be: '... <i>and/or</i> in addition to paper-based materials. Anticipate that some materials would be better as purely digital. In general it would be appreciated if the agency could expand on guidance relating to digital material. Proposed change (if any): Add 'and/or' and provide further guidance on digital material.	

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161-165:		Comment: The guideline would benefit from having some view/guidance on formalizing electronic risk alerts/RMMs via these digital channels from the EMA and maybe consider having an Application to be used by Healthcare workers? Proposed change (if any): Suggest including language as per the above comment.	
161 - 165		Comment: Digital resources are only mentioned in the form of electronic dissemination. Can digital be considered its own category of aRMM? Or a sub-category? More Guidance is needed on the EMAs expectations regarding digital aRMM resources – e.g. Guidance on what video materials may contain/show. Social media should also be considered in situations when this is the manner by which the intended audience is likely to obtain their information.	
161 - 165		Comment: "... in addition to paper based." There may be scenarios where a digital solution is the most practical and preferred by HCPs & Patients, or scenarios where a paper-based equivalent of aRMM is not practical/possible (e.g. video, knowledge test). It is highly recommended that the format for dissemination be based on the best way to disseminate the information to the intended stakeholders. Insisting that paper is standard for all educational materials is extremely outdated and could potentially be detrimental in the effectiveness of the educational materials. For example, if a specific educational tool, such as a patient diary or patient card, was intended for a disease that is predominantly in young people, the use of paper materials would be a format that would not be suitable nor attractive to this age group and could greatly limit the uptake of this intervention. Many young people use their smart phone for everything and a paper patient card simply wouldn't be used. Proposed change (if any): Delete "... in addition to paper based" and modify to allow the format(s) of the materials to be suitable for the intended stakeholders.	
161 - 165		Comment: The GVP Module does not provide any guidance regarding when a digital aRMM resource crosses the boundary into becoming a medical device and/or Software as medical device (SAMD). Further, the Guidance does not reference any other Regulatory resource which may provide clarity in this regard.	

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		Proposed change (if any): Include guidance regarding when a digital aRMM resource becomes a medical device and/or include reference to existing Regulatory resources which provide clarity in this regard.	
161 - 165		Comment: It is welcomed that digital technology may be considered in addition to paper-based materials. Can clarification be provided as the technology details/description of the digital tools that would be need provided as part of the submission? Also, would details only need to be provided to Local Competent Authority (CA), or also to PRAC? Please consider including that digital tools may allow for use of more interactive features or graphics that are not feasible with the equivalent paper-based versions (so the two different formats of the same educational material may not be completely identical, although the content should still be aligned). Proposed change (if any):	
161-165		Comment: The acknowledgement of progress in technology for dissemination of RMM is welcomed. It is suggested to anticipate further progress and let flexibility to the MAH and Member States for selecting the appropriate tool. Paper-based material may become obsolete and redundant in some Member States in the future. Proposed change: As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and	

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		healthcare professionals, or for safety systems independent from location, may be considered <u>in replacement or</u> in addition to paper-based materials, as required.	
161-165		Comment: The guidance still advises of the use of digital technology for the distribution of aRMMs <u>in addition to</u> paper-based materials. There is evidence from surveys on physicians' preferences for route of presentation of educational materials that at this point in time three categories of preferences exist: physicians that prefer a) paper based, electronic b) web based c) both routes. It is a general trend that electronic/ web based communications are preferred by an increasing number of people, and that paper based communication in most areas will continue to shift to electronic materials over time. Considering this dynamic it would be prudent to maintain the requirement for paper based materials for the interim, but some RMM objectives may better be achieved entirely with e-materials (e.g. a PowerPoint presentation, a checklist, an algorithm) and should be assessed on a case-by-case basis and in consultation with local health authorities. Paper may be required e.g. only at launch and thereafter re-distributions and updates can be issued electronically. Proposed change (if any): <i>Consider modifying this text: "A variety of tools are currently available for use on their own or in combined manner as additional RMM. As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and foster interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered as an alternative or as a supplement to paper-based materials."</i>	

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162-165		As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials. Comment: Are web and app-based mechanisms subject to the same process metrics as paper-based dissemination? If so, would we need to capture download information or number of views of the materials? Proposed change (if any):may be considered as well as paper-based materials	
165		Comment: It is unclear whether digital tools can replace paper-based materials, or if paper-based materials should always be used. Proposed change: update to "...may be considered in addition to or as alternative to paper-based materials".	
171		Comment: There seems to be some overlap between the different tools, to allow a robust and appropriate selection it would be helpful to have an overview table summarising the key features for each tool. Proposed change (if any): suggest adding a table summarising the key features for each tool in this Educational materials introduction section, including what are the timing expectations for implementation of proposed RMP variations to accommodate tool name updates?	

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182 - 185		Comment: Audience input with regards to the format of educational materials is required, but this could be extended to specifically include digital formats. Proposed change (if any): When developing educational materials, it is therefore encouraged, where possible, to engage with healthcare professionals and patient representatives and user-test proposed materials for readability, accessibility, adequacy and user friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population. <u>These parameters and considerations could include the appropriateness of possible digital solutions, as well as physical (paper-based) options, in order to maximise the reach and effectiveness of the aRMM.</u>	
186		Comment: Except in the case of patients' cards for which there is an exception, black triangle information should be listed as one key element in this list of information elements. Proposed change (if any): suggest adding information about/refer to black triangle as an element in this list, as appropriate.	
198-200		Comment: Some MS competent authorities don't formally approve the educational material but only do a review. Proposed change (if any): Consider revising to accommodate for these differences in approval/review. Update the sentence to: "Statement explaining that this educational material is part of the marketing authorisation and has been approved by or developed in collaboration with the respective competent authority, including the version date/number and date of approval".	

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202		Suggest to add that any patient material should be written in layman's terms in order to ensure the comprehensiveness by non-medical audience.	
212-214		Comment: "...when handing out the guide ..." This language presumes a paper-based resource. In the modern world, including the health industry, more and more information is disseminated digitally. Proposed change (if any): replace "handing out" with "distributing" or "disseminating".	
214		Comment: genetic testing is missing Proposed change (if any): <u>...diagnostic or genetic test....</u>	
222-223:		Comment: Language is potentially confusing and introducing ambiguity as regard exact purpose of guides used for RMM purposes: are "healthcare professional guides" used "for reminding healthcare professionals of an on-going registry/study" considered ARMM? Proposed change (if any): Reword to avoid confusion	
224		Comment: Given such specifics of the tool requested, it should then be noted the precise location in the RMP that these sizes and other tool specifics should be specified. Should this be in the main body where aRMMs are described or should this only be in the appendix where details of the proposed/approved aRMMs are described?	
224 - 225		Comment: By only specifying physical format specifications, it is implied that digital solutions are not preferred. Consideration should be given to the format of digital solutions too - e.g. online video, online knowledge tests, apps etc. Also, a minor wording change suggested for the purpose of consistency	

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		Proposed change (if any): In the description of the tool in the RMP, details on the format (e.g. DIN A4 size or larger, online or digital resource [video, website etc]), its length (e.g. a short or a comprehensive guide) should be specified.	
224-225		Comment: Further details regarding where in the RMP this detail on the format of the patient guide should be provided. There is a concern that if prescriptive and specific information on the exact format of the patient guide is stipulated in the RMP this will not accommodate any local/country level requirements based on the healthcare system, some flexibility is needed. The final format of RM tools is agreed on a national level and may thus vary between MS. Therefore, providing this level of detail in the RMP appears redundant. From a practical perspective, would be difficult to specify details on the format, because usually the design of the tool is not systematically worked out at global level but at country level allowing some local adaptations to local health system or National Authority request. In addition, the artwork/mock-up is not longer appended to the RMP. It is quite time consuming to prepare such artwork/mock-up because involving many actors and sometimes CRO; thus would not be ready for RMP submission/approval steps. Proposed change: Please delete. Or replace the "should be specified" by " could be specified" and specify that the description can focus on what is common between countries, rather than providing details on the format, or delete.	

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226-230		Comment: although there might be a multiplicity of terms used to name educational materials, the examples provided here are quite self-explanatory. This is more practical to use evocative language to name a specific type of tool, ie slide deck, poster or HCP or patient guide. Why the preference/what is the rationale not to include qualifiers for different guides? How would these be distinguished if the Educational Materials include guides for different aspects of the RMM? Proposed change (if any): introduce the multiplicity of existing tools that could fall into "guides".	
231		Comment: Can clarification be provided as to whether Digital checklists might be allowable in line with advocacy for digital approaches now included in the guidance?	
231-259		Comment: It is not clear if an HCP checklist can be included within a Guide for HCPs (XVI.B.3.1.a) or if it must always be a standalone document. Especially given that several objectives listed seem those of a 'Guide' (e.g. lines 247-249; 250) Proposed change (if any):	
232-234		Comment: Considering information is in the SPC, the healthcare professional checklist is also developed to remind the prescriber actions that should be taken when prescribing a medicinal product to a patient. On top of prescriber and dispenser, one should add the counsellors: for OTCs, a strategy to improve the detection and resolution of misuse may consist of the creation of a counselling model to be first used in a study with customers requesting advice on non-prescription drugs for a specific condition. Such counselling model (or protocol) consists of a number of key questions to be covered routinely in the pharmacy practitioner's dialogue with the patient, questions that are often brought up in	

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		patient encounters but are asked in a more consistent way to all patients within a specific therapeutic group through the practice of counselling models. Proposed change: amend to: 'A healthcare professional checklist is a tool that provides recommendations and lists actions aiming to support the prescriber or dispenser / counsellor to check...'	
237-238		Comment: series of questions (check list like) can be part of guides to help healthcare professional on patient selection, but not aiming to be recorded. Proposed change: In contrast to guides (see XVI.B.3.1.a.), a checklist is presented as a series of questions which can generally be answered in a 'yes'/'no'/'not applicable' manner or with a very short answer, for which the completion will be recorded.	
247-249		Comment: This bullet does not read like the objective of a checklist but rather that of a guide. Proposed change (if any): Selecting the correct formulation, strength or dose in order to avoid medication errors	
251-253		Comment: Reminding physicians and patients of amount of time that is required to follow a patient would also be helpful. Proposed change (if any): Suggest adding 'and duration of monitoring or follow-up' to line 251	
254 – 258		Comment: should be part of the patient Guide instead of check list	
261-262		Comment: The remit of the risk awareness form appears to overlap with the Healthcare professional checklists for risk minimisation when targeting the HCP. As the Checklist is for the HCP, we suggest limiting the target audience for the Risk awareness form to the patient, for clarity of use both for the HCP and for Industry.	

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		Proposed Change (if any): "A risk awareness form is a tool that informs patients on (a) certain risk(s) of a medicinal product and the need for risk minimisation."	
265		Comment: Following a valuable reinforcement of provisions for collaboration with HCP and patients' organisation within this Draft GVP Module update, HCP engagement should be better reflected here to ensure these forms would be effectively used. It is stated that risk awareness forms should be used when it is considered essential for the product. However it is unclear what is different about these forms as all additional RMM should only be implemented if essential. Proposed change (if any): Suggest this statement should be rephrased – 'The HCP should ensure that the patient should receive...' Also, suggest this needs to be qualified as may be dependent upon the local healthcare system in which the form is implemented. Please provide examples of when a risk awareness form might be appropriate.	
265 - 266		Comment: A physical printed form of Risk Awareness Form is mandated in the Guidance without justification. At 277-281, the Guidance says the document may take several forms, including electronic. Given the acknowledgement that digital solutions have advanced and continue to advance, suggest that equal opportunity for physical and digital documentation of risk awareness is promoted. Digital solutions have myriad opportunities for metric collection, including innovative measures of understanding (e.g. knowledge tests). Proposed change (if any): Remove advocacy for limited paper-based solutions and offer more opportunities for leveraging the capabilities of digital solutions.	

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277-284		Comment: We would like to clarify, and it is our understanding, that this would be HCP responsibility to ensure and collect evidence (signature applied/box checked) that the information has been effectively delivered to the patient. We would also suggest reinforcing that, in order to easy collation and analysis, electronic format should be the primary/preferred media. Proposed change (if any): We suggest-language to be updated to reflect the above, and make it clear it is not the intend that MAH would be responsible to ensure such a documentation has been established.	
277-284		Comment: EMA and local competent authorities should function as partners and ensure that any local healthcare E-Systems support the broader dissemination and utilization of RMM tools. Can EMA provide further guidance on what the expectations of the MAH and national competent authorities are? It is not optimal (or even realistic) if MAHs contract software providers and establish independent processes without active support and coordination by a central authority. Proposed change (if any):	
281-284		Comment: It would be beneficial if the agency could expand on the role of NCA's in respect to the form and process, the alignment with the HC systems can be demanding – should be “preferably”, but not a requirement. Having the MAHs adapt their processes and forms across 27 different countries and systems will be difficult and a hinder to effective dissemination. For this to truly be effective we need a closer collaboration between the agency, local HAs and the MAHs and alignment in systems and processes. Just handing over the issues to the MAHs will not be effective.	

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		Proposed change (if any): Please provide clarification on this aspect.	
289-293		Comment: Since only the patient and HCP will know whether the patient situation has changed and whether this would require a new/updated form; we suggest language to be amended to reflect this and make it clear that MAH will only be able to react upon HCP request/feedback. We think that the proposal for specific additional follow-up risk awareness forms is an unnecessary burden and could lead to the follow up form being used inadvertently as the initial risk awareness form. The HCP, who again should be aware of changes to the patient's clinical situation, could re-review the risks to the patient (with appropriate documentation) using the same risk awareness form. MAH having no visibility here cannot be proactive unless made aware by the HCP or through RMM effectiveness study results. Proposed change (if any): Amend wording to reflect the above and remove the need for having specific follow up forms and that any reassessment is made using the same form.	
294-309		Comment: MAHs use some tools (e.g. videos) to train HCPs/patients on the appropriate use of some drug devices. Until now, those tools are not and should not be considered necessarily as aRMM, as they do not necessarily minimize one single safety concern. How to differentiate those "demonstration kits" from "already existing videos" in place to communicate on the appropriate usage of a drug. There might be a risk of overlap with regulation with drug devices. Proposed change (if any): A demonstration kit including videos might be considered as aRMM only if it supports a safety concern in the RMP, such as a medication error as ex.	
294		Comment:	

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		Demonstration kits may be used for different purposes than to address risks described in the RMP. Demonstration kits may be created as part of preparation for Commercialisation. Can it be clarified that Demonstration Kits are only considered additional RMM if the objective is to mitigate specific safety concerns e.g. medication error. Proposed change (if any): Add information that this section does not apply to all demonstration kits, only to the ones used for the purpose to address the risk as described in the RMP.	
303-309		Comment: Clarification is needed as regard what type of demonstration kit is foreseen here: would these be device trainers? They may not be the same materials/have the same specifications as the production device; also, how would 'training devices' intended for RMM purposes be distinguished from those intended for marketing/promotional purposes? Could these devices also be developed/manufactured by a 3rd party? Should demonstration kits be considered as true RMM tools falling into RMM requirements? What would be the regulatory requirements for notifying NCAs in case of AEs/Incident/Issues? How far does this has to be linked with National Device legislations/EU Medical Device Regulation? Proposed change (if any): Clarification is needed as per the above questions.	
310-337		Comment: This wording appears to expand the scope of RMMs to an area that is not under MAH control nor RMM focused (but rather more Pharmacovigilance focused). There is the potential to blur the disconnection between RMMs and measures of effectiveness (such as PROs) or Pharmacovigilance activities and could be viewed by clinicians as encroaching on clinical practice.	

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		The scope of such activities needs to be clearly defined and should be based on the collection of information that is absolutely per the SmPC/RMP to promote the safe use of the product. This comment applies to most of the section XVI.B.3.1.e, rather than the specific lines referenced. We also suggest not to use the term 'patient diaries' within the context of RMMs. If patient information must be collected to facilitate risk minimisation, propose to rename e.g., "patient logbook" or some other terminology which is not utilised for another purpose outside of risk minimisation context. Proposed change (if any): Suggest to either remove, remove ambiguity or reword to refocus on RMM tools purposes and replace 'patient diaries' by a more appropriate term. We would suggest deleting the sentence (line 328) as it is confusing and the purpose of an additional RMM is not to be a data collection tool.	
310 - 337		Comment: Consider advocating for digital solutions for patient diaries. The vast majority of people in Europe have access to a smart phone, laptop or tablet. Physical diaries can be easily lost, are very passive (i.e. they rely on patients remembering to complete them) and take time to be communicated to HCPs. Conversely, digital solutions can be carried easily on a phone or mobile device, can be programmed to send notification to remind patients to complete them, can be directly linked to monitoring devices (e.g. blood pressure machines) and can be uploaded to a HCP almost instantly. Programmed reminders or alerts for HCPs can then also be made available. Proposed change (if any): Include additional information on digital patient diary solutions and advocate for a digital approach over paper, where possible and appropriate based on assessment of the patient population needs.	
338		Comment: What about electronic "cards"? Most smartphones today support e-card functionality for credit cards, boarding cards or membership cards.	

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		Proposed change (if any): Please consider to add a section regarding electronic patient cards, can clarification be provided whether Mobile Phone Applications would be acceptable for patient cards, including push notifications..	
393		Comment: It is not clear what this statement means. Is this saying that even if the patient card is included within the packaging the HCP should still provide a copy to the patient at the time of prescribing? Whether the patient's card is inside or outside of the packaging has an impact on the requirement for the MAH to ensure that patients' card is always available to HCP and how the MAH could be responsible to <u>'ensure'</u> this, as the mechanism for patient card availability to the HCP and the point at which the patient is given the card may vary between healthcare systems? More guidance is also needed in cases where the patient's card is inside the packaging and the pack is split particularly because this not under MAH control. Proposed change (if any): please consider providing more guidance for these situations where the patient card is within the pack and the pack could be split by the pharmacist. Please consider to add information regarding digital distribution/re-distribution systems for information related to patient cards.	

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		It is proposed to replace the sentence as follows: 'Marketing authorisation holders should ensure that patient cards are always available to healthcare professionals when <u>dispensing the medicine</u> to the patient at the applicable point of care	
421		Suggest to add a clarification regarding the need to instruct the HCPs about the purpose and use of the Patient Card (when to provide it to a patient and what guidance is to be provided to the patient). It is particularly critical when the objective of the Patient Card is not for the Patient itself but to alert other HCPs, and so the Patient is expected to carry the patient card with him/her. The provision of the Patient Card to the patient is mainly supported by the HCPs, hence it is expected to ensure the HCPs is properly educated on this material.	
422-425		Comment: Cooperation between MAHs is the optimum approach but may be difficult to implement in many cases. An alternative recommendation should be provided in cases when a single patient card is unattainable. Will there also be coordination by the concerned Competent Authorities? How would <u>regular</u> dissemination be managed in this case? Proposed change (if any): Please clarify	
423 - 425		Comment: How will this work in reality? There are two scenarios: 1) The innovator card is already available or 2) A new risk emerges when generic/biosimilars are already available. In the latter, will the innovator be appointed the lead? It's hard to make this a recommendation. How will it function if some of the MAH do not wish to follow a recommendation that is not a requirement?	

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		Additionally, how practical is it if these materials are approved in individual member states and for individual MAHs? It would seem to require the format and language to be determined more centrally for all MAH and then imposed across all applicable MSs (Member States).	
428		Comment: A DHPC 'may also serve as an additional RMM'? We would like to have clarification and to prevent ambiguity as to whether DHPCs are only to be considered an aRMM when related to safety concerns in the EU-RMP? (e.g. is a DHPC requested by a Competent (National) Authority, not listed in the RMP, not to be considered an ARMM). Proposed change (if any): Suggest avoiding ambiguity and clarify that a DHPC listed in the EU RMP is considered as an additional RMM.	
453-454		Comment: How can the evaluation of an adverse pregnancy outcome be considered aRMM? Proposed change (if any): Please clarify	
455-456		Comment: when the forms for reporting pregnancy should be provided? With the PPP or after a contact by the physician? Proposed change (if any): Suggest the organised data collection for reporting of pregnancies should not be considered part of the PPP ARMM, as this does not minimise the risk. This should be considered separately under measures of effectiveness.	

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474-476		Comment: We suggest adding a reference to the relevant product specific current guidance. We would also welcome any update on the status of EMEA/149995/2008 rev.1 Committee for Medicinal Products for Human Use (CHMP) Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products: Draft. Proposed change (if any): Suggest referring to EMA guideline: EMEA/149995/2008: Guideline on safety and efficacy follow-up and risk-management of Advanced Therapy Medicinal Products (Effective 31-Dec-2008).	
477		Comment: centre accreditation systems: need for further details/clarifications such as: by whom these centers will be accredited? Will the accreditation be officialised post training? Post training with certification delivered by the MAH? Because of different national health care system in Europe, may be very difficult to implement in EU globally. Proposed change (if any): more details, clarity on roles and responsibilities to give accreditation to these centers, are needed. Idem for Feasibility at EU country level or otherwise need for a statement to adapt to local situations as per national health care system as in line 495.	
485-495		Comment: The role of MAH in ensuring the use of forms for patient information exchange between prescriber and dispenser (XVI.B.3.4.c) and dispensing forms (XVI.B.3.4.d) for the purpose of controlled access as a RMM is unclear. The burden of responsibility for these items rests on the prescriber and dispenser, not the MAH. The MAH may supply the forms, but can't be responsible for ensuring c) and d) are performed.	

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		Proposed change: roles and responsibilities of MAH versus prescriber and dispenser in sections XVI.B.3.4.c and XVI.B.3.4.d must be clarified. Suggest to write up in one sub-section	
488		Comment: We would suggest electronic format to be the primary/preferred media. Proposed change (if any): suggest rephrasing as follows "This information exchange can <u>preferably</u> take place via connected electronic systems, paper forms, or personal confirmation"	
496		Although there are likely to be national-specific requirements, it would be helpful if general guidance could be included in this section on web-based RMMs, for example when they should be considered, and monitoring and controlling access	
497		Guidance on submission of Dissemination Plans in timely relation to RMP submissions is missing. Suggest to add guidance on if Dissemination Plans should be submitted in parallel to a new/updated RMP, or after its approval (considering that there is some shared information in both documents) ? A risk minimisation programme and implementation plan template approved by EMA to be use for all NCAs would be helpful to align between member states and help ensure a harmonised and transparent approach to implementation of aRMM.	
501		Comment: The meaning of <i>target outcomes</i> is unclear Proposed change (if any): Add clarifying information of what <i>target outcomes</i> are in this context.	

