EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 November 2011
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EMA Comments on Implementing Measures for Pharmacovigilance (PCIM/11/01)

The Agency welcomes the public consultation on the Commission concept paper on the implementing measures and, hereby, provides its comments on the document published.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8660
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Proposed text from the draft Implementing Measures	EMA proposal	EMA background information and justification
A. Pharmacovigilance system master file		
2. Location (page 5) … Without prejudice to other requirements any change in its location shall be notified immediately after the implementation to EMA in accordance with Article 57(2)(c) of Regulation (EC) No 726/2004 in order to correct the information on the European medicines web-portal.	2. Location (page 5) … Without prejudice to other requirements any change in **the pharmacovigilance system master file location or changes to the contact details or name of the pharmacovigilance qualified person shall be notified immediately after the implementation to EMA in order to update the information on the European medicines web-portal (Article 57(1)(l) of Regulation (EC) No 726/2004).**	In an effort to simplify maintenance activities regarding QPPV and PSMF information for the regulators and the industry and to avoid unnecessary administrative variations, it is proposed to use the Article 57 database for administrative updates to the PSMF and QPPV information once the database is operational. Changes to QPPV contact details (telephone and fax numbers and email address) and changes to the address of the QPPV/PSMF (street, city, postcode) within the same country will have to be updated by the MAH in the Article 57 database. It is proposed not to require a variation for such administrative changes. A variation will only be required in case of change of country of the QPPV/PSMF or change of name of the QPPV. The MAH will update the Article 57 database following the variation for these

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		changes.
	3. Introduction (page 7) **The transitional measures regarding the obligations on the part of the marketing authorisation holder to maintain and make available on request a pharmacovigilance system master file are described in Article 3(1) of Regulation (EU) 1235/2010 and Article 2(1) of Directive 2010/84/EU.** **If a marketing authorisation holder wishes to switch to a pharmacovigilance system master file on a voluntary basis earlier than described in Article 3(1) of Regulation (EU) 1235/2010 and Article 2(1) of Directive 2010/84/EU, the relevant variation can be submitted.**	The EMA suggests adding a section 3. on the introduction of a PSMF to be located before the section on 'maintenance'. The EMA as well as Member States are supportive of an earlier introduction of the PSMF by MAHs on a voluntary basis, but it is acknowledged that in the absence of renewal before July 2015, MAH are not obliged to switch to the master file process before July 2015. Based on likely cost and resource savings a significant number of MAHs currently using a DDPS are expected switching to a PSMF at an earlier date.
4. Maintenance (page 7) **Consultation item no. 2:** **…** **Would it be nevertheless appropriate to require the marketing authorisation holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks? If so, how should this be done? Should the master file contain a date when**	4. Maintenance (page 7)	EMA supports the requirement to notify to the authorities significant changes to the PSMF. A clear guidance on what constitute a significant change to the PSMF will have to be issued. The intention will be to have a limited list and an annual update regarding the significant changes to the PSMF is considered sufficient. The MAH should submit the annual update to the competent authority where the PSMF is located. The annual update should be available to any

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it was last reviewed?		other authority as necessary.
7. Audit (page 8) **Consultation item no. 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?**	7. Audit (page 8)	The EMA proposes to include audit schedules in the PSMF. However, the retention of audit reports should be kept outside of the PSMF. Audit reports should be kept available and provided on request if required.
B. Quality systems for the performance of pharmacovigilance activities – Common obligations		
10. Audit (page 9) Audits of the quality system shall be performed at regular intervals, and not less than every two years, to assure that the quality system is in compliance with the established quality system requirements and to determine its effectiveness. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited.	10. Audit (page 9) **Risk-based** audits **of the pharmacovigilance system** ~~quality system~~ shall be performed **according to a common methodology,** at regular intervals, and not less than every two years, to assure that the quality system is in compliance with the established quality system requirements and to determine its effectiveness. ~~Quality~~ Audits **of the pharmacovigilance system** shall be conducted by individuals who do not have direct responsibility for the matters being audited.	<u>Risk-based audits</u> The EMA believes it is important to specify that the audit should be based on risks. Audits should be planned and should focus on risks identified prior to the audit (risk assessment). <u>Audit of the pharmacovigilance system</u> The EMA understanding is that the audit is not only on the quality system but also on the pharmacovigilance system so suggests keeping it general as "Audit of the pharmacovigilance system". Based on comments that it could be understood that there are two separate types of audits i.e. on the quality system and on the pharmacovigilance system, the EMA does not believe it is the case and suggests to clarify by referring to audit of the pharmacovigilance system only (including the quality system).

