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. These comments were prepared by the following individuals on behalf of the BRACE SIG: **Emily Freeman, MSc, PhD,** Senior Director, Global R&D Patient Insights, Lundbeck Pharmaceuticals, LLC, Deerfield, IL, USA **Terri Madison, PhD, MPH,** Vice President Scientific Affairs and Head Real World Evidence Strategy and Analytics, ICON plc, Michigan, USA **Monika Pietrek, PhD,** Managing Director & Senior Consultant, Pietrek Associates GmbH, Weinheim, Germany **Meredith Smith, PhD, MPA, FISPE,** Director, Risk Management, Alexion Pharmaceuticals, Inc, MA, USA; Adjunct Professor, International Center for Regulatory Science, School of Pharmacy, University of Southern California; and Adjunct Assistant Professor, Health Sciences Program, Rutgers University **Angela van der Salm, PhD,** Epidemiologist A, Director Pharmacovigilance, DADA Consultancy BV, Nijmegen, The Netherlands **Co leads:** **Alicia Gilsenan, PhD, FISPE,** Senior Director and Head, Epidemiology, RTI Health Solutions, North Carolina, USA **Rachel Sobel, DrPH, FISPE,** Executive Director, Head of Pharmacoepidemiology, Regeneron Pharmaceuticals, Tarrytown, NY, USA

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)*
	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 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. Minor: Add "right route of administration"	

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

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

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

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

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

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

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

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

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		factors of healthcare systems and patient life impacting on RMM implementation, e.g., 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 be 'released' ever? What types of evidence would 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)*
		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. Proposed change (if any): Please acknowledge the need for flexibility in threshold development due to local	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		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 provide evidence that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach (or only partially reaching) the pre-defined threshold requires further 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		Comment: "Collaboration with healthcare professional	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 914-924		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			
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”?	

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

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 6, Line 181		Comment: Suggest rewording to clarify Proposed change (if any): "concern~~s~~(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 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	

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

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

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

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Refer to Figure 1. in Smith MY et., The RIMES Statement. *Drug Safety* 2018; *41:*389-401.- 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"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 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"	
Pg 22, Line 698-700		Comment: *"Indicators for success or failure should be determined a priori and on a case by case basis.*	

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

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

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

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		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" after professional, as HCP and patient organizations are different Proposed change (if any): Collaboration with healthcare professional associations and patient organisations	

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

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		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 should be conveyed that this would be an approach rarely used.	

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