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510		Comment: It is not very clear whether the DHPC Communication Plan Template should be used as the Template for description of RMM Dissemination. Could the DHPC Communication Plan be made more generic to allow utility for other RMM as well, and to avoid confusion?	
514		Comment This section (Effectiveness Evaluation) is overly detailed with methodology information which seems beyond the scope for this guidance. As examples: • The extensive details about quantitative measurements / research. • The details about qualitative findings relating to behavioral change. • Figure XVI.3 – details about behavioral enablers / barriers Also, terminology use in this section seems to be more 'academic' in nature and not consistent with wording in prior sections. For example, terms such as "stages of the communication process", "factors influencing risk perception and knowledge adoption", "prior information awareness". Also, the terminology does not align with the framework for effectiveness evaluation – process indicators (as noted in prior version [rev 2], GVP V and CIOMS IX).	
520-521		Comment: Regarding the statement: "Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine (see XVI.B.1.) and additional RMM (see XVI.B.3.)", can the agency provide clarification about cases where additional PV monitoring is expected when <u>only</u> routine RMMs are in place? Proposed change (if any): It should be made clear that evaluation of effectiveness of routine and/or additional RMM should (only) be performed as described in the RMP. As such the RMP	

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		should indicate when routine PV is considered adequate to evaluate effectiveness of routine and/or ARMM	
524-526		Comment: Please make a clear reference to alignment with the RMP Part III PV Plan, we suggest to re-phrase as below. It is not clear from the wording of this sentence if protocols for all qualitative studies should be included in the Pharmacovigilance Plan of the RMP. Proposed Change: 'The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed and qualitative studies described in the pharmacovigilance plan of the RMP'	
536-541		Comment: Is the additional check point timeline meant to include a mandatory update of the RMP at this time? Or just a review of the RMP aligned with PSUR schedules? Reviews should include adding <u>or removing</u> element of the RM programme. It is stated that effectiveness should be evaluated a regular timepoints...e.g. After initial implementation of a risk minimisation programme (e.g. within 12-18 months), after 3 years. As evaluation of effectiveness is an iterative process, with some indicators being assessed at certain timepoints and other outcome indicators perhaps dependent on study completion, it is not clear if the intention is that an 'Effectiveness update report' is required to be submitted at the timepoints suggested? Effectiveness updates are provided in the PSUR. Proposed change (if any):	

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		Within 3 years of initial implementation of a risk minimisation programme to potentially remove or add further elements to the risk minimisation programme (see XVI.B.5.3.)	
542		Comment: "Within 5 years to assess the overall effectiveness of the risk minimisation programme (see 543 XVI.B.5.3.) or in time for the evaluation of the renewal of a marketing authorisation" Consider adding the possibility for dismissal from the program upon positive evaluation.	
545-556 and table Line 559		Comment: These are no absolutes and the degree of unintended effects needs to be considered too, for instance in adherence, which will never be 100%. How can MAH possibly measure unintended outcomes without posing an increased burden on the Healthcare System? (Please refer to the general comment section). The unintended outcome 'lack of adherence', if observed, will be very difficult to attribute to the aRMM; or would need to have some kind of control group or historical benchmark; still, the variability is so great that causality could be established; at the best a decrease of adherence may be observed. The unintended outcome 'switching' and 'non-treatment' seem relevant. 'Spill-over effect' or 'additional prescribing' may require very detailed and accurate data sources so not sure about feasibility. Proposed change (if any): Leave out the evaluation of unintended consequences.	
559		Comment Table XVI.1 – intended / Unintended – this table does not appear to be relevant information for this section. The concepts of switching, spill-over, non-treatment, would require further	

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		explanation and seem too 'academic' for this type of guidance. The general points relating to this table were covered in text. Proposed change (if any): Suggest removing.	
559		Comment: Within the table XVI.1, the row pertaining to lack of adherence could be misinterpreted. Lack of adherence to the medication of interest could be an unintended consequence whereas we are referring here to lack of adherence to the RMM which is in itself not an unintended consequence but a failure of the RMM. Table XVI.1.: Effects of regulatory actions on medicinal product use [...] Lack of adherence --- NA --- RMM is not adhered to in the target Population [...] Realistically, it may be challenging to identify these unintended effects, as HCPs are less likely to indicate if they are not adhering to the RMM. Proposed Change: Consider excluding this table row as it is inherent in the measures of effectiveness already described Complete table and avoid using 'N/A'. Maybe the intended effect of the regulatory effect in this example is "RMM recommends the close HCP/patient interaction to overcome potential obstacles for lack of adherence."	

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581-594		Comment: We would like to reinforce the use of behavioral change methods and research accordingly to implement and evaluate RMMs – majority of this is human-dependent and can be facilitated by technical systems and processes only. Proposed change (if any): suggested wording: “Depending on the scope of the effectiveness evaluation, a combination of research methods may be useful, <u>inclusive of behavioural</u>, and the objectives should be defined in the evaluation strategy in relation to the desired health outcomes of RMM. Marketing Authorisation Applicants/Holders and Competent Authorities should agree on indicators of success to be included in the evaluation plan”.	
606_654		Comment: Determining the “Proportion of” requires having knowledge about the denominator which may be practically impossible in many situations, eg especially for large patient cohorts. MAH may not be able to know which % of the patient was prescribed the drug, which % of these would have received RMM material, % of contraindicated patients exposed etc... Proposed change (if any): Please consider amend the wording to reflect this	
613		Comment: If “Level of comprehension” is being measured “within 3 years” (line 540) or “within 5 years” (line 542) in a patient who was on the treatment maybe only for 6 months overall this may be defeating the intended purpose. Proposed change (if any): Would suggest waiving line 540/542 to add “according to treatment duration and regimen”	

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615		Comment: What about the use of PROMs/PREMs and patient-orientated outcomes? We would suggest considering these as well as examples of outputs of qualitative research into knowledge adoption. Proposed change (if any): Please consider adding language about these	
615-624		Comments: (Risk knowledge) The qualitative findings are new and may only be measured via surveys or focus groups. HCPs' attitudes in term of feasibility, usability and time constraints are relevant and may drive some quantitative measurements down so should be included in the discussion in case of non-success. Proposal: to clarify how and when. A framework for translating the impact of qualitative findings into the success criteria would be useful.	
627		Comment: (behavioural changes) some of the qualitative findings overlap with some quantitative measurements from the knowledge section. Proposal: A summary table of qualitative and quantitative estimates for either risk knowledge or behavioural changes would be very useful.	
648-654		Comments: -What if a member state does not have an electronic healthcare database or medical records? Would surveys not constitute a burden to the Healthcare System? -What about the use of PROMs/PREMs and patient-orientated outcomes? We would suggest considering these as well, as examples of quantitative measurements of behavioural changes. Proposed change (if any): Please consider adding language about these	

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633		Comment: What does lack of diagnostic tools mean regarding difficulties in implementing RMM?	
698 - 700		Comment: "Threshold values may be defined by using for example baseline or historical data, expected frequency in comparable populations or of comparable risks." Please clarify the expected threshold within the different domains.	
706		Comment: Please consider reviewing the scope of what is feasible for the MAH within this table. Knowledge of all these factors within each individual Member State is not realistic (e.g. <i>Possibility of taking an informed decision (e.g. access to PL, need for urgent treatment, patients with different chronic disease), Variability between populations, Risk level accepted by society (e.g. insurance company, case law, from other technological areas), Level of public interest</i>). In addition, all these factors, and especially for acceptability, are very much contextual i.e. perception of risk during a pandemic. Proposed change (if any): Please consider rephrasing to reflect the above	
707 - 709		Comment: The text would indicate that an aRMM is either effective or failed; it does not allow for a partial success, indicating that aRMM is on the right track but does not fully meet pre-defined criteria for success – which of course would still necessitate further considerations as to how to accelerate/further improve. Suggest reference to the iterative approach of RM to allow for this.	

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		Proposed change (if any): Effectiveness evaluation where results indicate that pre-defined thresholds have been reached confirm that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach <u>(or only partially reaching)</u> the pre-defined threshold requires further investigation <u>as part of the iterative approach to risk management</u> to obtain a clear understanding of the reasons that could help explain the <u>failure lack of success</u> .	
711-712		Comment: it is not within the remit of the MAH to be engaging in the development of clinical guidelines and setting treatment standards. Proposed change (if any): Please remove.	
754 - 755		Comment: Clarity and guidance is needed with regards to what the relevant timepoints/events that should trigger or inform the critical assessment of an aRMM would be. As currently worded, this concept is vague and open to varying interpretations that would result in inconsistency across products and companies.	
Lines 779-789 Lines 798-801 Lines 821-824 Lines 837-849 Lines 879-894		Comment: The paragraphs listed in column A refer to implementation and dissemination of aRMMs and highlight the importance to consider specificities of Member States requirement and diversity in terms of healthcare systems, national languages, accessibility to information and the need for the MAH to discuss plans for RMM well in advance. On the other hand, the GVP raises the importance of implementation of aRMM in a coordinated manner. Proposal: Include further clarification and details on how RMM agreement will be discussed and communicated between the MS and with the EMA to ensure a coordinated approach and ultimately effectiveness of the RMM.	

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782-783		Comment: Does the use of 'RMM' here refer specifically to 'additional RMM' (as lines 775 to 779 RMM do)? Proposed change (if any): <i>Consider referring to 'additional RMM' in all instances in this sentence</i>	
797		Comment: The GVP XVI Addendum I has not been updated to align with the revision of GVP module XVI. Are there plans to update GVP XVI Addendum I?	
809-815		Comment: in reference to the comment for lines 165-165 we would suggest the Agency to provide guidance reinforcing EU wide dissemination of RMMs and related communications through electronic risk alerts/RMMs via digital channels from the EMA; and maybe consider having an Application to be used by Healthcare workers? Proposed change (if any): Suggest including language as per the above comment.	
821-824		Comment: <i>"In order to respect the diversity of the different healthcare systems in Member States, some key elements will be specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State), but these should still be included in the RMP agreed at EU level."</i> Comment:- key elements for CAPs would apply in all 27 Member States. Key elements don't exist as such for non-CAPs. How do local HAS communicate between each other and with EMA?	

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		It might be difficult to have the exhaustive activities linked to the different MS healthcare systems. Proposal Rather it could be mentioned that some local adaptation remain possible depending on the healthcare system organisation, and these will be decided at nationla level. <i>It might be more effective if the PSUR is used to list differences, not the RMP, guidance would be appreciated.</i> Define "Key elements".	
832-857		Comment: The role of the Member State itself in a RMM implementation needs to be further reinforced as it cannot be the marketing authorisation holder's responsibility alone, and indeed that is not feasible in terms of any one healthcare system implementing a RMM, inclusive of appropriate resource provision. Proposed change (if any): suggest adding: "National Competent Authorities should support MAH in the implementation phase as needed "	
868		Comment: "Certain medicinal products may in some Member States permitted to be prescribed nurses or pharmacists with or without oversight by a general practitioner". Should materials be addressed to those nurses or pharmacists as "prescribers"?	
888 - 891		Comment: It is stated: <i>Specifically the implementation of risk awareness forms may vary significantly from one Member State to the other, a therefore a detailed description of the forms and dissemination</i>	

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		<i>processes in Member States to be followed by the marketing authorisation holder should be available within the RMP, as agreed with the competent authority(ies) in (the) Member State(s).</i> It is understood that the key messages of the risk awareness form would be included within the RMP, whereas the detailed description and dissemination plan is agreed and documented with the Member State (but is not included in the RMP). Proposal: Further clarification to be provided to this text. It does not seem feasible or in line with GVP V that specific Member State dissemination plans should be included in the RMP.	
888-894		Comment: <i>"User-testing of materials for risk minimisation in the local languages is recommended"</i>. In general user-testing in local languages would increase the complexity and prolong the MS implementation phase. Current writing is also unclear on when during the local implementation such user-testing is recommended to be performed. Need a clarification: If that means a form per country is required in the RMP is not realistic. In the same, user-test in each country is also not realistic.	
889		It would be helpful to receive clarification as to whether RMM dissemination would be agreed at the Member State level, as this would be after CHMP positive opinion and therefore the RMP would not include a detailed description of the forms and dissemination processes in Member States.	
896		Could you please specify for which type of issues encountered in dissemination process, the MAH should inform the Member state. It is usual to have minor deviations e.g. slight delay in the	

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		implementation, not 100% target reached...Would that be major issues only, and if so pls give examples? Additional clarity could be provided in relation to what constitutes 'relevant changes' to dissemination which should be agreed with the competent authorities in Member States.	
922		Comment: collaboration between the Agency, its committees, competent authorities in Member states and HCPs and/or patient representatives makes sense. It would also make sense to add in section XVI.C.3 language about the collaboration between MAH and HCP/patient representatives to be in line with the encouragement of engagement with HCPs and patient representatives when developing EM specified in section XVI.B.3.1 (lines 182-185). In addition, MAH are responsible for developing EM that expected to be practical and not too burdensome for patients or healthcare systems (lines 152 – 154) requiring connection with HCPs. Proposed change (if any): It would also make sense to add in section XVI.C.3 language about the collaboration between MAH and HCP/patient representatives to be in line with the encouragement for engagement with HCPs and patient representatives when developing EM specified in section XVI.B.3.1 (lines 182-185).	
935-936		Comment: The text introduces the possibility of evaluating the outcomes of RMM in the RMP, it is noted that this is 'should' rather than 'shall'. Please consider removing this suggestion. The RMP is a planning document rather than and report, and with this is mind it is considered that the PSUR is the appropriate place for such an evaluation. It is however acknowledged that should the evaluation result in a change to the RMM this should be included in the RMP. Regarding the text about summary evaluation in the RMP as well as the PSUR, please provide more clarification and	

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		guidance on the differences of what should be reported in the PSUR vs in the RMP. For example the evaluation is captured in the PSUR but the impact of the assessment would be in the RMP (e.g. adjustment of the aRMM). Please can clarification be added on which routine risk minimisation measures require evaluation of effectiveness for inclusion in the PSUR e.g. only those with formal assessments of the effectiveness as described in the RMP. Should results of the RMM evaluation now also be included in Section 12 of the RMP (in addition to Section 16.5 in the PSUR, as done currently)? Clarity is needed regarding the expectations for evaluation to be reflected in the PSUR for Generics. Proposed change (if any): PSURs should include a summary evaluation of the outcomes of specific RMM in the EU. If the evaluation results in a change to RMM the RMP should be updated and include a rationale as to why changes are being made to the RMM.	
940-942		Comment: Should this statement be further clarified as the PSUR and risk management plan common modules have become more divergent following the introduction of GVP V Rev 2? Proposed change (if any): please clarify accordingly	
949		Comment: EPAR. As a specific COVID-19 transparency activity EMA has disclosed the entire EPAR, in contrast to other compounds where only a summary of the EPAR has been disclosed. Proposed change (if any): Please clarify is the bullet here means disclosure of the entire EPAR.	

3. ANNEX 1 : Specific comments on text

#	Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
	83-84		Comment: "Amending" RMM refers to the process of altering an existing RMM in order to be more effective based on new evidence about its effectiveness or impact on the outcome of interest. However, the word 'correction' is then used to describe the same concept in line 86. Proposed change (if any): Consider using the word 'modification' of the RMM in both instances or use the same word throughout (e.g., 'amending')	
	85-87		Comment: "Monitoring" and "amending", in the context of RMM are defined (which is helpful), but then the wording switches back to "assessment of effectiveness". Proposed change (if any): Consider adding information/detail regarding the roles of monitoring and amending RMM in the context of assessment of effectiveness, to link these sentences. E.g. "Monitoring and amending RMM are important elements in assessing the effectiveness of RMM" Line 85	
	88		Comment: In reference to the sentence: "The assessment of the effectiveness of RMM is important for risk management with an iterative process of evaluation, correction and re-evaluation of RMM, which is integral to the lifecycle benefit-risk assessment of medicinal products", and in consistency with sections XVI.C.2. and XVI.C.4, a reference to GVP Module VII should be added. Proposed change (if any): suggest adding: "This GVP Module should be read together with GVP Module VII - Periodic safety update report (PSUR)"	
	98-99		Comment: Extending the word 'patient' to cover carers and representatives is confusing. How to avoid confusion when targeting true patients and not carers or representatives? Example given below. Line 144: "Consider the need for advice to healthcare professionals for appropriate patient selection and excluding patient exposure where the use of the medicinal product is	

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			contraindicated, patient monitoring during treatment to prevent adverse reactions or early detection and management of adverse reactions;" Proposed change (if any): Allow differentiation between true patients and the whole group of patients, carers and representatives.	
	98-100		Comment: This is our understanding that GVP Module XVI and its addendum is also applicable to vaccines, hence the term 'patient' may be misleading for vaccines. Proposed change: The term 'patient' in this guidance covers patients using or considering the use of a medicine, subjects using or considering using vaccines, parents and other carers, and patient and consumer representatives. It also includes the (unborn) child in the case of exposure during pregnancy.	
	115		Comment: about the labelling on outer packaging: as an ex. would add pictogram, warning texts Proposed change: <i>'...the labelling on the immediate or outer packaging of a medicine, pictogram, warning text, pack size...'</i>	
	140 - 142		Comment: "In determining whether additional RMM are needed and which measures would be most effective, marketing authorisation applicants/holders and competent authorities should: • Consider the target population, frequency, seriousness, severity, context of use, possible impact and preventability of the risk for which the additional RMM is meant to be developed" Please also consider expected benefit of the treatment and treatment duration for line 142.	
	144-147		Comment: This point is extremely complicated as written.	

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			Proposed change: "Consider the need for additional advice to HCPs for appropriate patient selection when treatment is indicated, which patients to exclude from treatment where the medicinal product is contraindicated, monitoring patients during treatment to either detect adverse reactions early or prevent them and management of adverse reactions"	
	149		Comment: With reference to 'impose on the system', to which system does this refer? E.g., risk management system, local public health system? Proposed change (if any): Please clarify Suggest to add "healthcare" prior to "system"	
	153		Comment: What can be understood as "timely" manner? This might be very much open to interpretation. Proposed change (if any): Remove the term "timely manner".	
	162 - 164		Comment: "As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s)..." This is a challenge for industry with dissemination to pharmacists and nurses. We welcome the electronic assimilation possibility, however there are some challenges with the availability of a valid source for email addresses for HCPs and data privacy concerns associated with the usage of email addresses. Please revise as:	

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			As digital technology advances, the potential of electronic dissemination, such as through electronic medical records or web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s)".	
	172- 174		Comment: The text here is difficult to follow Proposed change (if any): An educational material should have a clearly defined scope and objective and add value beyond the SmPC and PL. The material should only refer to safety issues or measures that are included in the SmPC and PL but should not be a mere repetition of the SmPC/PL content or parts of it.	
	173 - 174		Comment: "Although it should not be a mere repetition of the SmPC/PL content or parts of it, it should not relate to safety issues or measures that are not included in the SmPC and PL." Proposed change (if any): "Although it should not be a mere repetition of the SmPC/PL content or parts of it, it should not relate to safety issues or measures that are not included in the SmPC and PL."	
	181		Comment: suggest rewording the sentence: "...concern(s) and when the objectives of RMM cannot be reached with the SmPC and PL alone." Proposed change: "...concern(s) and when the objectives of RMM cannot be reached with the SmPC and PL and outerbox labeling alone."	
	189-191		Comment: "... (where warranted, information can be provided in more detail or in a different way than in the SmPC/PL e.g. by the use of tables, flow charts or illustrations)";	

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			Proposed change: "...information can be provided in more detail or in a different way (for ex. by using a different wording) than in the SmPC/PL ..."	
	196-197		Comment: in reference to digital tools, hyperlink to the SPC/PL are proposed. What about QR code? Proposed change: update the sentence as: "Reference to the SmPC or the PL whenever possible; in the case of digital educational materials, these could refer to the SmPC or PL through a hyperlink or a QR code;"	
	203		Comment: a guide does not only highlight actions to take but also information or recommendations on the risk. Proposed change: amend the sentence as "A patient or healthcare professional guide is a tool that highlights information and the specific actions to take for risk minimisation (see XVI.B.1.) to healthcare professionals or patients"	
	229 - 230		Comment: "It is preferable not to add qualifiers to describe the content (e.g. 'administration guide')" The reason for the preference to not add qualifiers is unclear. For example, a sponsor may want to clarify that the Pharmacist Guide is to provide the pharmacist with further information about how to minimise or prevent medication errors. Proposed change (if any): Please remove this sentence. "It is preferable not to add qualifiers to describe the content (e.g. 'administration guide')"	
	244		Comment: amend the sentence "Exclude pregnancy before/during treatment, record pregnancy testing results...."	

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			Proposed change: "Exclude pregnancy before/during treatment, by conducting a pregnancy test and record pregnancy testing the results...."	
	295-296		Comment: Only the demonstration kit for the management of Important Identified Risk should be considered as Educational Material. Proposed change (if any): A demonstration kit for the management of Important Identified Risk is an educational material and is a tool that trains healthcare professionals or supports healthcare professionals in training the patient for administering the medicinal product safely.	
	295 – 300		Comment: Regarding demonstration kits. Please consider adding a possibility for a demonstration video.	
	306		Comment: It is not clear what kind of reporting advice is supposed to be included here. Proposed change (if any): The marketing authorization holder should include <u>reporting advice</u> to healthcare professionals and patients in the instructions of the demonstration kits, investigate such reports and notify the competent authorities of any action needed to improve the demonstration kit, the device or product information of the actual medicinal product, and initiate the necessary actions.	
	339-342		Comment: correct a typo and amend the purpose of the card which may also contain safety information. Proposed change: A patient card is a tool that (a) may include the key safety information on the risk and/or (b) reminds the patient of (a) certain action(s) to take for risk, and /or (c) precautions	

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			of use, eg: instruct patients to separate their med from antacids or calcium supplements to prevent the drug not working as well as it should. It aims to ensure that information regarding the patient's current treatment with the medicinal product and its risks is held by the patient at all times. Patient card can and be used as a communication aid with healthcare professionals (e.g during prescribing or dispensing).	
	359		Comment: in case of signs of symptoms advice from medical may also be recommended Proposed change: Certain signs or symptoms of the adverse reaction require the patient to seek (urgent) medical advice or care;	
	367		Comment: Proposed change: There is potential for clinically significant interactions with other therapies and that concomitant treatment with those should be avoided or need to inform any prescriber;	
	379-381		Comment about the material of the patient card. "Used over a long time, therefore their material should be of sufficient durability to sustain considerable wear and tear, e.g. be laminated and not be a cut-out or tear-off paper sheet as part of the PL". This described in row 397-399 paragraph describing patient card inside or affixed to the outer packaging:" Patient cards placed inside or affixed to one of the sides of the outer packaging (e.g. patient card attached to the outer packaging as a flap side with a tear-off section)" It might be difficult to have the same support for patient cards sent by email. Proposed change: e.g. be laminated if feasible and not be a cut-out or tear-off paper sheet as part of the PL	
	410-413		Comment: please clarify interim measures. In addition it is not clear what "or to allow for dispensing existing pharmacy stock of the medicinal product" means.	

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			Proposed change: In the case where the patient card inside or affixed to the outer packaging becomes a new requirement in the post-authorisation phase, the marketing authorisation holder may need to distribute stand alone patient card to the target audience take interim measures until the new packages with the patient card are available distributed or and to allow for dispensing existing pharmacy stock of the medicinal product supplied in the former package without inside or affixed patient card.	
	419-421		Comment: standalone cards like affixed cards can also facilitate discussion between the patient and the pharmacist or prescriber at dispensing. Proposed change: amend the sentence and move it in section on the objectives of the patient card, after line 395 as: 'standalone patient cards (whether inside: affixed to the outer packaging or standalone as described below) can also facilitate and be an opportunity for a discussion between the patient and the prescriber or pharmacist during prescribing or at dispensing independently from the dispensing process of the package.'	
	437-441		Comment: It is suggested to replace the word 'avoid' by 'prevent' in the context of PPP. Proposed change: The typical objectives of a PPP are to: - Prevent that female patients are pregnant when starting the treatment; and - Prevent that female patients become pregnant during and, if relevant, for a specific period after stopping treatment; - Prevent, if applicable, that a male patient father a child during and, if relevant, for a specified period after stopping treatment.	
	442		Comment: a PPP can combine tools alone or in combination Proposed change: A PPP can combines the use of different RMM tools – alone or in combination- and the following...	