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		Common methodology The EMA suggests including the notion of common methodology for audits to have a harmonised approach across member states.
C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders (MAH)		
13. Resource management (page 10) A sufficient number of competent and appropriately qualified and trained personnel shall be available in the operation of pharmacovigilance activities. In that context, it shall be ensured that the qualified person for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. If the qualified person is **not medically qualified**, access to a **medically qualified person** should be available. The duties of the managerial and supervisory staff, including the qualified person for pharmacovigilance shall be defined in job descriptions.	13. Resource management (page 10) A sufficient number of competent and appropriately qualified and trained personnel shall be available in the operation of pharmacovigilance activities. In that context, it shall be ensured that the qualified person for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. If the qualified person is **not a physician**, access to **a physician**, should be available. The duties of the managerial and supervisory staff, including the qualified person for pharmacovigilance **and all staff involved in pharmacovigilance activities** shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart.	Some clarifications are required concerning the definition of 'medically qualified'. The term 'medically qualified' in the context of QPPV would benefit to be further clarified as proposed. Indeed as opposed to ICH interpreting 'medically qualified' for the purpose of reporting as a synonym to healthcare professionals, e.g. as physicians, pharmacists, nurses, dentists, coroners (se ICH-E2D Healthcare Professionals), it should be more specific to allow to request access to a physician specifically . EMA suggests having job descriptions for all staff involved in pharmacovigilance activities.
15. Record management (page 11)	15. Record management (page 11)	

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A quality system shall be in place for maintaining a record management system for all documents used for pharmacovigilance activities, ensuring the retrievability of these documents as well as traceability of how safety concerns have been investigated, the timelines for these investigations and how and when decisions have been taken. In this context, marketing authorisation holders shall establish mechanisms enabling traceability and followup of adverse reaction reports while complying with data protection legislation.	A quality system shall be in place for maintaining a record management system for all documents used for pharmacovigilance activities, ensuring the retrievability of these documents as well as traceability of how safety concerns have been investigated, the timelines for these investigations and how and when decisions have been taken. In this context, marketing authorisation holders shall establish mechanisms enabling traceability and followup of adverse reaction reports while complying with data protection legislation. **At each stage of storage and processing of pharmacovigilance data, measures should be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of the data.**	If the paragraph on data protection in the quality system for EMA and NCA relates to patient data protection and confidentiality, it should apply for the MAH too.
D. Quality systems by national competent authorities and EMA		
17. Resource management for EMA and NCA (page 12)	17. Resource management for EMA and NCA (page 12)	EMA suggests including explicitly the requirement of job descriptions and an organisation chart for personnel involved in the operation of pharmacovigilance activities at the EMA and NCA (as requested for the MAH).

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19. Record management for EMA and NCA (page 13) At each stage of storage and processing of pharmacovigilance data, measures should be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of the data.		The scope of 'data security and confidentiality' should be clarified as to whether it covers only commercially confidential information. If it covers patient data protection and confidentiality, this paragraph needs to be included in the implementing measures for MAH (see comment above for QS for MAH).
19. Record management for EMA and NCA (page 13) Pharmacovigilance system-related documents. shall be retained as long as the system as described in the pharmacovigilance master file exists and for a further 10 years after it has ceased to exist. Product-related documents shall be retained as long as the marketing authorisation exists and for further at least 30 years after the marketing authorisation has ceased to exist.	19. Record management for EMA and NCA (page 13) **Documents related to the pharmacovigilance system of the EMA and NCA** shall be retained as long as the system ~~in the pharmacovigilance master file~~ exists and for a further 10 years after it has ceased to exist. Product related documents shall be retained as long as the marketing authorisation **or a marketing authorisation for another medicinal product containing the same active substance** exists and for further at least 30 years after the **last** marketing authorisation has ceased to exist. **Documents related to the pharmacovigilance system of that MAH should be retained for at least 30 years after the last marketing authorisation of**	The pharmacovigilance system master file is not applicable for EMA and NCA. MAH-related documents should be kept as long as a MA exists and for a further 30 years after the expiry of the last MA has ceased to exist. The EMA believes it is important for the EMA and NCA to retain product-related documents for reference medicinal products, for example to keep the product-related documents for an originator even if the MA for the originator is withdrawn in case issues arise at a later date

