EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2024
EMA/341741/2024

Comments received from public consultation on 'Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation'

The draft of this addendum was released for public consultation during the period of 3 February t 28 Aprill 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.

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

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 April 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation ' (EMA/419982/2019)

Comments from:

Name of organisation or individual
APCER Life Sciences

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	None	

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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)*
9-33		Comment: Information in the addendum covers both qualitative and quantitative methods. However, sections and subsections are focused on qualitative methods only. Separate subsections depicting quantitative methods / parameters are required for better understanding and clarity. e.g.: XVI.Add.II.2.1. Data sources XVI.Add.II.2.1.1. Qualitative research XVI.Add.II.2.1.2. Quantitative methods	
63-66		Comment: Consider providing more guidance on focus groups with examples	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25th April 2021

Submission of comments on Guideline on good pharmacovigilance practices (GVP): Module XVI Addendum II – Methods for effectiveness evaluation (EMA/419982/2019)

Comments from:

Name of organisation or individual
Chartered Institute of Ergonomics and Human Factors (CIEHF) Pharmaceutical Human Factors Sector Group

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EUROPEAN MEDICINES AGENCY
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The same as with the Draft for public consultation on Module XVI; it appears this Addendum to Module XVI also overlooks the Human Factors/Usability Engineering (HF/UE) risk management and usability engineering processes conducted on medicinal products, premarket authorisation, on *information for safety* such as, labelling, Instructions for Use (IFU), packaging, and training. Of note, PRAC issued a Good practice guide on risk minimisation and prevention of medication errors, where it was recognised that use related risk analysis and human factor/usability engineering was recognised as important in ensuring safe use of medicinal products combined with devices (Section 5.1.3) https://www.ema.europa.eu/en/documents/regulator	

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Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	y-procedural-guideline/good-practice-guide-risk-minimisation-prevention-medication-errors_en.pdf so it would make sense to be consistent.	

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: By overlooking the premarketing authorisation HF/UE work, data sources concerned directly with the product are not mentioned. For example, there is no mention of the availability of data on the products' *intended users*. This information is fundamental to ensure that a study population is representative of the products' stated intended users. **Proposed change (if any):** Section XVI.ADD.II.2.1.1 discusses at some length the importance of sampling the population of interest. Add a reference that the HF/UE work previously done, premarket authorisation, should have a *Use Specification* which defines and describes the products' *intended users*, and may include detailed *user profiles*.	
		Comment: HF/UE expertise and techniques directly applicable to understanding user needs and use errors are not mentioned. For example, *User journey mapping* could be used to identify where users are experiencing difficulties which are likely to result in *use errors*. **Proposed change (if any):**	

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Consider adding references to HF/UE expertise and techniques as data sources or research methods; for instance, usability tests, Perception/Cognition/Action (PCA) analysis or Root Cause Analysis (RCA).	
		Comment: Poor sampling strategies and low responses might be associated with the demographics of the patient population in question. Whilst internet use has exponentially grown in the last 10 years, there are still many non-internet users who could be excluded from these surveys who could provide key data feedback on the effectiveness of the RMMs in place. The mix of respondents is key as is the source of the survey respondents. **Proposed change (if any):** Add a statement that the study technique does not introduce a selection bias, particularly in the case of participants' familiarity with technology.	
		Comment: The MAH should be satisfied that any contracting out of in-house operations for these RMMs survey studies to Third Party Providers (TPP) will ensure that the requirements of the GVP are adhered to. Contracting out this work might	

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		just go to non-pharmaceutical organisations who regularly undertake surveys and utilise interview methodologies, but it is vital to be sure that the outsourced party has a real understanding of what is needed in pharmaceuticals. So, for MAHs, any recruitment strategy should also include appropriate due diligence before engaging these organisations. **Proposed change (if any):** Interview organisations and general research type companies are not always familiar with what is needed for the MAH, so maybe a sentence in this module to advise MAH to what is advisable when selecting third parties would be helpful.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 April 2021

Submission of comments on 'GVP Module XVI Addendum II – Methods for effectiveness of evaluation' (EMA/419982/2019)

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.