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	455-456		Comment: The language "...collection by means of specific forms for reporting pregnancy ..." suggests a paper-based system. Clarity could be added that such programmes and forms might consist of, at least in part, electronic media too (e.g. apps or web-based forms for reporting). Proposed change (if any): ... by means of specific forms <u>(either paper and/or electronic)</u> for reporting pregnancy ..."	
	497-509		Comment: Clarity is needed regarding what constitutes a format and what is a dissemination channel. The same information can be presented as text in a paper document or on a website, as well as in the form of a video. We recommend that the dissemination channel is the mode/method to provide the chosen formats to the intended audience and the term 'format' is reserved for the medium of the aRMM itself. E.g. a dissemination channel might be a website, e-mail, app or a mailed paper document, whereas a format would include video, text, image(s), sound recording etc. it looks there is a mix up between aRMM support types (eg paper, audio, video, web-based, training slide-deck, cell phone Apps, electronic platform) and dissemination channels (eg email, mail, QR Code, link to an electronic platform (NCA or MAH), Face to Face). Printing documents is possible with multiple channels. Training program should be considered as educational material, no? In addition, electronic features as described in the paragraph correspond to channel of dissemination. The term "digital" is now broadly recognized & used; thus, would word "electronic or digital" Proposed change: section should be updated as above commented to make clear support type, channels of dissemination, communication and dissemination: <u>aRMM support</u> should be: paper, audio, video, web-based, training slide-deck, cell phone Apps, and any electronic digital tool. <u>Channels of dissemination</u> should be: any digital support/ platform such as e-mails, QR code, website such as MAH website or website specifically developed towards HCPs or patients, hyperlink to a digital platform, face to face)	

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			Supportive communication: amend the sentence line 503 as "... interventions strategies (e.g. where feasible: through learned societies or patient organizations). Additionally, involvement of national competent authorities in safety awareness campaigns towards HCPs / patients could also be considered, further to national competent authorities agreement)". Repeated RMM dissemination: amend the sentence line 509 as: ... may require repeated RMM interventions in various formats and/or channels which may differ at each repeated dissemination".	
	497-498		Comment: An 'a' missing in front of RMM. Proposed change (if any): Marketing authorisation holders should submit plans for the dissemination of aRMM to healthcare professionals and patients for agreement by competent authorities.	
	528		Comment: the 1st principle of effectiveness is not clear? What does "should focus on RMM of major patient and public health importance" mean? This wording appears to indicate that if the RMM concerned is not of major patient and public health importance, there is no need to conduct an effectiveness evaluation? Pls clarify. Proposed change: reword as "should focus on key objectives or key safety messages conveyed in the aRMMs impactful in terms of patient safety or public health" Please also provide examples which illustrate a focussed evaluation.	
	576-579		Comment: In Figure XVI.1, a key to explain what the white and blue boxes represent will be helpful. Proposed change (if any): Consider adding a key to the graphic.	

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			Propose to describe the key messages of the figure XVI,1 and what needs to be achieved more clearly and tailored to actions by the MAH	
	576, 603, 665, 683		Resolution of Figures should be increased.	
	603		Comment: Step 3 in Figure XVI.2 is labelled identification of materials, this is miss-leading as it implies the identification of materials to be used but this comes earlier in the pathway. Proposed change (if any): Acknowledgement of materials or receipt of materials	
	637		Comment: "Proportion of patients exposed to medicinal product in accordance with the authorised indication" Do you mean compliance or adherence?	
	666		Comment: fig XVI.3 would it be integretability or integrability ?	
	670-671		Missing word in the sentence 'Monitoring and investigating health outcomes <missing word> evaluate whether implemented RMM have improved patient and public health.	
	690-691		Comment: Over time, aRMM may not be considered necessary to widespread knowledge of the risk and the aRMM materials. There is not necessarily new evidence on the risk itself to lead to the conclusion that aRMM is no longer necessary. There may also be new evidence on the risk management measure itself (e.g. become routine clinical practice) which might lead to removal of the RMM tool.	

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			Proposed change: New <i>evidence on the risk or effectiveness of risk management measure may lead to the assessment conclusion that a RMM tool is no longer necessary.</i>	
	742		Comment: wording Proposed change: amend to: '...choose to have additional RMM to best address safety concerns that are considered might not to be fully mitigated in clinical practice with routine RMM only	
	785-789		Comment: Is the role of the marketing authorisation holder <u>AND</u> the Member State delineated, as both have responsibilities for RMMs implementation success here? Proposed change (if any): Proposed wording: "a Commission decision may be addressed to Member States, giving them the responsibility for ensuring that specific conditions or restrictions are <u>collaboratively</u> implemented by the marketing authorisation holder in their territory."	
	856		Typo - "maybe be"	
	889		Typo - "a therefore a"	



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<26 April 2021>

Submission of comments on GVP Module XVI Rev 3 (EMA/204715/2012 Rev3*)

Comments from:

Name of organisation or individual

European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	EUCOPE would like to congratulate and thank the EMA for defining the requirement and options around Risk minimisation measures and their effectiveness assessment.	

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
774-76		Comment: This sounds like aRMM are not Industry initiatives. Proposed change (if any):risk minimisation measures (RMM) required by <u>agreed with</u> the competent authorities.....	
77		Comment: Important wording should be added to the introduction. Proposed change (if any): Add before line 77. <u>Planning for the design as well as the evaluation of the effectiveness of the additional risk minimization measures (aRMMs) should begin early during the development of the product.</u>	
77		Proposed change; Provide specific guidance as to when (under what types of circumstances/conditions) 'additional' risk minimization measures might be required to improve the benefit-risk balance of a product. The US FDA has a guidance on factors to consider in determining when a Risk Evaluation & Mitigation Strategy (REMS) is needed; it would be very	

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		valuable to industry stakeholders if a similar type of explicit were included in this Revision 3 of the GVP Module XVI.	
148		1) Please include a statement here to the effect that planning for the design, implementation and evaluation of Risk Minimization programs should be guided by the use of Theories, Models and Frameworks (TMFs). Please include a reference to the US Department of Veterans Affairs Quality Enhancement Research Initiative (QUERI) which provides a clearinghouse of relevant TMFs at: https://www.queri.research.va 2) In line 148, please add that sponsors should select aRMMs that have been empirically shown to be effective (i.e., those that are evidence-based) – and that empirical evidence of effectiveness can be derived from a variety of sources including: a) reviewing published literature and systematic reviews(e.g., Cochrane Reviews) of interventions, and b) conducting usability tests during a pilot (pre-implementation) phase. Both are examples of ways to generate evidence of effectiveness a priori. 3) Additional proposed change: State that unintended effects must be evaluated, propose best practices in this regard, and provide examples of assessment tools to use in this regard.	

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		4) Additional proposed change: Please add in a statement/discussion regarding the importance of planning for 'de-implementation' (that is, the discontinuation of a specific aRMM or entire Risk Minimization Program that has proven to be ineffective)- discontinuing ineffective approaches based on results obtained in an evaluation is another important step in the continuous cycle of risk management continuous improvement.	
153-154		Comment: Can the Agency provide more guidance as to how a sponsor is to determine in advance whether specific aRMMs are "risk-proportionate, potentially effective, practical and not too burdensome"? Proposed change (if any): Does the agency have guidance to provide on best practices for how to assess risk-proportionality of aRMMs, their potential effectiveness and their degree of burden in advance of implementing them in the real world; and provide examples of assessment tools to use in this regard?	
155-157		Comment: How is this coordination and oversight foreseen to be organised by the competent authorities?	
165		Comment: although we understand and agree that paper based material is essential for some age groups we would like to urge that several patient groups could better be	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		reached without paper based material. Having paper based material available in all languages is an unneeded financial burden for the MAH. We would like to change the wording " in addition to" to enable assessment on whether paper based material is needed. Proposed change (if any):may be considered in addition to paper-based materials. <u>The availability of paper based material can be waived when clear reasoning can be given.</u>	
166-170		Comment: Suggest to add categories as set forth in CIOMS IX which are more expansive and inclusive, and also include mention of other types of tools that could be appropriate to use if they manage the risks? There are more types of tools for use as additional risk minimization measures than those listed here. Pregnancy Prevention programmes are one form of controlled access. Proposed change (if any): Use the CIOMS IX categorisations of additional risk minimization tools; in addition, indicate that other types of tools including digital approaches/tools for risk minimization are appropriate to use (e.g., new types of tools that new technologies permit (e.g., gamification approaches, simulations, avatars, etc.) could be used as well as long as they reduce or prevent the risk from occurring.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
177-179		Comment: Reference the importance of using Social Marketing practices (including referencing such classic texts as Lee & Kotler's Social Marketing, 4th Edition). Specify that the 5 precepts of Social Marketing and associated techniques should be used in designing aRMM dissemination plans. Proposed change: 1) Add above mentioned reference 2) Add in statement regarding the critical importance of describing/measuring contextual factors (e.g., specific settings in which the RMM Program is being implemented; type of staff involved in implementation; training provided; etc.)	
355-388		Comment: add that QR codes are optional to refer to for example the information in other languages (for foreigners) or the patient leaflet. Proposed change (if any): Patient cards can have a QR code that refers to identical information in other languages and/or the Patient Leaflet.	
374		Comment: When a patient card is used as a tool to remind the patient of certain actions to take for risk minimisation it is not always logical that the patient always carries the card in wallet or pocket. Example; when the card is used to	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		warn for severe diarrhoea and actions to take – the card should be preferably be placed in the bathroom. In this scenario, a wallet does not seem adequate. Proposed change (if any): Carried <i>or kept</i> easily.....	
437		Comment: currently it reads "Avoid that female patients are pregnant when starting treatment" Proposed change (if any): Avoid that female patients are pregnant when starting treatment. <i>Prevent initiation of treatment in female patients who are pregnant</i>	
438 and 440		Comment: Both bullets begin with "Avoid" rather than prevent (as in pregnancy prevention plan (PPP) as referred to in line 442... Proposed change (if any): Replace "Avoid" with <i>Prevent</i>	
497		Comments: some authorities take long time for review. Suggest to add timelines in order the approval does not interfere with the launch. Proposed change (if any): Add <i>When the competent authorities do not provide feedback within 8 weeks the plan should be considered approved.</i>	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
715-718		Comment: As described in line 155 the content and dissemination are coordinated by the competent authorities. Would it be good when also the evaluation is coordinated by the authorities? Proposed change (if any):	
838-840		Comment: Key elements are to be agreed at EU level and finalisation and dissemination is agreed with the Member States. Proposed change (if any): Please define key elements and indicate what would fall under finalisation	
		Comment: Proposed change (if any):	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23-APR-2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)'
EMA/204715/2012 Rev 3*

Comments from:

Name of organisation or individual

EUCROF (European CRO Federation), Pharmacovigilance Working Group

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

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SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	EUCROF is pleased to have the opportunity to provide their comments and suggestions on this guideline.	

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2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
Line 127		Comment: The reference to "GVP Module V" throughout this document sounds too general Proposed change (if any): We would suggest to provide detailed reference, e.g. GVP V.B.5.8.3.	
Line 128		Comment: The definition of "seriousness" as used here could be ambiguous. Is it classical "seriousness" definition criteria, see ICH e2d, point 2.3 or something else? GVP V.B.5.8.3. does not characterise the risk based on its "seriousness". Please see how "seriousness" is defined in the Table XVI.3, line 706, which differs from the above. Proposed change (if any): The discrepancy to be either aligned or a new definition provided	
Line 139		Comment: To which definition in "GVP Annex I" is this reference made? "Important Safety Concerns" are not defined in Annex I. Proposed change (if any): It is suggested to remove the word "important"	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Line 170		Comment: As specifically requested from stakeholders for this public consultation, it is suggested to use the term "Sentinel Program" instead of "Controlled Access Program" Proposed change (if any): replace with "Sentinel Program"	
Line 204		Comment: Reference to "XVI.B.1" can be confusing as it does not help to define nothing here Proposed change (if any): Provide correct reference, if at all	
Line 224		Comment: It could make sense to provide examples of guides using other media than paper as well. Proposed change (if any): Suggest to add example of other media, e.g. video tutorial	
Line 457		Comment: As specifically requested from stakeholders for this public consultation, it is suggested to use the term "Sentinel Program" instead of the term "Controlled Access Program" Proposed change (if any): replace with the term "Sentinel Program"	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Line 521		Comment: The fact that now in the revised module XVI the evaluation of effectiveness of <u>both</u> routine <u>and</u> additional RMMs is explicitly mentioned is highly commendable, nevertheless, the fact that this revision is not in line with the text of GVP module V and the Guideline on Formats of RMPs should be also explicitly highlighted and indicated on how to read these documents in conjunction with this revised GVP module (e.g. GVP V.B.8.(page 25), GVP V.B.8.1; Guidance on Formats of RMP section V.3 etc). Proposed change (if any): We would suggest to align reference to the need of evaluation of both routine and additional RMMs in all relevant guidelines, e.g. GVP V.B.8. (page 25), GVP V.B.8.1; Guidance on Formats of RMP section V.3, etc.	
Line 525		Comment: qualitative studies are not necessary surveys and surveys can be based on quantitative approach. Thus, "Surveys" seems missing. Proposed change (if any): We would suggest adding the term surveys: "The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed and protocols for qualitative studies <u>and surveys</u>	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		be included in the pharmacovigilance plan of the RMP (see GVP Module V)."	
Line 609		Comment: There is not necessary a download of a document. Simple online consultation of a tool may also happen. Proposed change (if any): We suggest adding "page hits": "Proportion of target population for which RMM tool dissemination has been completed over time (in total and e.g. by RMM tool, country or type of healthcare professional) or download or page hits total/frequency if electronic tools are provided;	
Line 706		Comment: see Line 128 above Proposed change (if any):	
Line 734		Comment: Considering that according to revised XVI.B.5.1. we have now to evaluate both routine and additional RMiMs, the question is why this section talks about additional RMiMs only? If one is also assessing the effectiveness of routine RMiMs should not he/she be able to reclassify/amend them? Proposed change (if any): see above	
Line 906-908		Comment: The addition on requirement to report changes to RMM as an ESI should be indicated on the title page of the revised GVP Module XVI, lines 7-24	

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

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on '<Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)>' (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

Excelya Greece CRO

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	The Agency's efforts to provide a more structured methodological approach to Marketing Authorisation Holders (MAHs) for the assessment of the effectiveness of RMMs is a positive step at ensuring that the benefits of a particular medicinal product continue to exceed the risks. However, more pragmatic and less complex methods of evaluation in terms of implementation and cost should be considered. The present proposed revision will be a real challenge for small and medium-sized enterprises to implement, therefore specific waivers and/or financial support should apply to overcome the entailed cost burden. In addition, electronic dissemination should be promoted as the preferred method for increased engagement, simplification and cost-effectiveness purposes.	

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 155-157		Comment: Additional RMMs are not subject to dissemination for authorised/non-marketed products in most EU countries Proposed change (if any): If several medicinal products, including generics, biosimilars or hybrids, containing the same active substance have been authorised<u>are available on the market</u>, there should preferably be a consistent approach to developing and disseminating additional RMM coordinated and overseen by the competent authorities	
Lines 162-165		Comment: electronic dissemination should be the preferred and only distribution method of materials when applicable and not an additional method to paper-based materials Proposed change (if any): As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may should be considered <u>as the preferred dissemination method, in addition to paper-based materials</u> if and as applicable.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 498-503		Comment: Clarity is needed on whether timeframes for the finalization of the dissemination are requested and/or periodicity for re-dissemination should be included in the dissemination plan. Proposed change (if any): The plans should list the RMM tools (see XVI.B.3.), the target audiences, the audience-tailored formats and contents, the dissemination channels (e.g. paper, printable documents, audio, video, web-based, training programmes), use of electronic features (e.g. QR codes, hyperlinks or references), targeted outcomes, <u>estimated timeframes of dissemination, timeframes periodicity of (re)-dissemination</u> for ensuring continuous availability of materials, and supportive communication interventions strategies (e.g. through learned societies or patient organisations).	
Lines 648-650		Comment: EU restrictions on medical record access due to data privacy regulation and lack of electronic databases in most EU countries should be taken into consideration. Proposed change (if any): N/A	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 715-718		Comment: Additional RMMs are not subject to dissemination for authorised/non-marketed products in most EU countries Proposed change (if any): If several medicinal products, including generics, biosimilars or hybrids, containing the same active substance have been authorised <u>are available on the market</u>, there should be a consistent approach to planning the evaluation of RMM, overseen by the competent authorities, to ensure that the RMM effectiveness can be achieved for each individual product as well as for all products collectively (see XVI.B.2.).	
Lines 719-723		Comment: Either specific criteria for exclusion from the evaluation of effectiveness for generic, biosimilar or hybrid products should be added or a clear statement that the waiver should be based upon the decision of local Competent Authorities. It should be noted here that information on the RMM of the originator/reference product may not be available in terms of content, format and dissemination method to the generic/biosimilar/hybrid MAH. Additionally, clarification is needed on whether a waiver still applies if an extended period of time has passed from originator dissemination. Proposed change (if any): N/A	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 902-906		Comment: Clarification is needed on reporting responsibilities of RMM effectiveness evaluation results; it is not clear whether the results should be included in the updated RMP only or submitted also as a separate report to Competent Authorities upon finalization of dissemination. "Addendum II- Methods for effectiveness evaluation" provides only a checklist for reporting PASS results. Competent Authorities should be encouraged by the Agency to align local guidance accordingly on this matter. Proposed change (if any): N/A	
Lines 963-966		Comment: Stronger commitment for the Competent Authorities to publish RMM data for the purpose of alignment and harmonized approach among MAHs with products having the same active substance. Proposed change (if any): To promote public health, it is recommended<u>required</u> that the Agency and the competent authorities in Member States make the following additional information available via their websites: • Details of additional RMM (e.g. electronic copy of RMM tools/materials that are to be disseminated by marketing authorisation holders in print).	



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<12 April 2021>

Submission of comments on '<Guideline on good pharmacovigilance practices (GVP)>' (EMA/204715/2012 Rev 3*)

Name of organisation or individual

Fecc (European Association of Chemical Distributors)
EU Transparency Register: 0346440357-87

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
470 - 476		Comment: It should also be indicated how the RMM is monitored if the supplier is coming from a member state, and if it is coming from a third country? Proposed change (if any):	
475 - 476		Comment: Additional text Proposed change (if any): further RMM may be needed for ensuring an adequate distribution, supply, storage, preparation, handling and use of the product.	
581 - 585		Comment: It should be clarified that marketing authorisation applicants/holders and competent authorities should not only agree on indicators of success to be included in the evaluation plan, but concrete actions should also be proposed if a consensus is not reached	
706 (table)		Comment: It should whether patients with pre-existing co morbidities should also be classified as an example of a population at risk	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<25 Apr 2021>

Submission of comments on '**Module XVI** – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3)

Comments from:

Name of organisation or individual

International Society of Pharmacovigilance Medication Errors Special Interest Group

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EUROPEAN MEDICINES AGENCY
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1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	It is suggested the module specifies when qualitative studies should be conducted. Patients and health care professionals can have very different attitudes that can lead some to be compliant with risk minimization actions and some to be not compliant. The reasons for being non-compliant (or partially compliant) can also vary from a patient/health care professional subpopulation to the other. Therefore, conducting the same qualitative study in all patients/health care professionals could result in diluting the frequency of importance of the barriers (or missing them) for the risk minimization action to be successful in a specific subpopulation. Since qualitative studies explore the behavioural barriers causing a reduced effectiveness of the risk minimization action, they should be conducted once the outcome of the risk minimization action is known. If the risk minimization action has not reached its aim (completely or partially), trying to identify the characteristics of who is not compliant should be the first step. Then a qualitative study should be conducted in the subpopulation(s) that is(are) not compliant and the study questions should be targeted to these subpopulations so as to provide more informative answers that could help to tailor the risk minimization actions in those who are not compliant.	
	The list of factors (listed in table XVI.3) to be considered for determining the success or failure is welcome. It is suggested to specify how they should be applied in practice to determine the threshold for determining success or failure of a risk minimization action. A practical guide on how to define a threshold and how to use the factors to determine the threshold would help to	

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	avoid running the risk of having very different interpretations on how to quantify these factors (or not knowing how to use them) for determining the threshold of risk minimization success.	
	It is very welcome to see that media exposure has been included in Figure XVI.3 and XVI.4 as a source of knowledge that can influence the behaviour towards a drug and its risk minimization measures. Social media are also mentioned as a possible data source for qualitative research (paragraph XVI. Add.II.2.1.1) We are in the era of the internet and social media that influence people's behaviours and attitudes, unluckily also through fake news and infodemia easily accessible by both patients and healthcare professionals. This can have a profound effect on patients' adherence to risk minimization measures and their willingness to take drugs. A recent example can be the use of hydroxychloroquine for Covid19 even after multiple studies have shown it is not effective in this pathology and carries the risk of QT prolongation. It is therefore suggested we expand on the methods and need of monitoring fake news on medicines that appear in social media (and the internet in general) and how to mitigate their effect. This could be done whenever it is found that fake news is a significant cause of non-compliance with risk minimization measures or of unintended outcomes.	
	MAHs often have challenges getting access to databases for the purpose of studies such as epidemiology or retrospective studies. Will EMA have any suggestions?	
	As mobile devices, computers and the internet become more accessible to patients, what is EMA currently thinking of utilizing electronic tools as RMMs?	
	It is understood that the purpose of patient diaries in the context of RMMs is not intended for the collection of AEs. However, when the information reported in the patient diaries meets the criteria of AEs, MAHs are still responsible for collecting and reporting them. It might be good to clarify this in the guidance and whether they should be regarded as spontaneous or solicited.	
	Line 6- Regarding the suggestions for possibly replacing the established term 'controlled access programmes' to avoid confusion with the concepts 'access to medicines' and 'controlled substance', below are some suggestions: "limited access programmes", "special access programmes", "restricted access programmes", "access enrolment programmes", "medication access programmes", or "programmes to limit access", "regulated access programmes", "authorized access programmes" "focused access programme" (which may be further specified as "Focused access and follow-up programme" if follow-up measures are added to focused access measures)	
	It is great that the definitions for different RMM tools have been streamlined in this revision. What will happen to the relevant documents containing the terms not aligned with the proposed terms? What is the expectation for MAHs?	
	Line 527, "Principle 2: Regular evaluation" It is very helpful to include the timeline in the document. Would it be possible to deviate from the proposed timeline especially for rare-disease indications where patient exposure could be limited and/or low-incidence risks with delayed onset? What about data from other countries outside the EU which we assume would be relevant. We suggest explicitly stating this.	