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	that MAH has ceased to exist.	with the generics.
Annex I – Electronic submissions of suspected adverse reactions		
1. Definitions 1. (b) Medication error, which refers to inappropriate use of a medicinal product while in the control of the healthcare professional, patient, or consumer.	*1. Definitions* 1. (b) Medication error, which refers to ~~which refers to inappropriate use~~ **any unintentional error in prescribing, dispensing or administration** of a medicinal product while in the control of the healthcare professional, patient or consumer.	In order to better distinguish the term 'Misuse' from 'Medication error', the Agency is proposing to amend this latter definition as proposed.
Annex II – Risk management plans		
Pursuant to Article 1 point 28c of Directive 2001/83/EC a risk management plan contains a detailed description of the risk management system. To this end it shall: • Identify or characterise the safety profile of the medicinal product(s) concerned • Describe how the safety profile will be assessed and monitored • Document measures in place to prevent or minimise the risks associated with the medicinal product including the assessment of the effectiveness of those interventions.	**The purpose of the RMP is to:** • **Describe what is known and not known about the safety profile of a medicine or group of medicines** • **Plan how to characterise further the safety profile of the medicine(s)** • **Document what measures will be put in place to prevent or minimise the risks associated with the product and how the effectiveness of those interventions will be assessed.** • **Document the need for studies on effectiveness and long term efficacy to facilitate integration with post-authorisation pharmacovigilance plan**	The description should be revised as proposed to capture the essence of risk management. Bullet point 2 does not really reflect the purpose of the Pharmacovigilance Plan as it is to plan how to find out more about the safety profile of the drug rather than just assessing and monitoring. There is a clear legal reference to post authorisation efficacy studies being included in the RMP, therefore the 4th bullet point is needed.

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The risk management plan (RMP) shall consist of seven parts, which may be subdivided and will include the following modules: Part I: Product(s) Overview Part II: Safety Specification Module I: Epidemiology of the indications and target population Module I: Non-clinical part of the Safety Specification Module III: Clinical trial exposure Module IV: Populations not studied in clinical trials Module V: Post Authorisation Experience Module VI: Identified and potential risks Module VII: Additional EU Requirements for the Safety Specification Module VIII: Summary of the safety concerns Part III: Pharmacovigilance Plan Part IV: Plans for studies on effectiveness and long term efficacy	The risk management plan (RMP) shall consist of seven parts, which may be subdivided and will include the following modules: Part I: Product(s) Overview Part II: Safety Specification Module **S**I: Epidemiology of the indications and target population Module **SI**I: Non-clinical part of the Safety Specification Module **S**III: Clinical trial exposure Module **S**IV: Populations not studied in clinical trials Module **S**V: Post Authorisation Experience Module **S**VI: Identified and potential risks Module **S**VII: Additional EU Requirements for the Safety Specification Module **S**VIII: Summary of the safety concerns Part III: Pharmacovigilance Plan Part IV: Plans for studies on effectiveness and long term efficacy	There was a mistake in the module numbering. Should perhaps consider giving the modules an S prefix in case we subsequently split any other parts into modules – eg Module S1

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Part V: Risk Minimisation Plan(s) Part VI: Summary of the RMP Part VII: Annexes Where a RMP covers several medicinal products, a separate Part VI shall be provided for each medicinal product	Part V: Risk Minimisation Plan(s) Part VI: Summary of the RMP Part VII: Annexes Where an RMP covers several medicinal products, a separate Part VI shall be provided for each medicinal product	
1.3 Updates of the Risk management plan	Marketing authorisation holders for medicinal products authorised under Directive 2001/83/EC prior to 21 July 2012, or under Regulation 726/2004 prior to 2 July 2012, which have an existing risk management plan shall submit the next update to the Agency or national competent authority, as appropriate, in the format of an RMP. This update shall be submitted within 12 months of the applicability of the legislation so that the provisions of Article 106(c) of Directive 2001/83/EC and Article 26(c) of Regulation (EC) No 726/2004 can be complied with.	Need to have legal basis for getting RMPs into new format. This is necessary to aid publication of a more extensive summary of the RMP than we are currently providing in the EPAR. There are some additions to the RMP which were designed specifically to improve the summaries which we publish. Revising the rest of the RMP is straightforward as the content is similar to what we already have in existing RMPs but its location in the specific part of the RMP may have changed. This is in partly due to an attempt to have common modules with the PSUR to decrease the burden on industry.
Annex III – Electronic period safety update report		
• Signature Page by the qualified person responsible for pharmacovigilance • Title Page • Table of contents	• Signature Page by the qualified person responsible for pharmacovigilance • Title Page • **Executive Summary**	The Executive summary should be before the table of contents (instead of after) and immediately after the title page to be in line with the current draft of ICH-E2C R2 and to improve the readability of the document.

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• Executive Summary	• Table of contents • ~~Executive Summary~~	
Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies		
1. Scope and definition	To include a provision for MAHs to ensure that non-interventional post-authorisation safety studies concerned by the Implementing Measure are registered in an European registry of non-interventional post-authorisation safety studies maintained by the Agency i.e ENCePP register of pharmacoepidemiology and pharmacovigilance studies. More detailed guidance for this registration could be provided in the Good Pharmacovigilance Practice guidance.	Paragraphs 5, 6 and 8 state that information on the study, including the study protocol, any revised study protocol and the final study report including a public abstract are submitted to the EMA. Details on how this submission should be performed are not provided. Submission could therefore use different channels of communication and retrieval, archiving and review of these documents would be complex and time consuming for the Agency. In addition, Art 26 (h) of Regulation (EC) No726/2004 states that by means of a web-portal, the Agency shall make *public protocols and public abstracts of results of the post-authorisation safety studies referred to in Articles 107n and 107p of Directive 2001/83/EC.* Art 102 (c) of Directive 2001/83/EC as amended by Directive 2010/84/EU states that *Member States shall ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product.* This important information may include PASS protocols and abstracts of study reports.