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EUROPEAN MEDICINES AGENCY
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1. General comments

#	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		Comment: Please consider further recommendations from ISPE Whitepaper 2016: 'Evaluating the Effectiveness of additional Risk Minimisation Measures via Surveys in Europe: Challenges and Recommendations'. https://pharmacoepi.org/pub/?id=f46953df-de69-31e7-8f74-725bd7fa685f	
		Comment: Measuring effectiveness is a joint effort between EMA/NCAs and MAHs, therefore, guidance on the agreement process for defining success metrics would be welcome, e.g. on threshold for determining whether intervention is successful.	

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#	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		For most situations agreeing on standards should be possible. It can be added that if these standards cannot be met that this is to be justified. Without pre-defined expectations, databases might not evolve to accommodate effectiveness assessment. There also might be a risk of different interpretation and application during the assessment by the member states'.	
		Comment: The considerations for the data sources are not specific to the investigation of the effectiveness of risk management procedures – they could also apply to PASS or PAES. It is noted that the PAES guidance also contains scientific guidance around the use of health care databases, yet slightly different. It is proposed to create a separate scientific guidance on data sources to which the current guidance and PASS and PAES guidance can refer, preferably taking into account the feedback from the current review for its content.	

2. Specific comments on text

#	Line number(s) *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
	55-60		Comment: we assume this will also be impacted with the operation of the EU DARWIN network in time Proposed change (if any): Suggest referring to DARWIN network in addition to ENCePP.	
	62		Comment: (Please see also comment on GVP Module XVI Draft revision 3: Line 615, Lines 648-654, and Lines 673-685) 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 the potential role of PROMs/PREMs and patient-orientated outcomes.	
	62		Comment: It might be beneficial to add examples of how qualitative methods contribute to evaluation; e.g. support of in-depth understanding 'why' RMM may demonstrate less effectiveness than hypothesised. Proposed change (if any):	
	62-88		Comment: From the perspective of non-prescription drugs (eg OTC medications), social media listening might have deserved being specifically addressed in this section. Data mining of social media	

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			conversations regarding medication use allows a better understanding of individuals' perceptions and knowledge about medications, often uncovering conversations that are not conducted within the healthcare setting. These findings may be used to improve healthcare by pre-emptively addressing areas of concern, and also demonstrate that more easily accessible healthcare information for the general public would be beneficial. It may be interesting to repeat those studies to determine if any changes in how drugs are discussed on social media platforms since the introduction of risk minimization measures. The advantage of using web-based information collection includes the ability to gather information from individuals who might not otherwise take part in studies, as well as the ability to conduct global analyses with real-time collection from a broad sociodemographic range. While this method has advantages over traditional information-gathering, there are also limitations, including the fact that this is based on the web user's declaration and can be heavily driven by advocacy groups. Proposed change (if any): propose some guidance on web-based information collection regarding use of social media listening and web based information to monitor impact of Risk MM plan	
	72		**Comment:** Consider highlighting the need for diverse viewpoints collated via methodologically robust tools versus "saturation of data" (of which the meaning here might be unclear) when referencing information gleaned from focus groups/interviews. **Proposed change (if any):**	
	82		**Comment:**	

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			The underlying epidemiology of the patient or healthcare population of interest should inform the choice of sample strategy; representativeness may require oversampling specific subpopulations due to possible participation barriers. **Proposed change (if any):**	
	87-88		**Comment:** Response bias or recall bias? If response bias, consider adding that basic demographics/characteristics for responders and non-responders should be compared to assess the possible introduction of systematic error. If recall bias, consider specifying it as such and update "expected" to "potential". **Proposed change (if any):**	
	Lines 90-95		Comment: We would like the Agency to clarify whether the use of an application would be appropriate here and if yes to add language accordingly. Proposed change (if any): add language accordingly.	
	101-104		**Comment:** Flaws in the study design, data collection or analyses could lead to deviations from the "truth". Proposed change (if any): Consider broadening the paragraph to highlight the need to consider bias throughout the development, administration & interpretation of the surveys. Highlighting the need for non-leading questions within the survey instrument as well.	