	It is recommended to perform user-testing of educational materials. If there are guidances on the user testing, could they be included as references in the revision for further reading?	
	It is good to point out that HCPs and Patients play more active and important roles in risk minimisation. The Agency, its committees, and competent authorities in MSs are encouraged to engage with HCPs and the patient representatives. Can you elaborate on how to accomplish this? In particular what about involving the wider family as may be appropriate in patients with the elderly needing extensive community support, psychiatric indications or dementia	
	Line 964, the Agency and the competent authorities in MSs are recommended to make the details of additional RMM available via their websites. This is an important initiative. What is the timeline for MSs to roll this out?	
	In Rev 3 Section A. Introduction "risk management includes the identification, characterisation (including quantification), prevention and minimisation of risks." While in smaller MAHs signal detection and risk management tend to be integrated into one department, in larger companies these tend to be organisationally separate groups. If there is an intention from the EMA to reinforce formalisation of collaboration between signal detection and risk management to achieve a fully integrated risk management approach within the MAHs, further specifying that could be considered.	
	A question regarding EMA's long term vision: Revision 2 of Module XVI distinguishes between RMM and aRMMs from the second paragraph on. Revision 3 is more general during the Introduction. Additionally, in rows 520-521 it states "Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine (see XVI.B.1.) and additional RMM (see XVI.B.3.)." Is that part of a vision where we steer towards a dynamic system where measures (both additional and routine) are continuously improved?	
	The change with regards to medication errors, going from "specific measures may be developed" in section XVI.B.2. Risk minimisation measures in Rev 2 to "this includes preventing or reducing" prominently placed in XVI.B.1. in Rev 3. Definition and principles of risk minimisation measures for medication errors are highly welcome.	
	XVI.B.2.: Appropriate patient selection: Provided verbiage on this topic is now stronger and more prominent, which seems very aligned with the strategic mid/long-term development of risk management. As this might also be a certain shift of focus for MAH's RM departments, additional guidance (or examples) might be helpful.	

	A general comment with regards to the use of technology, respectively digitisation of materials. While electronic versions of materials are mentioned throughout the Module, it is not evident what the EMA's position is. Digitisation, where it makes sense (data privacy, patient demographic etc.), could play a pivotal role in measuring and evaluating effectiveness, evaluate and reduce burden as well as drive behavioural change. I have encountered hesitation within the MAH to digitize based on the anticipated health authority response. A clear position by the EMA might be beneficial. On a more detailed note, in the long run I recommend moving from format definition (e.g. DIN A4) in the RMP to defining what the format needs to achieve to allow flexibility for example change of format (digitisation), tailoring (e.g. heterogeneous patient demographic).	
	It is recommended for the new Module XVI to address in more detail the use of applications for portable devices as tools to support educational risk minimisation, and patient follow-up, especially in the case of Focused access and follow-up programmes. I would recommend Module XVI to address how the MedSafety-2 App may be used and provide guidance to make such Apps qualify for a system to operate Additional Risk minimisation as well as collection of data for measuring the effectiveness of risk minimisation interventions.	
	The COVID-19 pandemic and the subsequent vaccination campaign has highlighted the importance of a coordinated and consistent communication of vaccine risks and of the consistent and coordinated implementation of risk minimization measures. In a globalized world where the news is instantly spread everywhere, member states should coordinate risk minimization measures and their communication. The absence of uncoordinated risk minimization actions and communication plans can cause unwanted consequences (e.g. increased vaccine hesitancy). These unwanted consequences occur regardless of the risk minimization measures included in an RMP, the efforts to monitor their effectiveness and to improve their outcome. Therefore, guidelines on how member states should implement consistent risk minimization measures and convey consistent safety messages should be implemented as part of the risk minimization activities.	
	The module should remind MAHs that risk minimisation measures can apply to all forms of authorisation including pharmacy or over the counter medicines e.g. paracetamol. Thus consumer health companies will still need to reflect on their responsibilities as MAHs.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
91-92		Comment: Regarding the statement "Marketing authorisation holders should also take into consideration specifications and any specific processes that are already in place in Member States" Is it implied that if a MAH already has an existing process in place in a Member State that it would then be encouraged to maintain local specificities?	
96-97		The GVP module can only be applied indirectly to healthcare professionals.	
99		comment: other carers, and patient and consumer representatives. Proposed change (if any): other caregivers, patients and consumer representatives (e.g.XXXX).	
109-110 and 122 and 124		We agree that in addition to ADR prevention, risk minimisation should include optimising use. However, this is not stated in the GVP glossary. Proposed change: align definition of RMM with definition in GVP glossary which may mean updating the glossar.	
133		Comment: Additional RMM should be completely separated from promotional activities. In practice this may be difficult. Do you really mean that sales representatives should not discuss actions to minimise risk? Proposed change (if any): This is an important distinction. could it be moved to the beginning of this section? Need to explain further what you mean by 'completely separated'.	
149		Comment: "impose on the system" is it referred to the healthcare system?	

		Proposed change (if any): impose on the healthcare system...	
158		By adding 'in principle' implies there may be situations where generic products do not need to implement same RMM Proposed change Unless examples can be given about what is meant, suggest deleting 'in principle'	
177		Comment: For certain indications, caregivers play an important role in RMM. It might be worthwhile including them as an example. Proposed change (if any): Add caregivers as an example e.g. elderly with dementia	
184-185		Comment: @user-test proposed materials" Can you clarify or provide an example? Proposed change (if any): If user testing for all the educational materials would be required in future, consider clarifying and provide references in this revision for further reading if specific user testing framework or the PIL user testing guide can be used for this purpose	
192-195		There is no agreed process for validation, and regulatory review and approval of such material based on the principles of task analysis. Proposed change: EMA to publish template of regulatory assessment report based on principles of task analysis	
212-213		Discussion may have to be with more than one healthcare professional or even physician: initial prescribing physician (may be in tertiary referral centre), original referring physician who is patient's regular consultant and then physician who will monitor (such as in general practice) plus pharmacist and nurse may have roles Proposed change: educational materials may need to be tailored to meet needs of different healthcare professionals involved in care of the patient	
248		It is important to check for potential for drug interactions Proposed change: Add check for 'potential for drug interactions'	
257-258		We are not sure why the importance of not donating blood has been included in the sense how does these relate to	

		minimising the risk of medicine? This is more suitable for general advice already provided by transfusion services Proposed change: suggest remove unless there is a specific risk certain medicines might pose	
263-266		As mentioned above, there may be several physicians involved in patient's care. Who is responsible for providing risk awareness form: the initial prescribing physician? Proposed change: Clarify which physician should provide risk awareness form and when	
276		Comment: Considering Risk awareness forms are specific to certain types of risks and also seem indirect / add-on additional RMM, examples of risk awareness forms for specific risks can help the readers to understand better. Also, what is the difference between 'important' and 'very particular' risks? Proposed change: Explain what is meant by 'very particular' and how this related to important risks in the risk management plan	
284 799-801		Not only competent authorities but also authorities for healthcare systems may have a view on what can be done. Is that what is meant? What is meant by 'national guidance'? This could be a professional society or HTA agency. What are "appropriate terms"? Proposed change: As there will be concern that at national level additional requirements may be required from authorities, please can EMA explain how they will streamline and facilitate RMM roll out nationally specially to prevent 'gold plating' of RMM. This is related to 'collaborate on designing' comment concerning line 424. Please can EMA clarify what is meant by 'national guidance' and 'appropriate terms'	

XVI.B.3.1.d		Should demonstration kits be governed by the GMP quality system? How should reporting occur: in PSURs? Separate report? At discretion of MAH? What should the role of QPPV be? Proposed change: Cross reference to GMP quality requirements required. How regulatory reporting should occur should be clarified.	
297		Who decides whether an administration procedure is 'complex'? This would be a situation where human factors studies would be even more appropriate. Proposed change: Clarification required about additional RMM required when 'administration is complex'	
304		Comment: "in real healthcare" does it mean in the real-world clinical practice? Proposed change (if any): in real-world clinical practice...	
328-331		As patients will not expect their diaries to be directly shared with the MAH (assuming that is what is meant), this paragraph should more explicitly state whether MAHs are expected to inform and train healthcare professionals about what to do with these diaries and how to report especially as it might be more than adverse reaction of interest but other problems Proposed change: Explain obligations of MAH to explain how patient diaries are to be examined and that patients can always report direct to MAH	
333		Comment: "other patient diaries" -It seems that separate diaries for risk minimization and efficacy monitoring may apply. Proposed change (if any): A consideration needs to be taken to evaluate the need of minimising the number of diaries (e.g. having only one diary) to reduce the burden on both the patients and healthcare professionals.	

333-337		Why mention other patient diaries when these are not RMM? This is confusing Proposed change: Suggest removing lines 333-337	
377-378		What is the relation of patient information leaflet testing to patient card testing? At the same time? Same techniques? Proposed change: Explain how patient card evaluation relates to current PIL testing	
396-404		As stated, how does this relate to the GMP quality system? What is the role of GMP QP? Should they check if the card is inside or affixed? What about QR codes and apps? How do they apply here? We note these are mentioned in passing in line 501 but for some patient groups such as adolescents and young adults this would be very important. Proposed change: Clarify relationship to GMP quality system and place of QR codes & apps rather than paper	
424		Comment: "collaborate on designing" what is the platform for MAHs to collaborate? Proposed change (if any): What is the role of EMA and PRAC in this?	
497-509		Does EMA expect the MAH and EU QPPV to produce a plan or protocol to demonstrate dissemination and evaluation Proposed change: Suggest template for table of contents of such a plan or protocol	
510-512		Comment: DHPC communication plan template as per GVP Annex II do not cover parameters specific to content and format of dissemination. Hence, a separate basic dissemination plan template should be considered to be provided as an appendix to this module.	
574-575		Comment: What about the products where effectiveness evaluation is carried out by means of Routine PV activities and no study protocol designed? Hence, suggest to add additional below <u>underlined</u> text: Proposed change (if any): Measurements and indicators of RMM effectiveness should be defined as part of the study	

		protocol. <u>If effectiveness of RMMs is assessed by routine PV activities, milestones should be defined in RMP Part V.2, and should be agreed with NCAs within the dissemination plans along with indicators and thresholds.</u>	
576-577 and Figure XVI.1		Comment: In the Figure XVI.1, white boxes are not clear. Proposed change (if any): please consider adding a legend that explains what white boxes refer to and the differences between blue vs the corresponding white boxes, (behavioural change and health outcome).	
709-710		What does EMA propose should be suitable investigation techniques for investigating failure to minimize risk? How will EMA encourage cooperation between MAHs or MAHs and device companies?	
719-726		Comment: 1) Can you elaborate on how MAHs of reference products collaborate with MAHs of generics, biosimilars or hybrids? 2) Considering market coverage, generics, biosimilars and hybrids may provide additional or different data as compared to those from reference products. Therefore, these MAHs should submit process indicators along with the dissemination plan and submit the data periodically to NCA to ensure compliance. It might not be easy to distinguish the originators' contribution to success (or failure) of a RMM as compared to the MAHs of generics/biosimilars/hybrid products.	
738		Suggest change 'RMP' to 'The RMPs'	

744		Safety experience once marketed could well be outside the EU. Does EMA suggest that RMM should start elsewhere in the world so that results can support an EU MAA? Proposed change: EMA to clarify place and importance of post-approval experience from outside the EU to contribute to RMM.	
753		Suggest change 'incorporation in' to 'incorporation into'	
759-762		Where should this discussion take place: PBRER? Proposed change: EMA to clarify regulatory reporting process required for 'thorough discussion'.	
868		Comment: permitted to be prescribed nurses or ... Proposed change (if any): permitted to be prescribed by nurses or ...	
871-2		Please can EMA explain how RMMs should also be adopted by sponsor of Clinical Trials with EU authorised products	
880		What is meant by 'as early as is feasible'? Does this mean before reimbursement has been agreed? Is there a need for discussion at a national level if the healthcare system will not reimburse for the product?	
889-890		Comment: Ideally, additional RMMs are approved by NCAs after approval of RMP by the Agency. Hence, inclusion of risk awareness forms implementation details in RMP prior to NCA	

		approval will be difficult for centrally authorised products. Consider providing pragmatic approaches to follow.	
894		Comment: User-testing of materials for risk minimisation in the local languages is recommended. Does it refer to “user-testing of educational materials”? Proposed change (if any): User-testing of educational materials for risk minimisation...	
902-906		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention effectiveness evaluation results unless it is removed. Hence, consider providing more guidance on this.	
935-936		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention a summary evaluation of the outcomes of specific RMM in the EU. Hence, consider providing more guidance on this.	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3), ver 3 Feb 2021

And

Guideline on good pharmacovigilance practices (GVP) - Module XVI Addendum II – Methods for effectiveness evaluation, ver 3 Feb 2021

Comments from:

Name of organisation or individual

International Society for Pharmacoepidemiology (ISPE)'s Benefit-Risk Assessment, Communication, and Evaluation Special Interest Group (BRACE SIG).

These comments were endorsed by ISPE on 26Apr2021.

ISPE BRACE SIG members who are employees of EMA or members of a committee or working party of EMA have excluded themselves from contributing, reviewing or supporting these comments submitted by the ISPE BRACE SIG.

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	Overall, the Agency should be commended for producing this update to GVP Module XVI- it advances the science of risk minimization significantly, particularly in terms of its inclusion of principles and practices from Implementation Science.	
	This document should add in a statement that evaluation frameworks should be used to guide the design of the risk minimization program, and cite sources where different frameworks can be found.	
	The agency should be commended for its use of helpful figures and graphics in this revision (and Addendum 2).	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	There are several instances within this document (see Minor Comments section) where the focus appears to be on regulators, and where we would suggest to rephrase to also add the responsibility of the MAH in the concerned process.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Pg 4, Line 124-125		Comment: As written, it is unclear if additional risk minimisation material should be included in the annexes of the RMP. We strongly recommend to not include these as RMP annexes. The RMP should state what the measures will be (eg, pt alert card, HCP checklist) and why. Product Information Annex IID is where the key messages are listed for each included aRMM (and the messages are carefully reviewed/agreed with PRAC/EMA, often over a few iterations prior to recommendation for authorization). This way there is agreement with the key messages, and then the materials can be adapted by local affiliates (eg, mode - online, paper, etc.) plus adapt to each local NCA requirements). It would be burdensome to revise the RMP Annexes for each country's materials to be appended to the RMP as they become available. Proposed change (if any): Explicitly state that the aRMM do not need to be included in the RMP annexes, and that the selected measures (such as Patient Card, HCP Brochure or Checklist, etc.) should be listed in Annex IID of the Product Information along with proposed key messages for each measure.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Minor: Add "right route of administration"	
Pg 4, Line 133		Comment: "Additional RMM should be completely separated from promotional activities." Is a clear but high-level concept, and local NCA assessments of this educational vs. promotional perception may vary in our experience, and Patient Support Programs can be useful for aRMM material distribution Proposed change (if any): Suggest emphasizing that these aRMM are educational materials and not promotional. Furthermore, it would be helpful if the EMA could comment on the role of Patient Support Programs which can be instrumental in effective distribution of educational materials.	
XVI.B.2 p. 5, Line 148		Comment: Criteria for requiring aRMMs Proposed change (if any): Suggest clarifying what is meant by 'potential' for effectiveness of the aRMM and how to assess this. This could mean what measures 'make sense' (eg, a Prescriber Checklist for a drug only given inpatient to persons in the ICU with a life-threatening infection would generally not be suitable given usual ICU workflow), or it could mean to actually have conducted a pilot of the intervention, or could mean to conduct qualitative research to assess if	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		the measure will be accepted/used vs. will be burdensome.	
Pg. 5 lines 150		Comment: Consider the intended behavioural changes of healthcare professionals and patients during each -> What about unintended consequences in creating behavioral change for patients and healthcare providers? Proposed change (if any): Consider documenting unintended consequences within the system related to intended behavioral changes.	
XVI.B.3 p. 5, line 161		Comment: Categories and tools of aRMMs. This list does not include all of the aRMM tools set forth in <i>CIOMS IX</i> Proposed change (if any): Suggest not limiting the set of aRMMs to only these types/categories. Could cite them only as examples and state that any type of intervention that is not considered as routine pharmacovigilance activities and designed to support safe and appropriate use of the product would qualify as an aRMM.	
Pg 6, Line 172-174		Comment: Some of this text is less clear/directive. Current GVP language states, "This information should focus on clearly defined actions related to specific safety concerns described in the RMP and should not	

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		be diluted by including information that is not immediately relevant to the safety concern and that is already adequately presented in the SmPC or package leaflet. Educational tools should refer the reader to the SmPC and the package leaflet. Proposed change (if any): Suggest reverting to prior text and/or further clarifying what concepts such as “add value beyond the SmPC and PIL” could entail.	
XVI.B.C p. 6, lines 182-185		Comment: “When developing educational materials it is therefore encouraged to....user-test proposed materials for readability, accessibility, etc.” This can vary by healthcare setting. For example, products used in an inpatient setting, especially for acutely serious conditions, have a completely different workflow for prescribing decisions / pharmacy fulfillment to the floor to be administered than outpatient / chronic settings. Furthermore, this could be extraordinarily burdensome if local CAs require this be done in each country	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): Need to add that they should be assessed for “understandability and actionability”. Consider recommending use of the PEMAT to do such assessments. Also, it should be specified whether results of those assessments should be submitted as part of the RMP. Also, please specify what types of study designs are acceptable in this regard. Recommend to add “suitability to the workflow of the healthcare system where the product will be used” (or similar); also suggest this be rephrased to emphasize user testing and engagement of stakeholders is a best practice but a small sample is usually sufficient. Recommend use of “Message Maps” when developing educational materials - this is a tool to show how each key risk communication message has been incorporated into a specific part/section of the educational material.	
Pg7, Line 226		Comment: Would recommend for certain products that a qualifier actually is important, for example CAR-T products, there is very specific information needed for ‘handlers/pharmacists’ that is very different than information for physicians/nurses to manage specific toxicities that may occur (eg, CRS)	

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		Proposed change (if any): Consider “It is preferable not to add qualifiers to describe the content (e.g., ‘administration guide’) unless the target audience for 1 guide (pharmacists) is different than for another guide (nurses), or the target audience is very specific (eg, applies only to post-dose monitoring of the patient).	
Pg 8, Line 244-5		Comment: Proposed change (if any): Consider adding consideration for avoiding pregnancy for a specified time after the end of drug administration if applicable Similar comment applies to Lines 251-3	
Pg 8, Line 260		Comment: Risk Awareness Forms: It may be helpful to explain the difference from informed consent forms As currently written, a patient card seems to be a type of a risk awareness form (currently the patient card is called out separately in the guidance document). Proposed change (if any): It may be helpful to more clearly delineate that risk awareness forms are typically used to document that patient/provider conversation(s) have taken place.	

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Pg 9&10, Lines 310-337		Comment: We appreciate the clear distinction between patient diaries for RM versus those to maximise effectiveness, however we think further emphasis should be provided to distinguish the use of patient diaries for RM versus patient diaries as a data collection tool for protocol-driven research (which would have to be in accordance with GDPR). Proposed change (if any): Clarify further the distinction of patient diaries for RM (intended only as communication between the patient and health care provider) versus patient diaries used as a data collection tool for a protocol-driven study (which would have to be implemented in accordance with GDPR or other applicable privacy regulations).	
Pg 13, Lines 455-456		Comment: Proposed change (if any): Clarify the difference between organized data collection for pregnancies as part of a PPP vs. as a pregnancy registry PASS requirement, i.e, please describe when would one vs the other vs both be required?	
p. 15 XVI.B.4 - line 496		Comment: Dissemination Plans: this is a very useful addition to the GVP Module XVI and authors of Revision 3 are to be commended for proposing this concept. Suggest, however, to call them Local	

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		Implementation Plans as the focus is on more than dissemination only. Content of these local implementation plans could also be expanded to include specific elements regarding the implementation strategies, and a reference to support other elements for consideration could be provided. Proposed change (if any): 1. Rename “Dissemination Plans” as “Local Implementation Plans” 2. Consider adding to the specified content of these plans: a) include operationally defined implementation strategies, b) Suggest that Figure 2 from Kilbourne A. et al. “Quality Enhancement Research Initiative Implementation Roadmap” 2019, <i>Medical Care</i> 2019;57(10);3 be consulted for further ideas as to how to develop robust local implementation plans.	
Pg. 15 lines 507-509		Comment: Periodic provision of the materials locally is systemically considered at competent authority level at time of implementation. The knowledge adoption and behavioural change of healthcare professional may	

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		require repeated RMM interventions in various formats. What is the trigger to have RMM in different formats for the provider? Proposed change (if any): Could a sponsor offer the RMM in various formats to providers depending on the effectiveness of the interventions?	
Pg 15-18, Section, lines 565-594		Comment: A major issue not addressed in this section is that with local variation and the ability for Competent Authorities to modify the aRMMs, much of the effectiveness evaluations will be hard to measure and impossible to interpret Proposed change (if any): Add acknowledgement that local variation may make design and interpretation of effectiveness evaluation studies difficult.	
Pg 18 Line 591-593		Comment: "The evaluation strategy should consider which methods are proportionate and likely to provide accurate results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients" Consider how burden will be defined and measured. Proposed change (if any): Consider measuring burden for patients & providers separately. Consider if burden	

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		could be part of unintended consequences for RMM. What is the threshold for a RMM to become too burdensome to both patients and providers?	
Pg 18, lines 596- 597		Comment: Dissemination and Risk Knowledge “Knowledge” seems to be used in a broader sense whereas patients may become aware rather than knowledgeable Proposed change (if any): Please clarify if this section is implying that sponsors should, moving forward, be using both quantitative and qualitative approaches for evaluating the impact of risk communication measures such as educational materials?	
Pg 19 Fig XVI.2 .		Comment: Many readers may be confused by the order of the figure, i.e., identification of materials should come before dissemination of materials. Proposed change (if any): Suggest reorganizing chevron bar graph order slightly, and /or clarifying what “identification” of materials at the individual level means. Perhaps “Receipt of materials” would be a better descriptor following dissemination.	
Pg 19, lines 606- 614		Comment: There are various trusted sources from which HCPs in particular learn about risks associated with a medicinal product (DeVries et al; Drug Saf 2017;	

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		40(8):729-42 is 1 of several publications showing this). In our qualitative research, patients routinely don't see a difference between the MAH-provided RMMs vs. what their doctor has provided. This makes it nearly impossible to separate out if the RMMs or other sources are the reason for the knowledge. Overall, does it matter? If knowledge levels are high/outcomes are mitigated, yet use of the MAH-provided aRMMs is low(er), is this really important or does it instead demonstrate a successful outcome? Proposed change (if any): Suggest to add a bullet "Proportion of HCPs and patients who report learning the information from other sources (other sources can be listed, eg, SmPC, learned society, product website, etc.)".	
Pg 19, lines 620-621		Comment: Another healthcare system component to consider is workflow. For example in an inpatient setting, RMMs attached to product packaging will often get separated by the pharmacy before the product is dispensed to the floor for administration. Proposed change (if any): "Identification of environmental factors of healthcare systems and patient life impacting on RMM implementation, e.g.,	

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		resource issues, time constraints, system workflow constraints;"	
pg 21 graphic 666 Figure XVI.3.		Comment: Pathway from risk awareness to risk minimising behaviours including enablers and barriers of behavioural change. This should also consider a patient's risk tolerance/health literacy/numeracy understanding of the associated risks. Proposed change (if any): Consider health literacy, risk tolerance within the associated pathway. Also, a further definition of the adapted behaviors should be defined as this would vary with health conditions, status, and outcomes.	
Pg 22 Fig XVI.4		Comment: More labelling of the graphic is needed as it is not clear what the different shaded boxes for behavioural change and health outcome are supposed to be showing Proposed change (if any): Please clarify/add labeling.	
Pg 22 XVI.B.5.3 lines 690-691		Comment: "New evidence on the risk may lead to the assessment conclusion that a RMM tool is no longer necessary." Proposed change (if any): Please expand on this point- could a controlled distribution program commitment	

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		be 'released' ever? What types of evidence would be needed to support that? What type of results would need to be provided to release other types of (less restrictive) aRMM programs? "lead to the assessment conclusion that" What would this evidence look like? I think this should be further defined, especially for RMM that have been in place for many years- could it become part of the practice of medicine if it has been known for many years by patients & HCPs?	
Pg 22, Lines 701-703		Comment: Another factor in variability and the consideration of appropriate thresholds is how much variation in the aRMM programs and contents occurs by local Competent Authority-required changes. In other words, if local Competent Authorities institute very few changes, a 'stricter' threshold might be acceptable, whereas an aRMM program or assessment may require lower thresholds as a result of Competent Authority-mandated variability. A conundrum of course is that these thresholds are often defined with the EMA before the extent of Competent Authority variation is known. Flexibility and acknowledgement of these issues in the guidance would be helpful.	

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		Proposed change (if any): Please acknowledge the need for flexibility in threshold development due to local Competent Authority variability.	
Pg 22, lines 707-8		Comment: "Effectiveness evaluation where results indicate that pre-defined thresholds have been reached confirm that the objectives of the regulatory action..." Confirm is strong and contradicts some of the earlier language in the guidance about multiple influences on physician and patient behavior - there are so many things that influence the "effectiveness" of risk minimisation, and most of these studies are suggestive of effectiveness at best. Rarely can these studies be designed to answer an actual causal inferential question. Proposed change (if any): Suggest changing "confirm" to "provide evidence"(preferable) or "suggest". Said another way, effectiveness evaluation where results indicate that pre-defined thresholds have been reached <u>provide evidence</u> that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach <u>or only partially</u>	

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		<u>reaching</u> the pre-defined threshold requires further investigation <u>as part of the iterative process of risk management</u> to obtain a clear understanding of the reasons that could help explain the <u>failure</u> <u>lack of success</u> .	
Pg 29, XVI.C.3 line 914-924		Comment: "Collaboration with healthcare professional and patient organisations" Further clarification on expected collaborations and modalities within these organizations to help disseminate the message associated with RMM would be beneficial. For example, it would be more effective, and would likely provide more generalizable data, if these organizations facilitated effectiveness assessment among their memberships by posting announcements of these studies and how to participate. Proposed change (if any): Please clarify whether sponsors are expected to collaborate with HCP and patient organizations, as well as the Agency, and NCAs in obtaining input regarding the aRMMs and the aRMM program.	
MINOR COMMENTS			

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
General		Comment: Addendum I contradicts the wording in the draft GVP MXVI (line 226 – 227) as it refers to an “educational leaflet for the patient”. Proposed change (if any):	
Pg 3, Line 75		Comment: “required by the competent authorities” appears to imply that the MAH cannot volunteer to implement RMMs for their products. Maybe better to state: “in agreement with”? Proposed change (if any): “required by” -> “<u>in agreement with</u>” the competent authorities	
Pg 3, Line 98-100		Comment: appreciate the definition of this broader concept of a patient, as it is not in line with that in other GVPs or the (not defined in Annex I -Definitions GVP). Proposed change (if any): add “and individuals being accidentally exposed during occupation”	
Pg 5, Line 148		Comment: “Assess the potential for effectiveness of the aRMM” reads as if the word “measuring” is missing. The intent of this wording appears to say that when designing the aRMM, it should be assessed to what extent these are thought to obtain the intended effect,	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		i.e. risk reduction or benefit increase. This defines the threshold for success. Proposed change (if any): “Assess the potential for effectiveness of the aRMM” -> “Assess the potential that the aRMM will be effective in achieving its objectives (e.g., level of burden on the system, ability to incorporate into routine clinical practice, and possible unintended effects).”	
		Comment: Proposed change (if any):	
Pg 5, Line 153		Comment: Suggest to rephrase Proposed change (if any): “-risk-proportionate and effective in timely manner in minimising the risk” -> <u>“-risk-proportionate and effective in minimising the risk in a timely manner”</u>	
Pg 5, Lines 157 159		Comment: Collaboration across biosimilar, hybrid, and generic medicinal products to implement the same RMM in terms of content and dissemination may not be feasible.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): Consider adding language in case collaboration or implementation of the same RMM is not feasible.	
Pg 5, Line 161		Comment: Missing word Proposed change (if any): “for use on their own or in <u>a combined manner</u> ”	
Pg 5, XVI.B.C. line 161-165		Comment: Digital aRMMs should be able to be used in lieu of (as opposed to “in addition to”) paper-based aRMMs as long as sponsor can demonstrate that they are reaching the target audience(s) adequately. Proposed change (if any): Consider adding social media and various digital technologies as <u>complementary or optional</u> modalities for educational materials & behavioural change interventions.	
Pg 6, Line 181		Comment: Suggest rewording to clarify Proposed change (if any): “concerns(s)”; “ when the objectives of RMM ” -> “ <u>when the risk minimisation objectives</u> ”	
Pg 6 Lines 182-185		Comment: Educational material should be adapted to the target audience. When developing educational materials, it is therefore encouraged, where possible, to engage with healthcare professionals and patient	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		representatives and user-test proposed materials for readability, accessibility, adequacy and user friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population -> In the adaptation of RMM material for educational purposes could this include social media? Proposed change (if any): Consider adding social media and various digital technologies as complementary or optional modalities for educational materials & behavioral change interventions.	
Pg 6, Line 187		Comment: "Up-to-date" is open to interpretation as to what is considered up to date. Proposed change (if any): The EMs should be "consistent with the current SmPC, as soon as practicable"	
Pg 6, Line 198		Comment: Rephrase Proposed change (if any): "<u>A</u>sStatement"	
Pg 7, Line 236		Comment: While we appreciate the attempt to use uniform language to describe the educational materials, there may be instances where it is more useful/clear to the stakeholder to use a more	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		descriptive term, such as dosing guides or pharmacy posters. Proposed change (if any): Consider allowing modifiers, perhaps only to “Healthcare Educational Guide-- [pharmacy poster]” when needed Consider adding “A Checklist can be specific to certain patient types, for example, for drugs contraindicated before or during pregnancy, the Checklist could be ‘for Women of Childbearing Potential’ only.	
Pg 9, Line 301-2		Comment: Test kits would also be recommended without other additional RMMs Proposed change (if any): Delete Lines 301-2	
Pg 10, Line 338, Title		Comment: Should “safety” be added to Patient Cards to clarify risk minimisation intent? Proposed change (if any): This should read “patient safety card” since the goal is to inform about a medicinal product risk and is used as a risk minimisation tool	
Pg 10, Line 348		Comment: Proposed change (if any): <u>patient concerned</u>	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Pg 13, Line 422- 423		Comment: Suggest to delete “to all these products” because it may not apply to all product formulations Proposed change (if any): Whenever more than one medicinal product contains the same active substance and the same messages of the patient card, it is recommended that marketing authorisation holders	
Pg13, Line 424- 425		Comment: The issue with the active substance is that patients tend to remember the brand name of their product better than the active substance. Proposed change (if any): Recommend allowing both the brand and active substance on patient-directed materials; perhaps the brand name could be limited to the first appearance of the product on each patient material if there are significant concerns. However given the goal of these materials is fundamentally to increase patient safety, allowing more than one use of the brand name may be beneficial to patient comprehension and retention.	
Pg 14, line 477		Comment: Proposed change (if any): Suggest to clarify that accredited centers can train their own HCPs (newly hired HCPs, refresher training, etc.) using the current	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		aRMM training materials (vs. requirement for MAH to provide all training directly)	
Pg 15, line 496		Comment: There is published evidence that the most preferred senders of safety information were NCAs and professional bodies (deVries et al; Drug Saf 2017;40(8):729-42). Proposed change (if any): Suggest to add that dissemination to the memberships of applicable learned societies is encouraged.	
Pg 16, Line 542		Comment: “within 5 years to assess the overall effectiveness...” Given the long delay in some countries to obtain reimbursement, it is not clear if this ‘clock’ starts at first approval or reimbursement, and thus may only represent 1-2 years of RMM dissemination. However, going well beyond the renewal may not provide much additional information. Proposed change (if any): suggest, "within 5 years to assess the overall effectiveness <u>or as available in time for the evaluation of the renewal of a MA.</u>"	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		In addition, suggest clarifying whether these programs should continue on after the 5 year renewal, or upon what grounds they can be stopped. Suggest to propose timelines applicable to the specific medicinal product or indication (for example, shorter for vaccines like COVID-19, longer as applicable for long-term outcomes like dementia following administration of radiodiagnostics for breast cancer.	
Pg 16, Line 552		Comment: Proposed change (if any): undue burden of RMMs on the patient, healthcare professional, healthcare system or MAH;	
Pg 16, Line 562		Comment: Proposed change (if any): that simultaneous events such as changes in clinical guidelines, reimbursement policies, <u>events impacting healthcare (e.g. pandemic events)</u>	
Pg 18, XVI.B.5.2 Line 576, Figure XVI.1		Comment: This is not a comprehensive depiction of RMM evaluation considerations. It does not include consideration of the program design and how that should be integrated with the evaluation planning; it does not address the context and setting of the	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		intervention and the characteristics of the implementing organizations and individuals; and it does not address sustainability, and impact on patient access to treatment. Proposed change (if any): Refer to Figure 1. in Smith MY et., The RIMES Statement. <i>Drug Safety</i> 2018; 41:389-401.- for a more comprehensive set of domains to be assessed.	
Pg 18, line 581		Comment: Proposed change (if any): scope <u>and objectives</u>	
Pg 18, Line 587		Comment: Unclear statement: “Qualitative research is useful for defining the objectives of quantitative research” Proposed change (if any): Suggest to delete or re-consider, as it may be misunderstood	
Pg 18, Line 593		Comment: Proposed change (if any): placing undue burden on healthcare systems or patients <u>or MAH</u>	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Pg 20, Line 630		Comment: Unclear wording: presuming that the intention is to talk about “the targeted HCPs and patients” Otherwise, the phrasing should be: Proposed change (if any): “needs to be feasible and <u>the</u> targeted” or “needs to be feasible and targeted, <u>and</u> healthcare professionals”	
Pg 20, Line 651		Comment: Proposed change (if any): <u>Additional</u> data analyses may also identify enablers or barriers for intended behavioural changes	
Pg 20, Line 653, again on Pg 21, Line 682		Comment: “a regulatory action” sounds like there is no MAH involvement in the matter. Similar to an earlier comment, perhaps rephrase to “the RMM” Proposed change (if any): “a regulatory action <u>the RMM</u>”	
P 21, Lines 673- 676		Comment: Changes in proportion of the SEVERITY of an outcome can be an important quant measure - especially since some patients may be willing to accept the risk, and/or the risk is unavoidable, but the aRMM might be deemed 'effective' if the # of severe cases is reduced/avoided.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): Add incidence rate of the risk by severity or similar	
Pg 21, Line 688		Comment: Proposed change (if any): “should provide evidence to regulators to determine”	
Pg 22, Line 698- 700		Comment: <i>“Indicators for success or failure should be determined a priori and on a case by case basis. Threshold values may be defined by using for example baseline or historical data, expected frequency in comparable populations or of comparable risks”</i> A priori definition may not be feasible, example Tysabri Proposed change (if any): Indicators for success or failure <u>of RMM</u>	
Pg 22, Line 706		Comment: Table XVI.3.: Factors to be considered when determining success or failure 706 of regulatory actions: Section on Risk Proposed change (if any): It should be expressed that risk has to be assessed in the context of the benefit	
Pg 22, Lines 711-712		Comment: While we appreciate the EMA's suggestion to engage with stakeholders involved in guidelines and	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		treatment standards, further specificity about who should be responsible (MAH vs. EMA) should be engaging with these societies would be welcome. As the EMA can understand, there are many instances where Industry is kept at arms' length, and having a regulatory authority be responsible for engaging with stakeholders may be the most successful approach. Proposed change (if any): Kindly clarify which entities are responsible for these corrective actions, and the MAH should not be held accountable when they are unable to influence clinical guidelines or standards.	
Pg 22, XVI.B.6 lines 716-718		Comment: Coordination of effectiveness evaluation across medicinal products containing the same active substance Proposed change (if any): How are sponsors to collaborate in instances where generics, biosimilars, or hybrids etc have been authorised? Will the EMA offer examples or models of how such collaboration should occur?	
pg 23- 24, Line 719 - 728		Comment: Comment on 719-726 Is it a fair balance of the burden between originator and generics ?	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): Where PASS for evaluating RMM effectiveness are required for generic, hybrid and biosimilar products, studies conducted jointly by all marketing authorisation holders (see GVP Module VIII) are encouraged <u>and all MAHs for the relevant products must be able to demonstrate their attempts to agree on a study strategy with the other MAHs</u> . This is in order to minimise the burden on the healthcare systems.	
Pg 24, Line 738		Comment: Proposed change (if any): “RMP <u>s</u> for initial”	
Pg 24, Line 742		Comment: Proposed change (if any): “lifecycle of <u>the</u> product”	
Pg 24, Line 750		Comment: Proposed change (if any): “the healthcare professionals have learned about how to mitigate”	
Pg 25, Line 767		Comment:	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change (if any): medical adequacy, <u>data</u> and scientific integrity	
Pg 25, Line 773		Comment: Proposed change (if any): Please elaborate on regulators' expectation regarding expired RM material	
Pg 25, Line 782		Comment: Proposed change (if any): "differently at the level in <u>of</u> Member"	
Pg 26, Line 821 – 824		Comment: Proposed change (if any): As per our earlier comments, we have concerns both about the process (including individual member state specific items in the RMP) as well as the implications on potential burden, consistency, and effectiveness of the RMM. Previously it was understood that key elements for CAPs would apply in all 27 Member States. As such, we suggest that only key elements are included in the RMP (what the measures will be, e.g., pt alert card, HCP checklist and why). The selected measures (such as Patient Card, HCP Brochure or Checklist, etc.) should be listed in Annex	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		IID of the Product Information along with proposed key messages for each measure.	
Pg 27, Line 829		Comment: Proposed change (if any): "The PRAC should assess as appropriate protocols and results of PASS which"	
Pg 27, Line 843		Comment: Proposed change (if any): The subsequent sections may benefit from increased clarity regarding resolution of potentially conflicting HA decisions	
Pg 28, Line 868		Comment: Proposed change (if any): permitted to be prescribed <u>by</u> nurses or	
Pg 28, Line 889 - 890		Comment: "therefore a detailed description of the forms and dissemination processes in Member States to be followed by the marketing authorisation holder should be available within the RMP" -> does this mean that Annex 6 of the RMP in this case would contain xx copies of the same form but then adjusted for each applicable territory? Should this also be incorporated in the next update to GVP Module V? Proposed change (if any): Please clarify and update GVP Module V as applicable.	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Pg 28, Line 896 – 897		Comment: “keep them informed of any changes or issues encountered in dissemination process.” -> How is this foreseen? To be agreed with the competent authorities of the applicable Member State? This seems to imply that there is an expectation to report more regularly than is happening now. Proposed change (if any): Suggest clarifying the expected reporting intervals if this is the intent of the text.	
Pg 29, Line 912- 913		Comment: Collaboration with healthcare professional and patient organisations is missing “associations” after professional, as HCP and patient organizations are different Proposed change (if any): Collaboration with healthcare professional <u>associations</u> and patient organisations	

EU GVP Module XVI – Addendum 2

1. General Comments

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Reference to the RIMES Statement publication: note that there is an effort underway to have RIMES Statement listed on EQATOR.	
		While this guidance is appreciated, it may be complex for non-epidemiologists to follow and perhaps could be best to summarise the various data sources and methods, and refer to more in-depth publications.	
2. Specific Comments			
Pg 3, Section XVI.Add.II.2.1 Data Sources		Comment: Overall, the value of XVI.Add.II.2.1 as written may not be clear. While it may be helpful to the general reader to list the wide variety of data sources that could be used to assess the effectiveness of (a)RMM, the information does not seem to be provided in sufficient depth to describe the nuances to assist the general reader in selecting the appropriate source(s). These topics are covered in much better detail in existing publications. While we appreciate the EMA is not trying to be proscriptive, we wonder if this section would be better served by simply providing a bulleted list of these possible sources as examples, and noting generally that each has their various strengths and weaknesses and should be considered in light of the issues unique	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		to each product/risk situation, and provide some select references for further reading. Proposed change (if any): Consider condensing this section into a simple bulleted list of these possible sources as examples, and noting generally that each has their various strengths and weaknesses and should be considered in light of the issues unique to each product/risk situation.	
Pg 4, Line 106		Comment: Proposed change (if any): “Patient registries <u>are</u> organised systems”	
Pg 10, Section XVI.Add.II.3.3		Comment: As above, this could be condensed into a short bulleted list since many of the strengths and limitations, and considerations, are best covered elsewhere in the existing literature. Proposed change (if any): Replace with bulleted list and suggested references	
Pg12, Section XVI.Add.II.3.3.5		Comment: If this section is kept and not reduced to a bullet mentioning randomized trials: Understand for completeness why this should be included, but given the complexity and cost of designing a randomized study solely to evaluate the effectiveness, perhaps it	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		should be conveyed that this would be an approach rarely used. Proposed change (if any): Include a statement conveying that randomized trials solely to evaluate the effectiveness of RMM would be an approach rarely used due to the complexity and resources typically required.	
Pg 7, Figure XVI.AddII.1		Comment: Great figure, very blurry. Proposed change (if any): Please use sharper/larger graphic	
Pg 13, Line 422		Comment: It may be worth clarifying whether the RIMES PASS template additions are required or recommended. As currently written it is unclear. Proposed change (if any): Clarify whether RIMES is required or recommended.	
<end>			

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on 'GVP: Module XVI: Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/ 204715/2012)

Comments from:

Name of organisation or individual

H. Lundbeck A/S

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Page 4, line 128		Comment: Current text: "...the selection of 128 RMM should take into account the seriousness of the identified or potential risk ..." Proposed change (if any): Question: according to this text we also need to make aRMM for potential risks, but it was my understanding that this was only for identified risks.	
Page 4, line 133		Comment: Current text: "Additional RMM should be completely separated from promotional activities." Proposed change (if any): Please add guidance how to define 'separation from promotion'. Is it e.g. allowed to let educational materials be distributed by a company (sales) representative? There are also differences per country regarding what is promotional. Is it possible to get more harmonization regarding this?	
Page 4, line 139		Comment: Current text reads: "Additional RMM should focus on important safety concerns" Proposed change (if any): Safety concerns means [imp identified risk, imp potential risk and Missing info]. Does this tekst imply that we have to make aRMM for missing info?	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Page 5, line 166		Comment: Current text reads: "...may be considered in addition to paper-based materials." Proposed change: 'paper-based' is the basis, but is rather old-fashioned. In general it is noted that the module refers not much to digital resources (which is essential in nowadays information world). Why no electronic risk alerts?	
Page 7, line 224		Comment: Current text reads: "...details on the format (e.g. DIN A4 size or larger),..." Proposed change: Too much details, Please focus on the relevant things:	
Page 8, line 251		Comment: Current text reads: "Remind the healthcare professional of the need to monitor the patient for specific signs and symptoms, including specific abnormal laboratory findings, in order to identify adverse reactions early; Proposed change: Please add also guidance on how long to monitor the patient	
Page 9, line 310		Comment: Current text reads: "XVI.B.3.1.e. Patient diaries for risk minimisation" Proposed change: Please consider if a patient diary is a pharmacovigilance tool instead of a risk minimisation tool.	
Page 13, line 424		Comment: Current text reads: "...it is recommended that marketing authorisation holders collaborate on designing and disseminating a single patient card referring only to the name of active substance, and not to any invented name of a medicinal product"	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change: This sound logical, but how is this done? Will the innovator need to take the lead? Or the MAH that discovered this risk first? Please add guidance regarding the process.	
Page 16, line 540		Comment: Current text reads: "Within 3 years of initial implementation of a risk minimisation programme to potentially add further elements to the risk minimisation programme..." Proposed change: Now it is only mentioned that after certain time points info can be added, but not that info can be removed. Suggest to add this.	
Page 19, line 608		Comment: Current text reads: "Proportion of target population for which RMM tool dissemination has been completed over time (in total and e.g. by RMM tool, country or type of healthcare professional) or download total/frequency if electronic tools are provided;" Proposed change: Please add guidance how to define the proportion in case only the amount marketed is known: with tablets with different amounts of medication: we can only estimate the number of patients.	
Page 24, line 754 to 758		Comment: Current text reads: "During the lifecycle of the product, the marketing authorisation holder should critically assess whether the materials are still up-to-date with the current knowledge on the safety of the medicinal product. Where applicable, based on experience and effectiveness evaluations since its implementation and considering current clinical practice, the content, format, layout and distribution modality may be revised or optimised."	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		Proposed change: Please specify what triggers such an assessment whether the materials are still up to date.	
Page 26, line 821		Comment: Current text reads: "In order to respect the diversity of the different healthcare systems in Member States, some key elements will be specific for only some Member States..." Proposed change: The text says 'some' key elements should be included. Please specify which key elements should be included, and which not.	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2021-04-20

Submission of comments on Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3) EMA/204715/2012 Rev 3* - Draft for public consultation

Comments from:

Name of organisation or individual

Medicines for Europe, Rue d'Arlon 50, 1000 Brussels, Belgium

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

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

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	MAHs welcomes proposal for naming different educational tools in clear and consistent way.	
	It is welcomed that where RMM for a generic, biosimilar or hybrid product are fully identical with the originator/reference product, and under the assumption that the RMM evaluation strategy requested for the reference product will be able to gather sufficient data, there is usually no need to request the MAH of the generic, biosimilar or hybrid product to evaluate effectiveness of RMM for their product (unless agreed otherwise in the RMP). However, guidance should be more specific on generic/ hybrid/biosimilar expectations. Also in case of PPP or controlled access programme (CAP), effectiveness evaluation could be also relevant for generics as failure of CAP relates to individual MAH. In this case annual evaluation of reports could be appropriate tools as explained in comments to GVP Module XVI Addendum II. Routine Pharmacovigilance activities such as case reporting and signal detection	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	should be also included in the evaluation of effectiveness. GVP XVI should clearly state that expectation from each MAH should be defined in the individual RMP.	
	Although purpose of GVP XVI is to provide more insight in potential tools and distribution methods, no information is given on harmonisation or centralised European approach to improve aRMM dissemination, incorporate it in different health system(s) and decrease burden to HCPs and patients receiving same aRMMs from different MAHs. In general, this is EU level guidance; however, more guidance is needed on the national level of implementation to achieve harmonisation, timely implementation and decrease burden to healthcare system. We are welcoming approach of some authorities that insist on consortium of companies implementing aRMM jointly and consistently (eg. After referral). Also, some authorities took DHPC dissemination as their own responsibility to improve visibility of aRMM. Countries have also different approaches related to digital tools and websites, some NCAs are posting materials on authority websites and some insisting on company websites. A more harmonised approach would help optimise the benefit-risk profiles of medicinal products and reduce burden on patients and HCPs at both, member state and EU level. Publicly available repository of aRMM interventions that have been found to be efficacious as well as tools to evaluate their effectiveness should be established at EU level (CMDh coordinated for national procedures similar to EMA EPAR for CP products).	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	Classification in Process indicators / Outcome indicators was dropped in the current version. Distinction between Process indicators and Outcome indicators and their role in evaluation of effectiveness of aRMMs was helpful. Figures XVI.3. and Figure XVI.4. are not completely clear and are not consolidated with Figure XVI.Add.II.1.	
	More clarification is needed in important area of pregnancy prevention. It is not clearly defined what is the trigger for addition of controlled access program to "standard" PPP. Also, some clearly teratogenic drugs have PPP exploring also PPP failure by the company using follow-up questionnaires and some do not. On the other hand, for some drugs there are only educational materials for HCPs and patients in place and no formal PPP.	
	In general, the updates are welcome in particular recognition of updated means of communication with HCPs e.g. web and app based mechanisms in addition to paper based materials. Suggest additional emphasis on using a digital approach as we evidenced it was necessary and required by Competent authorities during COVID-19 pandemic. Further examples of a digital approach would also be beneficial to mention in the module, as well as more emphasis on QR codes, to give the reader some ideas on different technologies available within the EU.	
	This guidance addresses RMM, routine and additional, as well as effectiveness evaluation of RMM. It has to be clearly stated that this guidance related to	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	additional RMM and effectiveness evaluation related to aRMM. More clarification on expected threshold for effectiveness evaluation or how an effectiveness threshold is defined is needed in this guidance	
	It should be seen how to incorporate aRMM better in the existing health system, including digital health tools to avoid having parallel tools eg. it has to be taken into consideration that many countries have implemented system for dispensing of narcotics or pregnancy prevention thru limited prescriptions for teratogenic drugs.	
	It is not clearly stated what is expected from MAHs in relation to update and re-evaluation of the currently approved and implemented aRMMs once the new guidance becomes effective. Medicines for Europe believes that updated guidance should be applicable for newly proposed aRMMs after guidance's effective date. Reasonable time should be given to update existing RMP and aRMMs, and decision should be given on a case-by-case bases, especially considering that generic companies need to align with innovator	
	The newly required methods and measurements of Evaluation of Effectiveness are more complex, requiring more engagement of different stakeholders from the national healthcare systems, which may be perceived as an "undue burden by patients, healthcare professionals and the overall healthcare systems".	
	Patient Alert Card could be disseminated in various ways: as part of labelling/packaging as well as outside of the packaging usually given by physician. Different requirements are than needed for each delivery route considering size, duration, capability of writing the physician's contact details on the card etc.	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	Based on the current requirements MAHs for generic products are required to align the aRMM with the originator and this is not always possible with Patient Alert Card. Clearer GVP XVI wording is needed for all scenarios and expectations related to patient Alert Cards. Preferable way of dissemination of the card when introduced with the launch of the product would be that Card is part of the labelling and could be teared off and delivered with each product package. When card is required for product already on the market (eg after referrals), it has to be taken into consideration that different Card appearances are possible as Card's design depends on the available packaging sizes. In this case suggestions on standards regarding the size, durability, paper weight/thickness for Patient cards would be beneficial. However, it should be taken into consideration that if there is possibility that physician could print Card for patient, in that case expectation that material should be of sufficient durability to sustain considerable wear and tear will not be met.	