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	106		**Comment: Missing "are"...** **Proposed change (if any):** "Patient registries are..."	
	120		**Comment:** Consider adding the voluntary nature of registries as a potential limitation. **Proposed change (if any):**	
	131-132		Comment: In section XVI.Add.II.2.1.4. Medical records it is stated that *"Where relevant outcome variables are not routinely collected, complementary primary data collection may be considered."* The collection of solicited data to compensate for unavailable routinely collected data may introduce bias. Proposed change (if any): add statement to indicate that a limitation of this approach is the introduction of possible bias.	
	133-135:		Comment: We would like to clarify that this is not a universal issue and some datasets are able to include both prescribing and dispensing information. However, no dataset includes actual adherence, i.e., did a patient take the therapy as prescribed. Proposed change (if any): Suggest amending the wording to reflect the above.	

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	145-149		Comment: Another limitation is the periodicity of refresh in the data over time. Proposed change (if any): Suggest amending the wording to include the above: "Furthermore, information on inpatient medication and diagnoses made in hospitals may not be available. Another limitation is the periodicity of refresh in the data over time"	
	151-154		Comment: We would like to comment that data linkage is currently impossible in many Members States and that it should be reflected/acknowledged in this GVP Module. Proposed change (if any): suggest adding after the first paragraph: 'Unfortunately in many Member States data linkage is prohibitively difficult under local and regional privacy restrictions'	
	156 - 161		Comment: Readability may benefit from structuring the "i - iv integrated listing to a bullet format. Proposed change (if any): insert bullets "i – iv"	
	156-168		Comment: We would like to comment that also the resourcing, emphasis and infrastructure for spontaneous reporting in each Member State is heterogenous and ought to be addressed. Proposed change (if any): Suggest amending the wording to reflect the above.	
	169		Comment: if we have a factor influencing for data sources, do we need one for methods? And if we do, do we need anything in between intro (36) and data collection (50) that refers to the overall objective of in the context of the underlying risk i.e. start with the end in mind type of approach (please see also our comment on the need for an overview table).	

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			Proposed change (if any): Please amend the wording to reflect the above.	
	Lines 178-179		Comment: it is likely to be extremely difficult for the MAH to realistically verify the reliability of data from secondary data sources. Proposed change (if any): Suggest to re-phrase to reflect the above.	
	194_196		Comment: "In case of evaluating non-targeted effects, the study population should preferably not be limited to the population targeted by the product-specific regulatory action" It is unclear what is meant by this statement, especially the expected study population Proposed change (if any): please clarify	
	Line 207		Comment: when would it be appropriate to monitor non-targeted effects? Proposed change (if any):	
	Line 203 figure		Comment: Case study is listed as a method for evaluating effectiveness of RRM. It is unclear how to evaluate effectiveness with a case study? (Are case series meant?) Chart review is not an effectiveness method on its own. A cross-sectional study or a drug utilization study can include chart review, for example.	

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			Proposed change (if any):	
	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.	
	327-331 & 353-357: same as 327-331		Comment: We would like to make the wording about control group clearer as it appears to be unfeasible while required to establish such group as per proposed wording. Proposed change (if any): we suggest swapping the paragraph around and start with saying it is generally not possible to include a control group, but on the occasion where it is feasible a control group should be included.	
	414-425		Comment: Reporting items derived from the RIMES Statement for reporting results of effectiveness studies is incorporated in the Table XVI.Add.II.1.: Additional PASS reporting items for effectiveness study reports. It is not clear whether these reporting items are mandatory to be utilised by the MAHs for reporting results of effectiveness studies. Proposed change (if any):	
	Lines 414-425		Comment: Consideration should be given to inhibitors of RMMs implementation in the marketplace (i.e., not directly in control of the Marketing Authorisation Holder). We suggest that EMA needs to consider how to include Member State active participation in a RMM implementation	x

#	Line number(s) *(e.g. Lines 20-23)*	Stakeholder number *(To 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):	
	425		Comment "Table XVI.Add.II.1.: Additional PASS reporting items for effectiveness study reports". This table is very helpful and the guidance would be strengthened considerably if elements of this table are further elaborated on.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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<26 April 2021>