2. Specific comments on text

1. Line number (s) of the relevant text 2. (e.g. Lines 20 - 23)	3. Stakeholder number 4. (To be completed by the Agency)	5. Comment and rationale; proposed changes 6. (If changes to the wording are suggested, they should be highlighted using 'track changes')	7. Outcome 8. (To be completed by the Agency)
9. 006	10.	11. Comment: With regard the EMA request for suggestions/thoughts on replacing the established term 'controlled access programme Pg.1) 'we suggest that there should <u>not be</u> a proposal to change this term as it is well understood/familiar within the pharma industry and recognised within the medical/HCP sector. 12.	13.
14. 019 - 020	15.	16. Comment: The guideline does not have section XVI.B.5.4. 17. 18. Proposed change (if any): <i>Changes to XVI.B.5.3.</i>	19.
20. 075	21.	22. Comment: RMM is not always required by CA but also can be set in place by the MAH 23. 24. Proposed change: to add "...required by or agreed with the authority..."	25.
26. 091 - 092	27.	28. Comment: Unclear what 'specifications and' ...'specific processes'...'already in place in Member States' would need to be taken into account, i.e. would interfere with implementation of RMP/RMMs. 29. Proposed change: Please provide explanation of specification or specific processes	30.
31. 155 - 159 32.	34.	35. Comment: For this purpose it would be very practicable if the need and content of additional RMM approved for the reference medicinal products could be revised some time before	37.

33. 734-735		patent expiration (possibly more emphasis on reference RMPs being up-to-date and rather prospective documents). E.g. HCPs might already be well aware about the risk and no educational material is needed any more (to reduce the amount of materials distributed to HCPs with generics/biosimilars/hybrids market entries). 36. Comment is also relevant for section XVI.B.7. Additional risk minimisation measures in the lifecycle of the product.	
38. 157 - 159	39.	40. Comment: Aspects of dissemination of referent product are usually not visible to generics and therefore are left at the discretion of national CAs. Moreover, there could be different or more appropriate dissemination method available when generics enter the market (eg. website). 41. 42. Proposed change: Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product. Dissemination plans should be developed in agreement with national competent authorities (NCAs). 43.	44.
45. 158 - 159 46.	47.	48. Comment: MAH agrees that generic/biosimilar products should in principle implement the same RMM in terms of content and dissemination as reference medicinal product. However, it should be taken into consideration that generic product could access market with several years delay and requirement could change. 49. Currently, healthcare professionals and patients are receiving, in some situations, duplicate educational materials for the same active substances (for instance, several generic medicinal products containing the same active substance are distributing similar additional RMM), resulting in loss of interest and consequent decrease in the effectiveness of implemented measures. Although NCAs encourage joint	54.

		distribution, more specific guidance should be in place to avoid duplicate distributions and to improve effective RMM. See also comments for lines 825 – 828. 50. 51. 52. Proposed change (if any): To add: "Moreover, it should be taken into consideration that generic/biosimilar product could access market with several years delay and that certain form of aRMM could not be applicable any more or could be even distributed in a different manner due to new requirements (e.g. through digital platforms not available for referent product). Any changes are agreed with national competent authorities." 53.	
55. 162 - 164	56.	57. Comment: Refers to dissemination not to categories and tools of aRMMs as heading suggests. 58. Proposed change: To move wording related to dissemination to section "XVI.B.4. Dissemination plans". 59.	60.
61. 162 - 165	62.	63. Comment: "Electronic dissemination, such as through web- and app-based mechanisms...may be considered in addition to paper-based materials." Digital methods of dissemination should not be limited only as supplementation to paper-based distribution. 64. Proposed change: "...may be considered in addition to paper-based materials or as main method of dissemination in agreement with NCA depending on healthcare system capabilities."	65.
66. 164 - 165	67.	68. Comment: 'or for safety systems independent from locations' meaning is unclear	69.
70. 178 - 179	71.	72. Comment: They should be provided in formats and through channels ensuring that the material is readily accessible... 73. Meaning of readily accessible is unclear.	74.
75. 184	76.	77. Comment: we agree with the concept of user testing of educational materials, but this should	79.

		be waived for biosimilars and generics since they follow the same design and content as the innovator's educational materials 78. Proposed change: To add: "Since applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM as required for the reference medicinal product, this requirement is waived for biosimilar, hybrid and generic medicinal product."	
80. 185	81.	82. Comment: To consider omitting colours and font type/size requirement: "user friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population." 83. 84. Proposed change: "...adequacy and user friendly formats as well as of channels in the target population." 85. 86.	87.
88. 185	89.	90. Comment: 'as well as of channels in target population' 91. meaning is unclear	92.
93. 187	94.	95. Comment: unclear wording 96. 97. Proposed change (if any): "summarizing the nature of the safety concern and the consequent risk for the patient." 98.	99.
100. 1 96	101.	102. Comment: Educational materials should be written in an easy-to-read style and not be overloaded with academic style cross referencing. 103. Proposed change: 104. "Reference to the SmPC or the PL whenever possible <u>where it delivers added value;</u>" 105.	106.
107. 2 04	108.	109. Comment: "to healthcare professionals or patients" 110. 111. Proposed change (if any): "by healthcare professionals or patients" 112.	113.

114. 2 05	115.	116. Comment: "Typical objectives of such guides include to:"- would these be physician guide or guide in general? (line 208 suggest that these are physician guide while line 215 refers to patient guide) 117. 118. Proposed change (if any): define separate objectives for patient and for HCP guides 119.	120.
121. 2 16/218 /220	122.	123. Comment: typo 124. 125. Proposed change (if any): to add "To" before verb I;e To ask, to instruct, to provide 126.	127.
128. 2 129. 22 - 223	130.	131. If there is both a registry and aRMM in place, it makes sense to mention registry in the aRMM, to encourage reporting into registry; if there is just the registry and no aRMM, issuing additional communication to healthcare professionals to inform them about the registry will add burden on MAHs	132.
133. 2 24 - 225	134.	135. Comment: With the update of <i>Guidance on the format of the risk management plan (RMP) in the EU – in integrated format</i> mock-up of the proposed aRMM is no longer requested, therefore to determine the format of the aRMM in the RMP would be a step back. Adding the description of the tool's format in the RMP (DIN A4 size etc) would be a burden on companies. Also, the proposed requirement is in contradiction with the GVP V rev2 when only key elements are part of the RMP, as aRMM need to be agreed with the (national) competent authority. The current presentation of key elements that would be covered by the educational materials should suffice. The full content and format is agreed with individual NCAs after RMP approval and cannot be foreseen in advance/stated in the RMP. 136. Educational materials are agreed also with national CA who may ask for a change in format, different from what would be stated in the RMP.	140.

		137. 138. Proposed change (if any): Delete or rephrase wording, as recommendation could be part of dissemination plan/competent authority review and such details should not be part of RMP considering that RMP provides only key elements. Full content and format is left at the discretion of NCAs. 139.	
141. 2 26 - 230	142.	143. Comment: Adding <i>qualifiers and other terms</i> to describe the content of the guide could be very useful, since "guide" can include different aRMMs such as posters, dosing guide, for the same target group. This is especially useful when HCP should give to the patient different materials or when different materials are intended for the same target group. 144. 145. Proposed change (if any): Materials for patients have to be nominated in a clearly way. 146.	147.
148. 2 60	149.	150. Comment: Title "Risk awareness form" could be misleading as it is not very clear who is the target audience. It is stated in the text that target is patient. 151. Also, Risk awareness forms would constitute a burden to MAHs and HCPs, as having them would increase the bureaucracy. Also, this may scare off the patient from taking the product if they have to sign an awareness risk form. 152. 153. Proposed change (if any): Consider to better define purpose of the form and replace "Risk awareness form" 154. with "Patient awareness form", in case if it would be part of GVP XVI. 155.	156.
157. 2 62 - 263	158.	159. Comment: Sentence 'It is also meant to support documenting that the patient has been made aware of the risk(s) during a discussion with	163.

		a physician and understands the risk and actions to take.' 160. is also providing an objective of risk awareness forms. 161. Proposed change: 162. add this sentence under 267-275 "Typical objectives of such forms include to:"	
164. 2 64 - 265	165.	166. Comment: "It is to be considered in situations where this is essential for using the product" –the sentence is not clear, especially "this". 167. 168. Proposed change (if any): consider removing or rephrasing	169.
170. 2 69	171.	172. Comment: It is unclear how teratogenicity RMM could be connected to the 'repeated prescriptions' 173. Proposed change: replace 'repeated prescriptions' 174. with 'anytime the physician renews the prescription'	175.
176. 2 73	177.	178. Comment: Reinforce healthcare professional checklists (see XVI.B.3.1.c.) 179. 180. Referenced section should be to XVI.B.3.1.b and not XVI.B.3.1.c 181.	182.
183. 2 89	184.	185. Comment: 'Depending on the seriousness of the risk and taking into account the need for treatment and typical changes in the patient's situation (e.g. change in the medical condition, risk factors, personal situations such as the wish for a child), it could be useful to consider the need for additional follow-up risk awareness forms aiming to renew risk awareness of the patient during treatment adapted to typical patient situations.' 186. 187. It is not clear if these risks are already considered serious and for all such cases renewal of risk awareness would be needed.	190.

		188. Is there a need for additional follow-up risk awareness forms since these medicines are already controlled by monthly doctor's visits, pregnancy tests,... 189. It would mean additional burden on healthcare systems.	
191. 2 89	192.	193. Comment: 'and taking into account the need for treatment' is not clearly defined in this context	194.
195. 2 89 - 293	196.	197. Comment: Sentence is not clear, i.e. does this mean that one (the same) risk may have different versions of risk awareness forms depending on a patient's situation.	198.
199. 2 94 - 309	200.	201. Comment: Demonstration kits-they should not be considered aRMM as they are out of the scope of the educational materials. In most cases, demonstration kits have the purpose of educating the recipient towards the correct use of the product and prevent medication errors. In case the aRMM for a product does not specifically target medication error nor it mentions medication error among the safety concern in RMP, there is no need to include the demonstration kits among the aRMM.	202.
203. 2 98	204.	205. Comment: Unclear meaning of visual material 206. 207. Proposed change (if any): to add example "(such as photographs, film, slides)" 208.	209.
210. 3 03 - 305	211.	212. Comment: It is not clear how would a concern arising from the use of a demonstration kit be reported to competent authorities e.g. as a ICSR linked to the product for which demonstration kit is related	213.
214. 3 29 - 332	215.	216. Comment: Reminder to HCP who suspects an adverse reaction to report by using the usual spontaneous reporting systems is applicable to all tools, not just for section patient diaries (with the exception of the card). 217.	220.

		218. Proposed change (if any): to move the reminder into the introduction of educational material as part of information elements, section XVI.B. 3.1. Educational materials (171) 219.	
221. 3 33 - 337	222.	223. 224. Comment: Digital patient diaries used through an App to monitor product efficiency could be enhanced to also record information for risk minimisation purposes. For practicality and to reduce patient's confusion, an electronic patient diary could be used also an additional RMM tool, as part of the RMP. 225. 226. Proposed change: However, those patient diaries are not categorised as educational material for risk minimisation and should not be proposed as part of the RMP, unless they can also collect information for risk minimisation purposes and/or provide relevant information to patients in order to minimise risks. 227.	228.
229. 3 47 - 350	230.	231. Comment: Since this section discusses the Objectives of patient cards, the bullets points for HCP are not directly related to the objectives of patient cards 232.	233.
234. 3 51	235.	236. Comment: 'Provide contact details of the prescribing physician' 237. 238. It is not clear who should provide contact details of the physician. Would it be the patient or pharmacist or physician? Contact details could not be provided if the card is laminated 239. 240. Proposed change: 241. To omit requirement for providing contact details of the prescribing physician or change the requirement for lamination. 242.	243.

244. 3 52 - 353	245.	246. Independently of the objective of a given patient card, other terms, such as 'alert card' or 'reminder card', should not be used as synonyms for patient card, and only the term 'patient card' should be used to ensure consistency and clarity of the requirements and application of RMM in practice 247. Proposed change (if any): 248. Suggest that this classification is revised, as it needs to be clear to the patient why a patient card is required. Proposal is that condition/reason for card is placed after 'card' in title such as 'Patient Card – for Pregnancy' or 'Patient Card – for liver monitoring'. 249.	250.
251. 3 79 - 381	252.	253. Comment: "It is suggested that used over a long time, material should be of sufficient durability to sustain considerable wear and tear, e.g. be laminated and not be a cut-out or tear-off paper sheet..." 254. We appreciate the rationale for mention of lamination; however, it is not always possible to implement same patient card related to material and size for generics. 255. It is also not always possible to implement laminated patient card since information regarding the indication, doctor's contact information needs to be written on the card. 256. It is not clear if the Patient cards inserted in each medicine pack also need to be of durable material since the patient receives a new one with each medicine pack. 257. 258. 259. Proposed change (if any): 260. Suggestion is to remove reference to 'lamination' and replace it with e.g. resilient material. 261. 262. Also, please refer to general comments – Patient card could be disseminated by doctor or as	264.

		a part of the labelling/packaging. Clear expectation and feasibility should be considered for each scenario. 263.	
265. 3 86	266.	267. Comment: It is not clear what is meant by other documents, i.e. is non-inclusion of black triangle only applicable for patient card or also to other aRMM as well, and should be available only in SmPC and PIL.	268.
269. 3 90 - 395	270.	271. Comment: "Applicants/marketing authorisation holders should submit a proposal during initial evaluation for how the patient card will be risk-proportionately disseminated for agreement by the competent authorities" – it is not completely clear if this refers to procedure/RMP level or national competent authority level. Namely, recently there were several referrals introducing patient cards, and due to the different origin of the products and production sites, different health authority request etc., way of distribution could only be agreed on the NCA level and not on the EU level, especially when introduced for already existing product (example valproate referral outcome). 272. Ideally patient card should be part of PIL And given with each product package.	273.
274. 3 93 - 395	275.	276. Comment: 'Marketing authorisation holders should ensure that patient cards are always available to healthcare professionals when handing over the card to the patient at the applicable point of care (e.g. prescribing or dispensing the medicine).' It is not clear if this is also applicable for the patient cards inside/affixed to the packaging. If HCP should hand the card to the patient why additional distribution in the packages is needed? 277. Perhaps there is a need to distinguish between the requirements for MAH regarding stand-alone patient cards and patient cards inside/affixed to the package. 278.	281.

		279. 280. Proposed change (if any): It is clear that patient card could be part of package or could be delivered outside of the package. Clearer GVP XVI wording is needed for all scenarios.	
282. 3 97	283.	284. Comment: It should be taken into account that some industrial constraint can limit the attachment of the patient card and that some countries required several information on the outer packaging (e.g. in France, specific pictogram for pregnancy) that can limit the space on the boxes	285.
286. 3 99 - 400	287.	288. Comment: 'Marketing authorisation holders should ensure that no information on the outer packaging is covered by an affixed patient card.' 289. 290. It is not clear how is possible not to cover the information on the package.	291.
292. 4 00 - 404	293.	294. Comment: 'A patient card inside the outer packaging or affixed to the outer packaging ensures that the patient always receives a new patient card with every new package and facilitates the information exchange between the patient and a healthcare professional at the time of dispensing. In addition, it will minimise the burden for the healthcare professional in terms of maintaining a stock of stand-alone patient cards.' 295. 296. This is contradictory to lines 393-395: 'Marketing authorisation holders should ensure that patient cards are always available to healthcare professionals when handing over the card to the patient at the applicable point of care (e.g. prescribing or dispensing the medicine).' 297.	298.
299. 4 16	300.	301. Comment: Dissemination of patient cards, if delivered by HCP, should not be done in an unsolicited way, but it should be made targeting specific HCPs in order to avoid card fatigue for HCPs not dealing with the medicinal product. 302.	305.

		303. Proposed change (if any): 304. If patient cards are provided separately from the packaging, marketing authorisation holders should ensure regular dissemination of a sufficient number of patient cards to healthcare professionals and easy access for healthcare professionals to new stock.	
306. 4 18 - 419	307.	308. Comment: Stand-alone patient card: In these cases, the cards has to be distributed through HCP together with HCP Cover Letter that informs him/her about the material included and the link/mailbox that they can use for requesting additional material (ES NCA requirement). All materials distributed to HCP (for their own use or to be distributed to patients should be distributed with an information Cover letter, that also include the link with NCA web to report AE/SAE). Also, MAH could provide access to HCPs to an online request service for additional patient cards and also to online versions of patient cards, including apps. 309. 310. However, in cases when the aRMMs are distributed as paper copies, this is not always easy to implement. It should be ensured that the HCPs have the MAH's contact details (phone number or email) where they could request additional patient cards. This would ensure the patient receiving the patient card in the requested format (their material should be of sufficient durability to sustain considerable wear and tear, e.g. be laminated and not be a cut-out or tear-off paper sheet as part of the PL), which would be the case if they were printed out by the HCP.	311.
312. 4 22 - 425	313.	314. Comment: Alignment between MAH using the name of active substance is applicable to all tools. 315. 316. Proposed change (if any): To move to the introduction part of section XVI.B.3.1. Educational materials.	318.

319. 4 22 - 425	320.	317. 321. Comment: "Whenever more than one medicinal product contains the same active substance and the same messages of the patient card apply to all these products, it is recommended that marketing authorisation holders collaborate on designing and disseminating a single patient card referring only to the name of active substance, and not to any invented name of a medicinal product." 322. Collaboration and designing a single patient card is applicable only to stand-alone patient cards, however it is not applicable for Patient cards that are inside or affixed to the outer packaging (if not part of PIL). The preparation of Patient cards (inside or affixed to the outer packaging) is adapted to MAH's technical procedures, standard floor plan, package size,... Additionally, harmonisation of Patient cards (inside or affixed to the outer packaging) among all MAHs once the product is already registered would mean additional burden and costs on MAHs and agencies. 323. In theory the proposal for MAHs to collaborate on designing/disseminating a single patient card is welcome however in practice can prove difficult – a lead MAH needs to be established – inter-company agreements needs to be prepared – difficulty with ongoing provision of cards to individual MAHs to supply to their HCPs on request. 324. 325. 326. Proposed change (if any): 327. Suggest that the following considerations are reflected: to establish a lead MAH, to reach inter-company agreement, to consider difficulty with ongoing provision of patient card. 328. The combined procedure is straightforward in some countries with established work-sharing schemes (e.g. BGMA in UK, CA in other countries), which could also be referred to as a	329.
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			guide of how the work-sharing schemes work in different Countries.	
330. 28	4	331.	332. Comment: 'that may also serve' Proposed change (if any): 333. Clarification is needed if there are instances where DHPC is not considered aRMMs	334.
335. 33	4	336.	337. Comment: The wording could be revised, as the PPP's main purpose is to prevent pregnancy from occurring with a product, whereas prevention of use of a teratogenic product during pregnancy is a secondary objective of the PPP this should not happen in case a PPP is functioning correctly. 338.	339.
340. 44	4	341.	342. Comment: The term Educational material tools is confusing since the categories of aRMM tools described in lines 166-170 include educational materials, DHPCs, PPPs, controlled access programmes. 343. The same term <i>educational materials</i> should be used throughout the document.	344.
345. 48	4	346.	347. Comment: The term Controlled access tools is confusing since the categories of aRMM tools described in lines 166-170 include educational materials, DHPCs, PPPs, controlled access programmes. 348. The same term <i>controlled access programmes</i> should be used throughout the document.	349.
350. 60 - 462	4	351.	352. Comment: 'It may restrict the time period of validity of a prescription or the maximum amount to be prescribed in a single prescription, or require a visual reminder ³ as part of the labelling of the outer packaging.' 353. 354. Time period of validity of a prescription is at the moment considered a routine RMM. 355. There is a 3 day validity of prescription for narcotics, 7 days for antibiotics as a national requirement. It is not clear if national requirement is now considered an additional RMM.	359.

		356. If a certain agency requires inclusion of a blue box, does this mean an update of RMP is required and inclusion of controlled access programme as aRMM? 357. Proposed change (if any): It should be seen how to incorporate aRMM in existing health system to avoid having parallel tools. This is also addressed under general comments. 358.	
360. 4 61 - 462	361.	362. Comment: Clarification or example is needed on what is expected from "visual reminder" in relation to controlled access programme. Visual reminders are not features of a controlled access programme and are not additional risk minimisation measures. Unclear why they should be mentioned here.	363.
364. 4 63	365.	366. Comment: It is clear that for some teratogenic drugs in addition to PPP there could be controlled access program; however it is not clearly defined what is the trigger for addition of controlled access program. Also, some clearly teratogenic drug have PPP exploring also PPP failure by the company, while some have only educational materials for HCPs and patients and pregnancy prevention is responsibility of HCP. Apparently this might be due to introduction of the PPP in EU at different points of product life cycle. However, PPP expectation should be better defined.	367.
368. 4 85	369.	370. Comment: What is a difference between Forms for patient information exchange between prescriber and dispenser and Dispensing forms. Perhaps only one category is sufficient.	371.
372. 4 90 - 495	373.	374. Comment: One category of controlled access programmes is not clearly mentioned - the need to ensure that HCP are trained before being able to prescribe. This is not part of the tracking drug system and neither the part of accreditation which focuses on administration. The only remaining possible category might be the dispensing forms, but this needs to be clearly specified. Dispensing	377.

		for could start at prescriber level or at dispensing level. 375. Also, difference between dispensing form and forms for patient information exchanges are not clear. 376.	
378. 4 97 - 503	379.	380. Comment: This section talks about dissemination of RMM, however it refers to section XVI.B.3 where aRMM are described. 381. Proposed change (if any): Changed RMM to aRMM	382.
383. 4 97 - 503	384.	385. Comment: Marketing authorisation holders should submit plans for the dissemination of aRMM to healthcare professionals and patients for agreement by competent authorities. The plans should list the RMM tools (see XVI.B.3.), the target audiences, the audience-tailored formats and contents, the dissemination channels (e.g. paper, printable documents, audio, video, web-based, training programmes), use of electronic features (e.g. QR codes, hyperlinks or references), targeted outcomes, timeframes of (re) dissemination for ensuring continuous availability of materials, and supportive communication interventions strategies (e.g. through learned societies or patient organisations). 386. 387. Proposed change (if any): 388. 'Dissemination plans' has been categorised as "supportive communication intervention strategies (e.g. through learned societies or patient organisations'. It would be appreciated if GVP XVI could expand or provide further clarity on CA's expectations for this type of procedure. MAHs can include patient organisations/societies in distribution of materials but it is not clear if MAH has to provide further breakdown. If yes, please clarify what is required e.g. if monitoring of returned educational material have to be mentioned.	390.

		389.	
391. 5 01	392.	393. Comment: Regarding targeted outcomes, it is suggested that GVP XVI provide how to consider reaching the threshold for educational materials and other aRMMs. 394.	395.
396. 5 02 - 503	397.	398. Comment: Supportive communication interventions strategies are not always relevant 399. Proposed change (if any): to add: "if relevant" 400.	401.
402. 5 07 - 508	403.	404. Comment: To update text 405. 406. Proposed change (if any): Periodic provision of the materials locally is <u>should be</u> systemically considered at 407. <u>between</u> competent authority level and MAH at time of implementation. 408.	409.
410. 5 10 - 513	411.	412. Comment: DHPC communication plan template (GVP Annex II) does not contain all requirements listed in rows 498-503. 413. 414. Proposed change (if any): Revision of DHPC communication plan template should be considered in GVP XV or consider to provide another template for aRMM in general in this guidance. 415.	416.
417. 5 16 - 520	418.	419. Comment: Expectation regarding monitoring of outcomes of RMMs implemented as a result of PRAC signal, PSUSA procedure, etc, that are not defined as part of RMP or which are not conditions of MA is not clear. 420.	421.
422. 5 21	423.	424. Comment: For evaluation of routine effectiveness, as generic are generally exempted from PSUR, it is not clear if e.g. it is suggested that signal detection and evaluation of Ae report	425.

		could be considered sufficient as a measure of effectiveness.	
426. 5 27 - 530	427.	428. Comment: Additional RMMs are already focused since they are set up for safety concerns determined by frequency, seriousness, severity and impact on public health. The principle of <i>focused evaluation</i> is not clear how it should be applied for already focused RMMs.	429.
430. 5 32 - 533	431.	432. Comment: GVP V foresees RMP Part V as the default section to elaborate on the plans how to evaluate the effectiveness of aRMMs, as visible from RMP Part V.2, subsection "Plans to evaluate the effectiveness of the interventions and criteria for success". Inclusion into the pharmacovigilance plan is only required in those exceptional cases where a PASS to measure the effectiveness of RMMs is required. 433. 434. Proposed change (if any): 435. Details of how aRMM effectiveness will be measured at regular time points should be included in the pharmacovigilance plan (<u>if applicable</u>) <u>or in Part V</u> of the RMP (see GVP Module V). 436.	437.
438. 5 36 - 539	439.	440. Comment: It is acknowledged that first evaluation of effectiveness should be conducted within 12-18 months after initial implementation. However, limited guidance was given regarding methods that can be used within first 12 -18 months when conducting a study is not feasible. Further guidance would be appreciated to better understand expectations regarding methods at all time points when their utilisation would be most useful. 441.	442.
443. 5 44 - 564	444.	445. Comment: Data regarding unintended outcomes may vary throughout EU territories, depending on the particularities of the healthcare system. This may lead to a divergence in RMM	446.

		effectiveness and ultimately may require country-specific updates.	
447. 5 71 - 572	448.	449. Comment: It is not clear how can a generic company present improved population health...in comparison to what, if generics disseminate aRMM with launch of our product. 450. To what extent objectives were met could be also screened by using routine signal detection and case reporting.	451.
452. 5 76	453.	454. Comment: Figure XVI.1 is blurry 455. 456.	457.
458. 5 84 - 588	459.	460. Comment: Meaning is unclear related to 'Evaluating the effectiveness of RMM based on quantitative measurements (e.g.....) is considered particularly important for decision-making on RMM and should be used where feasible.' 461. 462. Proposed change (if any): rephrase to 'Using quantitative criteria (e.g. ...) for evaluation of effectiveness of aRMMs is considered particularly important. This should be considered when deciding on the aRMM tool. '	463.
464. 6 04	465.	466. Comment: Figure XVI.2 is blurry	467.
468. 6 08	469.	470. Comment: "has been completed" 471. 472. Proposed change (if any): It is not clear if it should state completed or received	473.
474. 6 35 - 647	475.	476. Comment: In the context of generic prescribing, it is not always known what product is the patient receiving. Therefore, quantitative measurements of behavioural changes would be difficult to track.	477.
478. 6 84	479.	480. Comment: Figure XVI.4.is blurry 481. 482.	483.
484. 6 91 - 695	485.	486. Comment: These sentences are repeating the same concept that can be summarized in one sentence: RMM tool is no longer necessary, and	488.

		regulators may conclude to discontinue the RMM. Both of these sentences suggest the same, that "RMM tool is no longer necessary " and "regulators may conclude to discontinue the RMM". So, the word "Alternatively," is not clear. 487. Proposed change (if any): clarify the sentences per the above.	
489. 6 98 - 700	490.	491. Comment: Indicators for success or failure should be determined <i>a priori</i> and on a case by case basis. Threshold values may be defined... Examples of defined threshold for RMM effectiveness would be appreciated. It should be also clarified what would be the consequence in cases where the level of knowledge for targeted threshold is not sufficient. 492. 493.	494.
495. 7 09 - 710	496.	497. Comment: "On the other hand, failure to reach the pre-defined threshold requires further investigation to obtain a clear understanding of the reasons that could help explain the failure." The "further investigation" should be clarified. Does that mean that another study is required or the investigation should already build in the first study to be able to analyse unfavourable results. 498. 499.	500.
501. 7 11 - 712	502.	503. Comment: Does the corrective action falls within the MAH responsibility? If yes, it should be taken into consideration that MAH are not commonly engaging with stakeholders involved in developing clinical guidelines and setting treatment standards. 504. 505.	506.
507. 7 15 - 733	508.	509. Comment: Lines 719-725 seems to be not in line with lines 715- 718, and may not be in line with lines 727-733. 510. 511.	512.

513. 7 19 - 726	514.	515. Comment: Generics are welcoming this approach; however, it is not always clear what are the expectations from individual authorities related to the EoE and especially generic EoEs expectations during inspections compared to the PRAC and RMP assessors. 516. 517.	518.
519. 7 70 - 771	520.	521. Comment: "The marketing authorisation holder is responsible for updating the RMP, including its section on RMM, when new information becomes available." 522. 523. Proposed change (if any): Examples of new information that requires RMP update in relation to (a)RMMs would be appreciated. 524.	525.
526. 7 85 - 789	527.	528. Comment: Whether a Member State would ask for specific conditions/restrictions in addition to Commission decision, it is not clear how and when the MAH will be informed by Member State. Especially this concerns generic MAHs as they are not actively informed by authorities.	529.
530. 8 25-828	531.	532. Comment: Although NCAs encourage joint distribution, more specific guidance should be in place to avoid duplicate distributions and to improve effective RMM. 533. GVP should be clearer regarding the consistent approach to developing and disseminating additional RMM by different MAHs of the same active substance, and make aRMM from originator more visible to generics. 534. 535. Proposed change: More clear guidance for collaboration between MAHs and coordination on national level. 536.	537.
538. 8 41	539.	540. Comment: CA shall monitor the outcome of RMM. It is not specified in a high level how they will do it. Only oversight is specified.	543.

		541. Proposed change (if any): More guidance would help MAH to be more aligned with CA. 542.	
544. 8 50 - 854	545.	546. Comment: Generic MAHs do not have easy access to originator's materials/RMM elements and these should be made available (publicly) by EU CA to allow a faster and a more consistent implementation, to avoid any undue burden on the healthcare system.	547.
548. 8 58 - 861	549.	550. Comment: Patient cards included in the outer packaging are considered to be part of the labelling therefore product information requirements apply. As such, the text and the decision that the patient card is part of the PI should be the same throughout the EU for CPs, MRPs and DCPs and are not at the discretion of the national CAs. 551. It should be clear that for such situations national authority should not request additional changes. If a national authority requests changes to the text or wishes that a patient card is attached to the outer packaging in the post-authorisation phase, this needs to be discussed with all other CA and introduced by an EU procedure (variation, article 61 (3) procedure, PSUSA etc.) 552.	553.
554. 8 88 - 891	555.	556. Comment: Detailed description of the form should be available in the RMP as agreed with CA. For countries where the discussion of RMM are done with a different entity than the one approving the RMP our understanding is that after the material is approved we should resubmit the RMP. This is generating additional burden for limited added value. Another option when generic applications are available would be that CA as coordinator can advise/inform other MAH at the time of the material review on what has to be included to be aligned/ harmonised. 557. Mentioning the dissemination processes in Member States within the RMP, would imply	561.

		submitting an updated RMP just for the purpose of informing all Members states in a procedure about dissemination process. Many MAHs do not launch a product in all members states in the same time and sometimes there are years in between launches in different countries and having to update the RMP after all launches have taken place would constitute a burden. Furthermore, dissemination process is described in PSURs and mentioning it in the RMP and having it assessed by competent authorities twice (in PSUR and in RMP) would be a repetitive and burdening action. 558. 559. Proposed change (if any): RMP as per GVP V contains only key elements and should not contain description of the forms and dissemination processes in individual Member 560. States. The recommendation to update the RMP could be grouped with other reasons for RMP updates and not triggered by each implementation.	
562. 9 37 - 938	563.	564. Comment: It should be taken into consideration that if EoE is not mandatory to be performed for generics that PSUR (if submitted for generic) cannot include an evaluation of implemented measures, other than dissemination coverage. 565. Proposed change (if any): Expectations should be clarified. 566.	567.
568. 9 44	569.	570. Comment: To ensure that generic applications are rapidly aligned, information should be made available by the competent authorities in a timely manner. All MAHs should be actively informed about aRMM update including content, as well as on removal of aRMM from originator. 571.	572. 573. 574. 575. 576.

Please add more rows if needed.

28 April 2021

Submission of comments on 'Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012)

Comments from:

Name of organisation or individual

Good pharmacovigilance practice (GPvP) Inspectorate, Medicines and Healthcare products
Regulatory Agency (MHRA)

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

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

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
79		Comment: Proposed change (if any): Consider replacing “Articles 2(4b)” with “Articles 2(4)(b)”	
80		Comment: Proposed change (if any): Consider replacing “11(1a), 11(1e)” with “11(1)(a), 11(1)(e)”	
145		Comment: Proposed change (if any): Consider replacing “excluding” with “preventing”	
Lines 497-503		Comment: Consider referencing GVP Module XVI Addendum I.3 for further guidance on dissemination plans for educational materials Proposed change (if any):	
Section XVI.B.3.4 (Lines 457-495)		Comment: It’s not clear why text in relation to specific testing and/or examination of the patient in the context of a controlled access programme has been removed in this version. For example, in Rev 2 it states “<i>monitoring of the patient’s health status, laboratory values or other</i>”	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		<i>characteristic prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product."</i> Proposed change (if any):	
Lines 768-769		Comment: Consider providing more detail on the record keeping requirements for RMM. For example: - maintaining records of dissemination and (where appropriate) receipt of guides, checklists, patient cards, DHPCs, etc. - maintaining records that demonstrate that a controlled access programme or pregnancy prevention programme has been appropriately implemented and product shipments are traceable, where applicable. Records may include evidence of pre-treatment vaccinations/antibiotic prophylaxis or evidence that controlled access tools are being utilised by healthcare professionals. Proposed change (if any):	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on GVP Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators Rev.3 (EMA/204715/2012 Rev 3)

Name of organisation or individual

Otsuka Pharmaceutical Development & Commercialisation Europe GmbH

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	In relation to terminology used in the guidance, RMMs have been occasionally referred to as regulatory actions. Otsuka recommends that the Agency mention this in the Introduction to avoid any confusion.	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
162-165		Comment: Paper-based materials seem to be required regardless of electronic dissemination. Otsuka recommends that the Agency clarify whether dissemination of paper-based materials and electronic dissemination are considered equally and as interchangeable, or electronic dissemination is only a supplementary tool in addition to paper-based materials. Proposed change (if any): Added text in bold. As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to or as a substitute for paper-based materials.	
184-185		Comment: Otsuka recommends including further guidance on “user-testing” of educational materials. Consider clarifying if patient information leaflet (PIL) user testing guides can also be used for testing educational materials.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
186-191		Comment: Suggestion below in bold and strikethrough. Proposed change (if any): An educational material should contain the following information elements: Up-to-date, objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be provided in more detail or in a different way than in the SmPC/PL e.g. by the use of tables, flow charts, or illustrations or pictogram/infographics);	
215		Comment: Otsuka recommends the Agency add the following bulletpoint under line 215 "Other objectives of patient guides may be:" Proposed Change: Added bullet point below line 215 Instruct the patient on actions they can take themselves to minimise the risk (e.g. when it is important that the patient has sufficient water intake).	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
276		Comment: Considering risk awareness forms are very specific to certain type of risks, Otsuka recommends that the Agency include examples of forms.	
372		Comment: As reading the patient leaflet (PL) is always recommended, it is not clear in which situations a patient card with a message to read the PL would be a reasonable and justified RMM tool. Risks targeted by this measure seem nonspecific. Proposed change (if any): Otsuka recommends providing some examples of the types of medicinal products and/or risks where a patient card with this message would be applicable. If this is intended to be an additional message accompanying a more specific message in the patient card, that should be explained. Otherwise, Otsuka recommends removing this bullet.	
510-512		Comment: The direct healthcare professional communication (DHPC) communication plan template (GVP Annex II) does not allow most of the parameters for the content of dissemination plans to be included (as mentioned in the line 497 to 503). Otsuka proposes including a separate template for dissemination plans.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
622		Comment: Otsuka recommends including an example of information-related factors influencing knowledge uptake in patients and healthcare professionals.	
906-908		Comment: The aim of RMM is to influence the benefit-risk balance of the medicinal product. Hence, during evaluation of effectiveness, any finding could be impacting benefit-risk to some extent and therefore, would warrant raising an emerging safety issue. This could lead to overreporting of RMM related findings as emerging safety issues. Otsuka recommends adding the text in bold. Proposed change: If the marketing authorisation holder becomes aware of information regarding RMM that may impact the benefit-risk balance of the medicinal product, to the extent that it meets the definition of an emerging safety issue as per Module IX.A.1.1, this should be reported as an emerging safety issue.	



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
912-932		Comment: In terms of seeking input from a patient population in the planning phase and during implementation of the RMM, in addition to the described responsibility of the Agency, its Committees and competent authorities in Member States, is there any expectation regarding the marketing authorisation holder's (MAH) responsibility? If yes, any additional guidance would be helpful.	
935-936		Comment: In GVP Module V (Rev 2) or its integrated Template, there is no provision to mention a summary evaluation of the outcomes of specific RMM in the EU. Otsuka recommends providing further guidance on this.	

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SCIENCE MEDICINES HEALTH

26/04/2021

Submission of comments on ' Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

Pharmaceutical Group of the European Union (PGEU)

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

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SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	PGEU welcomes the revision of the EMA Guideline on good pharmacovigilance practices (GVP) module XVI. We are pleased to see that the revised GVP module XVI takes on board the general principles outlined in the 2017 key <u>recommendations</u> made by the EMA Healthcare Professionals' Working Party (HCPWP) Topic Group on Additional Risk Minimisation Measures. Within the revised guideline we find it useful that the terminology related to additional risk minimisation measures has been clarified and that duplication has been removed (i.e. patient cards vs. alert cards). In particular, we find the more detailed descriptions of the educational materials valuable, including defining already established materials used in clinical practice such as e.g. demonstration kits and patient diaries as	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	additional risk minimisation measures, which had not been specified yet in the previous version of the guideline. We also very much welcome the added section on collaboration with healthcare professional and patient organisations. As a general comment, we would like to reinforce that targeted dissemination and pragmatic integration in healthcare practice remain key attention points to ensure sufficient uptake of additional risk minimisation measures. Moreover, national/regional differences in organisation & delivery of healthcare services require a tailored approach for implementing aRMMs (e.g. differences in level of digitalisation/infrastructure) Lastly, we also encourage further integration of RMM into Good Pharmacy Practices, standard operating procedures, institutional protocols, point-of-care electronic tools such as Clinical Decision Support Systems, continuous education, continuous professional development and pharmacy education and training, which are actions that might fall outside the scope of this guideline.	

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>
	For more information and related best practices, please also refer to the PGEU Best Practice Paper on Pharmacovigilance and Risk Minimisation .	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
328-329		Comment: Patient diaries are already available today for patients in electronic formats, including via third-party mobile applications, and can be expected to become the most commonly used format for patient diaries in the near future. It would be useful to clarify that patient diaries can be made available in different (digital and paper) formats (as done for e.g. risk awareness forms lines 277-284). For any patient diary or educational material approved as additional risk minimisation material, it should be clarified that third-party applications should not store any personal information linked to using a patient diary for a specific medicine, which could then potentially lead indirectly to promotional activities or other unrelated actions. At the same time, it must be clarified how software, apps or websites will process and store patients' personal data when using a digital patient diary.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		The appropriate application of European and national data protection legislation should be guaranteed and closely monitored in these third-party applications or websites at all times. Proposed change (if any): Add a paragraph to reflect the comments made above.	
396-414		Comment: In particular for patient cards placed inside the packaging, it must be ensured that community pharmacists receive a communication from the MAH to announce this. With the introduction of the anti-tampering device as part of the implementation of the Falsified Medicines Directive, community pharmacists are not allowed to open the medicine package until after the package has been dispensed to the patient. Without this advance notice, pharmacists may therefore not be aware of the presence of the patient card and as such it might lose its important use to facilitate that the pharmacist informs the patient about the risk and the actions to be taken for risk minimisation at the intended point of care. Proposed change (if any): Marketing authorisation holders should ensure that no information on the outer packaging is covered by an affixed patient card <u>and that healthcare professionals receive an advance notice to inform them</u>	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		<u>about the upcoming presence of the patient card prior to the release of the updated packages in the market.</u>	
422-425		Comment: It can be confusing for pharmacists and patients when different positions for the patient card in relation to the package are used, either inside or affixed to the outer packaging, when several medicinal products containing the same active substance have been authorised. Proposed change (if any): Whenever more than one medicinal product contains the same active substance and the same messages of the patient card apply to all these products, it is recommended that marketing authorisation holders collaborate on designing and disseminating a single patient card, <u>including ensuring consistency whether the patient card is placed inside or affixed to one of the sides of the outer packaging, and referring only to the name of active substance, and not to any invented name of a medicinal product.</u>	
922-924		Comment: In line with the <u>recommendations</u> made by the HCPWP Topic Group on aRMM, we would like to stress the need to involve healthcare professionals earlier on in the	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		development process of additional & routine risk minimisation measures. Proposed change (if any): Where possible, it is encouraged that the Agency, its Committees and competent authorities in Member States, as applicable, engage with healthcare professionals and patient representatives <u>both early in the development process of aRMMs and after their release</u> for obtaining their contributions and discussing:	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on GVP Module XVI Risk minimisation measures: selection of tools and effectiveness indicators Rev.3 (EMA/204715/2012 Rev.3)

Comments from:

Name of organisation or individual

PHARMIG – Association of the Austrian pharmaceutical industry

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1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	Very well written GVP Module and just some minor comments.	

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Line 268		Comment: Delete "High" for consistency across the Module or replace it with "(potentially)" (see for example line 356). Proposed change (if any): Create awareness of specific serious risks e.g. raise awareness about high teratogenicity before	
Line 434/435		Comment: Comment: a teratogenic effect is specific, would it better to also include fetotoxic effects like "teratogenic/fetotoxic effects" to be considered for a PPP. Proposed change (if any):	
Line 455/456		Comment: to align with other GVP Module would differentiate between standardization and organization Proposed change (if any): For assessing the effectiveness of a PPP, organising standardized data collection by means of specific forms for	

Line number(s) of the relevant text (e.g. Lines 20- 23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		reporting a pregnancy, should it occur, may be part of a PPP	
Line 522/523		Comment: Would refer to the correct text in Dir Art 1 (15) and the "aim" is very important Proposed change (if any): Any study relating to an authorised medicinal product conducted with the aim of measuring the effectiveness of RMM is a PASS.	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28.04.2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3* - Draft for public consultation)

Comments from:

Name of organisation or individual

- Porto Pharmacovigilance Centre, Portugal.
- Lisboa, Setúbal and Santarém Pharmacovigilance Centre, Portugal.

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1. General comments

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2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 127-131 And 140-154		Comment: when choosing a RMM, one should be taken into account the availability (or not) of alternative medicines Proposed change (if any): "and the existence/absence of medicinal alternatives on the market"	
231-293		Comment: the obligation to sign these checklists/forms must be clarified. Proposed change (if any):	
496		Comment: In dissemination plans, consider the channel of professional associations to reach health professionals instead of directly through the MAH. Information is considered more credible Proposed change (if any):	
536, 537		Comment: sometimes recipients have never had contact with the materials Proposed change (if any): Consider an initial timepoint for the assessment of reception by HCP or patients of the materials provided (full coverage) before assessing changes in knowledge and behavior.	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
672-676		Comment: another example could be the incidence of pregnancies in women under treatment with a drug with pregnancy prevention programme. Proposed change (if any): incidence rate of pregnancies onset during a treatment with a medicine with PPP.	
933, 934		Comment: The analysis of the effectiveness of MMR in its various aspects - (dissemination, awareness, knowledge, behavior) must have established a mandatory timetable, as it happens in the PSUR. CAs may (on their own initiative) carry out inspection acts by sampling. Proposed change (if any):	

Please add more rows if needed.