Submission of comments on ' Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – 'Methods for effectiveness evaluation'

Comments from:

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

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SCIENCE MEDICINES HEALTH

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 39-49		Comment: No mention of the value of using evaluation frameworks to guide evaluation design. Change: Add *The design of the Risk Minimization program should be guided by the use of theoretical models and frameworks as per Implementation Science (Smith et al., 2014). In addition, the design of the Evaluation study should be guided by the use of an evaluation framework. A variety of relevant frameworks exist (e.g., RE-AIM, PRISM, CfIR, etc). The Risk Minimization program design team should reference the use of one or more relevant theoretical behavioural models and frameworks to guide the design of the program. Similarly, the evaluation team should describe the rationale for selecting a specific framework to guide the design of the risk minimisation program evaluation.*	
Line 41		Comment: Need to specify the importance of collecting qualitative data, not just qualitative research methods Proposed change (if any): Add; …..and qualitative *measurements* and research approaches" Please add more emphasis on the importance of using mixed methods research for evaluation studies. Specifically, quantitative methods can be used to address the question of whether the program had an impact, to	

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		what extent and for whom (e.g., specific subgroups of the target population); while qualitative methods can be used to explain 'why' there was an impact (or why there was little to no impact) and identify what aspects of the program need to be modified to ensure better acceptance by healthcare professionals and/or patients, and better integration into the healthcare system.	
Lines 53-54		Comment: Proposed change (if any): Change "should" ……primary and secondary data sources ~~should~~ *may* be considered to evaluate effectiveness…..	
Line 84		Comment: Proposed change (if *any): Specify that a rationale for appropriate sampling be provided as part of the evaluation research study protocol.*	
Lines 204-205		Comment: Figure XVI.Add.II.1- *This figure is not comprehensive.* *Proposed change: Include mention of the need to assess ecological setting.*	
Line 210		Comment: Qualitative data can help understand why a programme worked or not; it can also be used to understand contextual factors in the implementation	

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		environment that helped or hindered the program roll-out and impact. Proposed Change: …… address "Why did the risk minimisation programme work *or did not work*?" Add in that qualitative methods are important to use in order to understand contextual factors.	
Line 323		Comment: Mixed Methods designs enable the researcher to do more than **triangulate** the 2 different data types: such designs also function as follows: a) complementarity (where quantitative data are used to evaluate outcomes and qualitative data are used to evaluate process; or qualitative methods are used to provide depth of understanding and quantitative data are used to provide breadth of understanding); b) expansion or explanation, where qualitative methods are used to explain or elaborate on the findings of quantitative studies, but may also serve as the impetus for follow-up quantitative investigations; c) development (where one method is used to develop instruments, concepts or interventions that will enable the other method to answer other questions); and c) sampling, the sequential use of one method to identify a sample of participants for use with the other method. Proposed change (if any): Mention the other ways (described above) in which qualitative and quantitative data can be used in Mixed Methods designs.	

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Line 400		Comment: Use of randomised trials Proposed change (if any): Could text be inserted to describe how and under what situations a randomised trial could be used to evaluate a risk minimisation program, and what types of discussions (and when) a sponsor would need to have with the regulatory authority to enable such a design type to be used.	
Line 421		Comment: Regarding the reference to the RIMES Statement: this Reporting Checklist is planned to be submitted to EQUATOR in 2021 for inclusion as a standard quality reporting checklist. Recommend that that version be used. Note: Several very minor changes were made to the RIMES Statement as a result of the systematic review application (per Russell A. et al, 2020). Proposed change (if any): Retain reference to the RIMES Statement.	
		Comment: Proposed change (if any):	

Please add more rows if needed.

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<25 Apr 2021>

Submission of comments on 'Module XVI **Addendum II** – Methods for effectiveness evaluation' (EMA/419982/2019 Rev 3)

Name of organisation or individual
International Society of Pharmacovigilance Medication Errors Special Interest 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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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	A list of qualitative study designs has been added from line 220 onwards. It is suggested to add the pros and cons of each study design and when it should be preferentially used.	
	How widely are healthcare record linkages available in each member state? What ethical standards and privacy laws in place to regulate the usage of personal data and protect personal data?	
	There is no mention of techniques to investigate risk minimisation when it fails to meet agreed objectives. Examples include the following: A Systems Approach to Analyzing and Preventing Hospital Adverse Events Nancy Leveson, Aubrey Samost, SM, Sidney Dekker, Stan Finkelstein, and Jai Raman, MD, PhD J Patient Saf. 2020 Jun;16(2):162-167 Nancy Leveson, Matthieu Couturier, John Thomas, Meghan Dierks, David Wierz. Bruce M. Psaty and Stan Finkelstein Applying System Engineering to Pharmaceutical SafetyJournal of Healthcare Engineering · Vol. 3 · No. 3 · 2012 Page 391–414 Waterson, P.E. and Jenkins, D.P., 2011. Lessons learnt from using AcciMaps and the risk management framework to analyse large-scale systemic failures. IN: Anderson, M. (ed.). Contemporary Ergonomics and Human Factors 2011. Proceedings of the	

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	International Conference on Contemporary Ergonomics and Human Factors 2011. London: Taylor and Francis. McNab D, McKay J, Shorrock S, et al. Development and application of 'systems thinking' principles for quality improvement. BMJ Open Quality 2020;9:e000714. doi:10.1136/ bmjoq-2019-000714	

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9-33		Comment: Information in the addendum II covers both qualitative and quantitative methods. However, sections and subsections are focused on qualitative methods only. Proposed change: Separate subsections depicting quantitative methods / parameters are required for better understanding and clarity. e.g.: XVI.Add.II.2.1. Data sources XVI.Add.II.2.1.1. Qualitative research XVI.Add.II.2.1.2. Quantitative methods	
194		Comment: "non-targeted effects" is this referred to "unintended effects" or a different concept? Proposed change (if any): please clarify	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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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 *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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).	
	There are several instances within this document (see Minor Comments section) where the focus appears to be on regulators, and where we would	

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	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.	

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		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	

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		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 *CIOMS IX* 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 Proposed change (if any): Need to add that they should be assessed for "understandability and actionability".	

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		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.	
Pg 9&10, Lines 310-337		Comment: We appreciate the clear distinction between patient diaries for RM versus those to maximise	

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		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 Implementation Plans as the focus is on more than dissemination only.	

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		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, *Medical Care* 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 require repeated RMM interventions in various formats.	

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		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 could be part of unintended consequences for RMM.	

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		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; 40(8):729-42 is 1 of several publications showing this). In our qualitative research, patients routinely don't see	

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		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., resource issues, time constraints, system workflow constraints;"	

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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 be 'released' ever? What types of evidence would be needed to support that? What type of results would	

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		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 reaching)</u> the pre-defined threshold requires further	

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		investigation as part of the iterative process of risk management to obtain a clear understanding of the reasons that could help explain the ~~failure~~ lack of success.	
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			

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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~~" -> "in agreement with" 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, i.e. risk reduction or benefit increase. This defines the threshold for success.	

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		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~~" -> "-risk-proportionate and effective in minimising the risk in a timely manner"	
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. 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	

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		Proposed change (if any): "for use on their own or in a combined manner"	
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 complementary or optional 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~~" -> "when the risk minimisation objectives"	
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 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 ->	

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		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): "A s~~S~~tatement"	
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 descriptive term, such as dosing guides or pharmacy posters.	

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		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): patient concerned	
Pg 13, Line 422-423		Comment: Suggest to delete "to all these products" because it may not apply to all product formulations	

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		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 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	

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		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 **or as available in time for the evaluation of the renewal of a MA**." 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	

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		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, events impacting healthcare (e.g. pandemic events)	
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 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. *Drug Safety* 2018; *41:*389-	

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		401.- for a more comprehensive set of domains to be assessed.	
Pg 18, line 581		Comment: Proposed change (if any): scope and objectives	
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 or MAH	
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 the targeted" or "needs to be feasible and targeted, and healthcare professionals"	