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SCIENCE MEDICINES HEALTH

28 April 2021

Submission of comments on GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3) (EMA/204715/2012 Rev 3)

Comments from:

Name of organisation or individual

Pharmacovigilance Platform Netherlands (PPN, an NVFG knowledge society)

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	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>			
		This update to the GVP module in its current draft form includes improvement points that the PPN acknowledges and appreciates, including contribution of HCPs and patients (representatives), a broader concept of a patient, as it is not in line with that in other GVPs or the (not defined in Annex I -Definitions GVP), uniformity of terminology (guides and patient cards), etc.	
		On several occasions within this draft guidance, the focus appears to be on the regulators, while this GVP module applies equally to MAHs/MAAs. Therefore, where applicable, amended wording is proposed to cover the cooperation.	
		The GVP Addendum I is not in scope of an update. Please note that the Addendum I contradicts the wording in the draft GVP MXVI (line 226 – 227) as it refers to an “educational leaflet for the patient”. That however was the only discrepancy we identified.	

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#	Stakeholder number	General comment (if any)	Outcome (if applicable)
	<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
75		Comment: “required by the competent authorities” appears to imply that the MAH cannot volunteer to implement RMMs for their products. Proposed change: maybe better to state: “in agreement with”?	
133		Comment: “Additional RMM should be completely separated from promotional activities.” Is a clear but high-level concept, and local NCA assessments of this may vary. Proposed change: Define the separation: is this purely on content or also in the distribution process, e.g. can the materials still be distributed by the sales force? Can the materials be shared on a company/product website?	
138		Comment: The text refers to aRMM being considered for safety concerns, but as per the definitions in GVP V, aRMM are usually only considered for important identified risks, not important potential risks and missing information. Proposed change: Additional RMM should focus on important identified risks	
142-143		Comment: this first bullet point appears to be a near-replication of the wording in lines 128-131.	
148		Comment: “Assess the potential for effectiveness of the aRMM” reads as if the word “measuring” is missing, while the intent of this wording seems to say that when designing the aRMM, it should	

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		be assessed to what extent these are thought to obtain the intended effect, i.e. risk reduction or benefit increase. This defines the threshold for success. Proposed change: Assess the potential for measuring effectiveness of the aRMM	
148 - 149		Comment: it might be very challenging to design how to assess the burden of aRMM due to confounding factors, including of course the mentioned unintended effects. What are the criteria for considering aRMM a burden and who is responsible to make that assessment? Should this be addressed with each individual Member State to reflect the different healthcare systems?	
153		Comment: "risk-proportionate and effective in timely manner in minimising the risk" Proposed change: suggest to rephrase -"risk-proportionate and effective in minimising the risk in a timely manner"	
156 - 157		Comment: "there should preferably be a consistent approach to developing and disseminating additional RMM coordinated and overseen by the competent authorities." Preferably in this context still leaves room for national variations to this approach. Proposed change: clarify which competent authority (EMA/NCAs) would drive this coordination.	
161		Comment: word missing Proposed change: "for use on their own or in a combined manner"	

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165		Comment: '... in addition to paper-based materials.' Does this imply that there will always be a need for paper-based material distribution also if that is available in digital form? Or could it be "and/or in addition" to allow for distribution in digital form only when agreed with the NCA? Proposed change: provide further guidance on digital material and whether or not it can be distributed only digitally rather than still also on paper.	
181		Comment: Double s in "concerns(s)" Proposed change: "concern(s)"	
181		Comment: Suggest to rephrase "When the objectives of RMM" Proposed change: "when the risk minimisation objectives"	
198		Proposed change: "A statement"	
226-230		General remark: The change of terminology to the single term of "guide" is applauded for simplicity reasons, however this will also need to be reflected in local legislative/guidance documentation for (a)RMMs.	
285 - 286		General remark: This is similar wording to medication error guidance and a good reminder that patient rights are protected.	

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310-337		Comment: good to make a clear distinction between patient diaries for RM versus those to maximise effectiveness, however this is a fine line when reading back on lines 122-124 that "RMM should therefore support the optimal use of a medicinal product in clinical practice with the principal goal of providing the right medicine at the right dose and at the right time to the right patient and with the right information and monitoring." Presumably under PV legislation, this can be done in accordance with GDPR? Proposed change: clarify that the tool should follow data protection requirements	
352 - 354		Comment: Again, the simplification of terminology is highly appreciated, however this will also need to be reflected in local legislative/guidance documentation for (a)RMMs.	
355 – 372		Comment: presumably, this should all be in one patient card for easy carriage. So one card should contain all applicable safety messages. If that is patient-dependent (e.g. gender/age/indication-specific), would you need or could you develop different cards? – Note that this is a not something new, however it is currently not addressed in the available guidance. This could affect the distribution pathways as well (and the decision to add to packaging or as a stand-alone card). Proposed change: clarify the approach for different safety messages depending on different patient populations.	
424-425		Comment: the recurrent issue with only using the active substance is that patients tend to remember the brand name of their product better than the active substance. Perhaps include all	

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		related brand names once and then keep the active substance name? Or ensure the card refers to the PL of the medicine (which will include the brand name). Proposed change: Please clarify whether it may be useful to refer to the PL so the patient can retrieve the applicable brand name from there.	
446		Comment: the sentence “guidance on the need to use appropriate contraception, on the time period during which pregnancy is to be avoided after stopping the treatment” sounds a bit wobbly Proposed change: “use appropriate contraception while on treatment, as well as for how long on the time period during which pregnancy is to be avoided”	
451		Proposed change: “Restriction of the amount”	
457		Comment: also responding to the request for “We are specifically seeking comments on the need and suggestions for possibly replacing the established term ‘controlled access programmes’ to avoid confusion with the concepts ‘access to medicines’ and ‘controlled substance’.”: to the PPN, this wording is not confusing as we understand the concept. However, perhaps “Controlled distribution programmes” could prevent this confusion as all tools here are focusing on (a part of) the distribution chain from the supply to the dispensing of a medicine. At least this would not have the potential to confuse with the two terms above and it is still separate from the term “Controlled prescription and supply systems”	
472		Proposed change: “facilitates traceability”	

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482		Proposed change: "according to applicable nationally established procedures applicable"	
487		Proposed change: "e.g. a pregnancy test or blood counts"	
528		Comment: "focus on RMM of major patient and public health importance". This wording seems to imply that there are RMM that are not considered to be of major patient and public health importance, for which then there is no need to conduct an effectiveness evaluation. The term "focussed" here is confusing and there is no additional guidance available in the Addendum II on this evaluation. The intention of this sentence is probably that there would only be (a)RMM for concerns of major patient and public health importance, next to the routine RMM of PL/SmPC/package size etc.... . Proposed change: "Effectiveness evaluation of aRMM should take the nature, severity and seriousness of the risk, the magnitude of population exposure and the amount of public concern into account."	
556		Proposed change: "due to changes in behaviour"	
577 – 579, and related body text		Comment: it is understood and agreed that the concept of also investigating unintended (non-targeted) effects of RMM is important, however unintended effects are of course hard to anticipate. It is sometimes already difficult to define proper thresholds of success for the RMM, i.e. for the desired outcomes, so how can we measure deviations from baseline to assess non-targeted	

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		effects? The MAH can measure non-targeted effects (and ensure a placeholder in the effectiveness assessment planning) as they occur, but not predict beforehand. Proposed change: please clarify expectations.	
591-594		Comment: The assessment of whether the intended RMM are proportionate and likely to provide reliable results should already be considered when designing them. Proposed change: "The evaluation strategy should consider to confirm that the which methods used are proportionate and likely to provideing accurate results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients."	
624		Comments: "communication on the risk from other (preferred) sources." In the Netherlands, we have several platforms to share this kind of information and to prevent multiple sites hosting (slightly) different messages, we propose the text to state: Proposed change: "a central location (on a national level) to find the information would be preferred."	
630-632		Comment: Unclear wording. If the intention is to talk about "the targeted HCPs and patients", then the wording should be updated to "needs to be feasible and the targeted". Otherwise, the phrasing should be "needs to be feasible and targeted, and healthcare professionals"	

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		Proposed change: update to one of the proposed changes depending on the intention of the authors	
650		Comment: aren't surveys more a kind of qualitative research? Or would these specific kind of surveys then be targeted to collect quantitative data?	
653		Comment: "a regulatory action" sounds like there is no MAH involvement in the matter. Like an earlier comment, perhaps rephrase to "the RMM" Proposed change: rephrase to "perception of the RMM a regulatory action"	
682		Comment: "a regulatory action" sounds like there is no MAH involvement in the matter. Like an earlier comment, perhaps rephrase to "the RMM" Proposed change: rephrase to "implementation process of the RMM regulatory actions"	
688		Proposed change: "should provide evidence to regulators to determine"	
691		Proposed change: "lead to the assessment conclusion that"	
728 - 729		Comment: "studies conducted jointly by all marketing authorisation holders (see GVP Module VIII) are encouraged in order to minimise the burden on the healthcare systems."	

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		Although we highly support this statement, we urge to use stronger language than “encouraged” as in practice if this is not made mandatory on either side (innovator and generic(s)) then it will not happen and will dilute the data out there. Proposed change: Consider to include a coordinatory role for the EMA/NCA as described elsewhere in this module.	
738		Proposed change: “RMPs for initial”	
742		Proposed change: “lifecycle of the product”.	
750		Proposed change: “the healthcare professionals have learned about how to mitigate”	
782		Proposed change: “differently at the level in of Member”	
821-824		Comment: “In order to respect the diversity of the different healthcare systems in Member States, some key elements will be specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State), but these should still be included in the RMP agreed at EU level.” key elements for CAPs would apply in all 27 Member States. Key elements don’t exist as such for non-CAPs. Proposed change: define key elements and explain that these are referred to as safety concerns for non-CAPs.	

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829		Comment: "The PRAC should assess as appropriate protocols and results of PASS which"	
855		Comment: "authorised products," this comma looks like an unaccepted change.	
889 - 890		Comment: "therefore a detailed description of the forms and dissemination processes in Member States to be followed by the marketing authorisation holder should be available within the RMP" -> does this mean that Annex 6 of the RMP in this case would contain xx copies of the same form but then adjusted for each applicable territory? Should this also be incorporated in the next update to GVP Module V? Proposed change: clarify the intention and incorporate in applicable GVP Module when possible	
896 - 897		Comment: "keep them informed of any changes or issues encountered in dissemination process." -> How is this foreseen? To be agreed with the competent authorities of the applicable Member State? This seems to imply that there is an expectation to report more regularly than is happening now... Proposed change: Additional clarity could be provided in relation to what constitutes 'relevant changes' to dissemination which should be agreed with the competent authorities in Member States.	
922 - 924		Comment: "Where possible, it is encouraged that the Agency, its Committees and competent authorities in Member States, as applicable, engage with healthcare professionals and patient	

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		representatives for obtaining their contributions and discussing” -> given that the MAA/MAH is supposed to propose RMM to the NCAs, such consultation should occur also at the MAA/MAH level to ensure the efforts put in are not wasted. Imagine that after consultation of NCAs with HCP/patient representatives, the conclusion is that the proposed measures will not work, this would be highly inefficient. Or, the MAA/MAH only signal the safety concern and the NCAs and HCP/patient representatives will think of the best fitting RMM Proposed change: “Where possible, it is encouraged that the Agency, its Committees and competent authorities in Member States, and the Marketing Authorisation Holder(s), as applicable, engage with healthcare professionals and patient representatives for obtaining their contributions and discussing”	



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23 April 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) - Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3*)

Comments from:

Name of organisation or individual

Plasma Protein Therapeutics Association (PPTA)

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1. General comments

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	While PPTA commends EMA's and the Heads of Medicines' (HMA) efforts on providing additional detailed guidance on the different PV topics, there are aspects where successful implementation and therefore an improvement for patients' safety cannot only be achieved by the collaboration between competent authorities and pharmaceutical industry. This is particularly true when it comes to risk minimisation. Healthcare Professions play an integral role whether a risk minimisation activity will achieve the desired result or not, and current available data suggests that there is some room for improvement. Therefore, what plans do EMA and the national competent authorities have to have stronger engagement and commitment of Healthcare Professionals in terms of their adherence to risk minimisation activities?	

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	Likewise, detailed guidance is now available, a more common approach towards risk minimisation measures and their implementation should be possible by competent authorities in the European Union. Whilst it is appreciated that different health systems in the different EU Member States may require some country-specific adaptations there are still differences seen in the implementation which cannot just be explained by that. Therefore, what plans do EMA and EU national competent authorities have to achieve more harmonisation amongst the relevant competent authorities when it comes to the implementation of additional risk minimisation activities for a product authorised in more than one EU member state?	

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
74-76		Comment: Objectives of risk minimisation are not only achieved by risk minimisation measures required by competent authorities. Each Marketing Authorisation Holder (MAH) also acts self-responsibly, if and when required. Proposed change (if any): Change wording of this sentence to reflect that risk minimisation is not only achieved by regulatory action but also by actions of the MAHs.	
162-165		Comment: Paper-based materials should no longer be considered state of the art when it comes to the dissemination of information. Nowadays there are means that are, apart from environmental considerations, more efficacious and more accepted than hard copies. Ultimately, new or updated information can be made available and accessed much more rapidly. Certainly, it depends on the situation which means – either of them or both – are to be used. As such, electronic means should be considered an alternative to paper-based materials instead of just an add-on. Proposed change (if any):	

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		The wording of the sentence should be changed to allow for dissemination of relevant information by electronic means in addition to <u>or instead of</u> paper-based materials.	
Section XVI.B.3.1		Comment: While it is clear and acknowledged that the focus of educational material is to provide safety-relevant information, it may be prudent, particularly for materials targeting the patient population, to also provide information why it is important that the medicinal product is used by the patient as intended and prescribed by the physician. Experience has shown that there are situations where patients become uncertain regarding the risks of a product just because of the mere existence of educational material and therefore do not take that medicine. Such effect is a burden to the healthcare system and may have severe consequences for a patient with a severe or even life-threatening disease. Therefore, it should be considered to include some re-assurance that despite of the introduction of such a risk management tool the benefits of such a product outweigh the risks and that the prescriber has considered the patients individual situation when they decided to prescribe them the product. Proposed change (if any):	

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		Add some wording that on a case-by-case basis educational materials may contain some carefully worded information on the benefit of the treatment in order to prevent therapy non-compliance by patients out of the fear of its risks. This proposed change may also be applicable to GVP XVI Addendum I.	
265-266		Comment: The format of risk awareness forms should be tailored to the population it will be used by. Nowadays, there are quite a lot of people, particularly the younger ones, that prefer electronic means over paper. A hard copy may not be the most accepted tool and therefore not be used as intended. Also, electronic means usually provide better options for repeating the messages to be given and – if required – their acknowledgement. Hence, a hard copy or print out should not in every case be required but there should be freedom to agree on the most suitable format. See also comment on lines 162-165 Proposed change (if any): Change wording to allow for other formats of risk awareness forms. Perhaps it may then also be better to use a different term, i.e., instead of "risk awareness form" perhaps "risk awareness information".	

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422-425		Comment: In the interest of Healthcare Professionals and patients this paragraph should not only apply to patient cards but all educational material. Proposed change (if any): Move paragraph to section XVI.B.3.1 and replace "patient card" by "educational material".	
772-773		Comment: For some products, the authorised product information changes rather frequently and within a relatively short time frame. If such changes relate to printed risk mitigation measures (RMM) it should be considered by regulators that it takes some time to update, print and disseminate the material. Proposed change (if any): Ensure that competent authorities in the EU Member States align their implementation of an update to the product information and associated RMM thus providing the basis for the MAH to ensure the RMM can in fact be consistent with the current product information.	

Please add more rows if needed.



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Apr. 27th, 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3)

Comments from:

Name of organisation or individual

Regeneron Pharmaceuticals, Inc.

Global Corporate Headquarters: 777 Old Saw Mill River Rd, Tarrytown, NY, 10591

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1. General comments

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	Regeneron welcomes the initiative by the Agency in proposing this revised guideline on the principles for the development and implementation of additional risk minimisation measures; and for the evaluation of the effectiveness of risk minimisation measures	
	Regeneron would like to encourage the Agency to revisit this guideline to clearly outline requirements for the effectiveness of Risk Minimisation Measures (RMM), with respect to addressing the criteria required to determine acceptability of the Adverse Event (AE) rate. The goal of RMM is to control the AE rate at an acceptable level, and this depends upon various factors i.e. therapeutic area, and medical care setting. While the focus of this guidance is on the measurement, we feel the key component regarding effectiveness check and acceptability criteria is missing. It would be helpful for the Agency to explicitly address its expectations for these criteria to guide MAHs on how to best satisfy the	

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	RMM requirements, thereby minimizing ambiguity around acceptability criteria. These clarifications will ensure a consistent approach by Sponsors when designing studies within a programme to align with the Agency expectations. In turn, this may facilitate more efficient review by the Agency and the development of more robust study designs in the interest of delivering treatments to help improve the lives of patients.	

2. Specific comments on text

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Lines 182-185		<i>“Educational material should be adapted to the target audience. When developing educational materials, it is therefore encouraged, where possible, to engage with healthcare professionals and patient representatives and user-test proposed materials for readability, accessibility, adequacy and user friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population.”</i> Comment: Regeneron agrees that educational materials should be adapted to the target audiences and that the adequacy and user-friendliness of materials should be considered. However, we propose that the Agency remove from the guideline the new recommendation provided on user-testing of educational material. Currently, for centrally authorised products the key elements of educational materials are agreed at EU Commission level. Thereafter, drafts of the educational material(s) addressing the key elements are submitted by the Marketing Authorisation Holder (MAH) to the national competent authorities (NCA) of Member States (MS) for assessment and then be implemented in MS upon approval by the NCA. Thus, while the key elements for the competent educational materials will be the same throughout all EU MS, there may be differences in the final content and format of the educational materials as decided by each NCA. The requirement to user-test the Educational Materials could therefore present challenges to MAHs due to variability in the educational materials across Member States.	

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		Proposed change (if any): N/A	
Lines 186-191		<i>“An educational material should contain the following information elements: Up-to-date, objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be provided in more detail or in a different way than in the SmPC/PL e.g. by the use of tables, flow charts or illustrations);”</i> Regeneron requests that the Agency remove 'up to date' requirement as this is subject to variability in interpretation. As per the current Guideline (Rev. 2), the content of any educational material should be fully aligned with the currently authorised product information for the medicinal product, i.e. the summary product characteristics (SmPC) etc. Regeneron suggests removing this verbatim and instead state that the content of educational material should be consistent with the current SmPC. Proposed change (if any): <i>An educational material should contain the following information elements: “Up-to-date, Objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be</i>	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
		<i>provided in more detail or in a different way than in the SmPC/PL e.g. by the use of tables, flow charts or illustrations); The content of an educational materials should be fully aligned with the currently authorised product information for the medicinal product.”</i>	
Lines 224-225		<i>“In the description of the tool in the RMP, details on the format (e.g. DIN A4 size or larger), its length (e.g. a short or a comprehensive guide) should be specified.”</i> Regeneron requests the removal of the requirement to include a description of the tool in the RMP. Details of the format are decided at national level and usually after approval of the RMP. Different NCAs within the EU may request different formats for educational materials, therefore, the RMP would need to be updated each time education materials are approved in different countries. This may cause significant administrative burden to both MAH and NCAs within the EU and would require multiple updates to the RMP each time different formats were approved without providing additional value. Therefore, Regeneron would like to suggest eliminating such requirement from this guideline. Proposed change (if any): N/A	

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
Lines 573 - 575		<i>“Different approaches to data collection and analysis as appropriate may be applied for each step of the RMM implementation process (see Figure XVI.1.). Measurements and indicators of RMM effectiveness should be defined as part of the study protocol.”</i> Regeneron concurs with the suggested approach for the effectiveness evaluation of risk minimisation; however, Regeneron would like the Agency to recognize local variations that exists amongst National Competent Authorities (NCA) in implementing such criteria at national level. The lack of recognition of the variability at the Member State (MS) level is a significant area which appears to be lacking in this guideline. For example, the measurements and indicators of RMM effectiveness described in this guideline may be incorporated as part of the study protocol, however, it is challenging to address local variations that exists between different MS. The actual RMM tools/materials and their interpretations vary amongst MS, which create discrepancies in implementing the program cohesively at the regional EU level and poses a significant challenge for the industry to measure overall effectiveness of the program. Therefore, Regeneron requests the Agency acknowledge these potential variations within this guideline and provide clarity that there are limitations in the interpretation of effectiveness at national level due to these differences. Inclusion of this discussion in this guideline would help (both MAHs and NCAs) to formally acknowledge local variations around effectiveness evaluation of risk	

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		minimisation, and to drive more collaborative approach to better evaluate the safety and benefit-risk profile of a medicine. Proposed change (if any): N/A	
Lines 707-710		<i>“Effectiveness evaluation where results indicate that pre-defined thresholds have been reached confirm that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach the pre-defined threshold requires further investigation to obtain a clear understanding of the reasons that could help explain the failure.”</i> Regeneron recommends the Agency consider providing alternative language to the word ‘confirm’ as suggested in the ‘Proposed changes (if any)’ section below. The use of this wording reads as a conclusive statement and contradicts some of the earlier language from the Agency regarding the multitude of influences that may impact physician and patient behaviour. For example, there are many things that influence the "effectiveness" of risk minimisation, including information that is provided outside the risk minimisation materials such as lay and professional media, peer reviewed literature, etc., and most of these studies are suggestive of effectiveness at best. Rarely can they be designed to answer an actual causal inferential question, thus it is difficult to describe the results as confirmatory. Regeneron would like the Agency to consider alternative wording as suggested below. This would	

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		further help the industry and the EMA with more accurate interpretation and characterization of the results. Proposed change (if any): <i>“Effectiveness evaluation where results indicate that pre-defined thresholds have been reached suggest that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach the pre-defined threshold requires further investigation to obtain a clear understanding of the reasons that could help explain the failure.”</i>	

Please add more rows if needed.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)' (EMA/204715/2012 Rev 3)

Comments from:

Name of organisation or individual

Takeda

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
Takeda		<i>(To be completed by the Agency)</i>
Takeda	522: Could these be required/imposed as well as voluntary PASS? Can this be clarified?	
	528: Can you elaborate on the definition of "major importance"?	
	531 Principle 2: Regular evaluation. Please confirm if multiple timepoints of evaluation is required, or is it acceptable to do one study? If effectiveness is measured 5 years after implementation of the materials, the physician/patient/caregiver may forget that they received the materials and recall bias. Unless the MAH is required to redistribute the materials, please clarify	
	912 XVI.C.3: Due to the privacy laws it is very difficult to enrol patients in effectiveness surveys. Can you provide guidance on ways of recruiting patients in these surveys in the EU?	

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Stakeholder number	General comment (if any)	Outcome (if applicable)
Takeda		<i>(To be completed by the Agency)</i>
	935-936: Can you clarify if inclusion in PSURs and RMP updates of “summary evaluation of the outcomes of specific RMM” should include only final results rather than interim results?	

2. Specific comments on text

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

Please add more rows if needed.