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Pg 20, Line 651		Comment: Proposed change (if any): Additional 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~~ the RMM"	
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. 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"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 22, Line 698-700		Comment: *"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"* 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 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.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): 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 ? 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 and all MAHs for the relevant products must be able to demonstrate their attempts to agree	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		on a study strategy with the other MAHs. This is in order to minimise the burden on the healthcare systems.	
Pg 24, Line 738		Comment: Proposed change (if any): "RMPs for initial"	
Pg 24, Line 742		Comment: Proposed change (if any): "lifecycle of the product"	
Pg 24, Line 750		Comment: Proposed change (if any): "the healthcare professionals have learned ~~about~~ how to mitigate"	
Pg 25, Line 767		Comment: Proposed change (if any): medical adequacy, data 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~~ of Member"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 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 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	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 868		Comment: Proposed change (if any): permitted to be prescribed by 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 is 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.	
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"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		after professional, as HCP and patient organizations are different Proposed change (if any): Collaboration with healthcare professional associations and patient organisations	
EU GVP Module XVI – Addendum 2			
1. General Comments			
		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	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		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 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	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		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 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.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Clarify whether RIMES is required or recommended.	
<end>			

Please add more rows if needed.

2021-04-20

Submission of comments on Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation EMA/419982/2019 - 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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Effectiveness evaluation should address different aspects of risk minimisation measures in a risk proportionate way, i.e.: a) the process itself, b) its impact on knowledge level, c) behavioural changes, and d) the ultimate safety outcomes. The guideline focusses on aspects b). c) and d). However, aspect a) should be emphasized as being the basic indicator for all aRMMs, whereas not all aRMMs will be eligible for the other aspects. The guideline therefore should provide more guidance on the various different methods to evaluate the process metrics (i.e. to what extent the programme has been implemented as planned, or variations in its delivery).	
	Consideration should be given to define more clearly when generics are expected to contribute PASS or join PASS consortium.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 020-023)*	Stakeholder number *(To 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)*
154-166		Comment: It is stated that "continued spontaneous reporting of a very serious adverse reaction despite RMM may be taken as supportive evidence indicating that the RMM may not be effective in combination with evidence from non-interventional studies". However, despite the potential bias and the need to be very careful in the interpretation, the trend monitoring over time of the spontaneous cases can still support effectiveness evaluation, especially for generics. There were examples in the past when authority approved as part of the RMP effectiveness evaluation of aRMM thru **annual reports** of adverse experience from pregnancy or rare events cases when non-interventional studies could not be conducted (for generics and innovators). Proposed change (if any): It would be appreciated if authority could add annual reports or other examples in this section when **spontaneous reports could be acceptable**, eg. in case when non-interventional studies could not be conducted, for Pregnancy Prevention Programme (PPP) when each pregnancy case indicates prevention failure, for generic product in combination with originator's PASS study. In this way text would be also aligned with proposed health outcomes in Figure XVI.Add.II.1.	
170-171		Comment: Suggestion to update the factors.	

Line number(s) of the relevant text *(e.g. Lines 020-023)*	Stakeholder number *(To 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 other factors, such as - Precision and efficiency as well as feasibility	
178		Comment: Update sentence "The reliability of information on exposure and outcome…" Proposed change (if any): "The reliability and validity of information on exposure and outcome."	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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27 April 2021

Submission of comments on GVP Module XVI AddendumII – Methods for effectiveness evaluation (EMA/419982/2019)

Name of organisation or individual
Otsuka Pharmaceutical Development & Commercialisation Europe GmbH

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Comment: Otsuka recommends including examples (or references) of the appropriate use of each of the listed data sources in risk minimisation measure (RMM) effectiveness evaluation.	

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)*

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155-168		**Comment:** Limitations of spontaneous reports of suspected adverse reactions are clearly stated. However, there is no wording on how spontaneous report data can provide supportive evidence for RMM effectiveness. Otsuka recommends providing additional guidance or examples that show when spontaneous reporting data can be interpreted as supporting evidence of RMM efficiency.	

EUROPEAN MEDICINES AGENCY
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27 April 2021

Submission of comments on GVP Module XVI Addendum II – Methods for effectiveness evaluation (EMA/419982/2019)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	N/A	

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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)*
163-166		Comment: *Comment: it is not clear why for evidence of effect it cannot be used but for the evidence of a negative effect. So, it should be supportive for both kinds of effects and not just for the negative one.* Proposed change (if any): However, in specific situations, the continued spontaneous reporting of a very serious 163 …..not considered adequate for demonstrating that RMM has been 164 effective **or ineffective**…….. 165 adverse reaction despite RMM may be taken as supportive evidence indicating that the RMM **may or** may 166 not be effective in combination with evidence from non-interventional studies	
278		Comment: *Typo* Proposed change (if any): Construct validity: Items or variables ~~in the~~ in the data collection instrument should be	
408-409		Comment: *Typo* Proposed change (if any):	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		*All non-interventional studies **with the aim measuring** ~~evaluating~~ the effectiveness of RMM should be a priori registered in the EU PAS Register*	
420-421		Comment: Comment: "can be used" can be interpreted as must or should. The word "improve" implies that the current reports are inadequate. Proposed change (if any): "tailored to the study designs frequently used for risk minimisation evaluation (39), **can be considered to be utilized** to standardise ~~and improve~~ the reporting from such studies.."	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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28 April 2021

Submission of comments on 'GVP Module XVI Addendum II – Methods for effectiveness of evaluation' (EMA/419982/2019)

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.

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EUROPEAN MEDICINES AGENCY
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1. General comments

#	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		No general comments	

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2. Specific comments on text

#	Line number(s) *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
	106		**Proposed change:** "Patient registries are organised systems"	

Please add more rows if needed.

Apr. 27th, 2021

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation' (EMA/419982/2019)

Comments from:

Name of organisation or individual
Regeneron Pharmaceuticals, Inc.
Global Corporate Headquarters: 777 Old Saw Mill River Rd, Tarrytown, NY, 10591 European Business Office: One Warrington Place, Dublin 2, D02 HH27, Ireland
[redacted]

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Regeneron welcomes the initiative by the Agency in proposing this Addendum to GVP Module XVI, which provides additional guidance for marketing authorisation holders (MAHs)and national competent authorities (NCAs) on data sources and methodologies for monitoring outcomes of risk minimisation measures (RMM) in line with the principles for RMM effectiveness evaluation laid down in GVP Module XVI.	

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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 90-95		*"Surveys are a method to collect primary data from a sample of a population and typically apply a standardised questionnaire through in-person interviews or options for self-reporting with postal mailings or electronic communication (e.g. web panels). These may be supported by audio computer-assisted self-interviewing (A-CASI) or interactive voice response systems (IVRS). The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics, and the type of data to be collected."* Regeneron requests that the guideline acknowledge certain limitations which exist in conducting such surveys. In particular, during the time period following initial licensing, in many instances, there is a low volume of sales data at the member state or country level, and lack of reimbursement, which lead to limited data on patient prescription and exposure. This poses a major operational constraint and limitation to interpretation of surveys, which are often a primary component of the effectiveness evaluation. Regeneron would appreciate acknowledgement of this operational constraint and limitation in the guidance, and thus contributing to surveys that may be unfeasible or impractical to execute or those that may yield results of little value. Given these challenges, we encourage the Agency's flexibility in the method the MAH may propose or design to assess effectiveness is 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)*
		Inclusion of this discussion in this guideline would further help to streamline the application of Risk Minimisation Measures (RMM) tools. **Proposed change (if any): N/A**	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for effectiveness evaluation' (EMA/419982/2019)

Comments from:

Name of organisation or individual
Takeda

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EUROPEAN MEDICINES AGENCY
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	122. When will guidelines on Registry based studies be effective?	

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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' by cutting & pasting text directly from guidance into this form.)*	Outcome *(To be completed by the Agency)*
	[redacted]	Comment: Proposed change (if any):	[redacted]
	[redacted]	Comment: Proposed change (if any):	[redacted]
	[redacted]	Comment: Proposed change (if any):	[redacted]

Please add more rows if needed.