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		The obligations for MAHs to submit study documents and for the Agency to make them public and track studies would be facilitated if these documents were included in a public register that would facilitate their consultation by regulators and the public. Such register already exists as the ENCePP register of pharmacoepidemiology and pharmacovigilance studies, established and maintained by the Agency (www.encepp.eu). It could be upgraded with only limited cost and become a European register of non-interventional post-authorisation safety studies. As a major advantage, it would be populated and updated (under supervision) by the MAHs themselves rather than by competent authorities. Discussions between the Agency and Member States indicate that Member States would welcome such registry. PASS registries currently exist in three Member States but serve another purpose with different information. A European registry would not, therefore, represent double work.
1. Scope and definition	To add a provision to extend the scope of the Implementing Measure to all non-interventional post-authorisation safety studies that are voluntarily initiated, managed and financed by a marketing authorisation holder and included in the RMP. Studies conducted outside the EU/EEA	Art. 1 of Chapter 1 (Scope and Definitions) of Annex IV states that this annex applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by a marketing authorisation holder pursuant to obligations imposed by a national competent

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	and requested by a national competent from outside the EU/EEA may derogate from this provision.	authority or EMA (…). It is expected that such studies will represent a minority of all non-interventional PASS conducted by MAHs. Experience shows that most PASS are agreed between a competent authority and a MAH during the course of the evaluation of an application dossier or a safety issue, without being considered as a condition for the marketing authorisation (e.g. included in Annex II of the marketing authorisation for centrally authorised products). Protocols of many non-interventional PASS are also voluntarily submitted by MAHs as an additional pharmacovigilance activity aimed at evaluating a safety issue. Such PASS are included in the RMP only. Imposing a format for study protocols, abstracts and final study reports only to those studies that are categorised as an obligation of the marketing authorisation therefore introduces an artificial distinction between PASS imposed or voluntarily conducted, without this distinction being relevant to their public health importance and also considering that both are in the RMP. Public health considerations require that studies with potential benefit-risk impact for patients should not be subject to very different quality requirements for the protocol and study reports whether a condition of the marketing authorisation or in the RMP only. It has to be taken into consideration that RMP is part of the

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		marketing authorisation and agreed by the Competent Authorities and therefore its content is enforceable. Standards protocols, abstracts and study reports are elements supporting the quality of PASS that should apply to all studies in the RMP and not to a subset of these also being a condition of the marketing authorisation. In addition, studies included in the RMP may be at a later stage imposed as a condition of the marketing authorisation where information obtained during the product life cycle justifies. In such case, the study protocol should be rewritten to comply with the legal requirements. It is however acknowledged that some studies initiated, managed or financed voluntarily by MAHs are conducted outside the EU/EEA and have to follow rules established by non-EU countries.
1. Scope and definition	To add the following provisions supporting quality assurance of the study: • the MAH shall ensure that all study information shall be handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the study subjects remains protected; when the study makes secondary use of data from electronic records, verification of records shall refer to the analytical dataset;	Strict provisions exist in the legislation for quality assurance for interventional clinical trials, but none exist for non-interventional PASS. Insofar as non-interventional PASS could be imposed by competent authorities as an obligation including those part of the RMP, it seems appropriate to introduce in the implementing measure clauses supporting quality standards in the conduct of non-interventional PASS, as well as the possibility for audit and inspections.

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	• the MAH shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection; any change to the data shall be documented; • each individual involved in conducting a study shall be qualified by education, training, and experience to perform his tasks; the study shall be scientifically sound and guided by ethical principles; studies referred may be subject to inspection by the competent authority.	
2. Format of the study protocol 11. Management and reporting of adverse events/adverse reactions:	*2. Format of the study protocol* 11. Management and reporting of adverse events/adverse reactions: procedures for collecting, management and reporting of individual cases of adverse events or adverse reactions **and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is conducted**. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level,	It is proposed that this section should also include a description of the procedure for collecting and communicating any data on the benefit-risk balance of the product generated while the study is being conducted (Directive 2001/83/EC, Art. 107(m)(7)).

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	this should be stated.	
2. Format of the study protocol 12. Plans for disseminating and communicating study results	*2. Format of the study protocol* 12. Plans for disseminating and communicating study results, **including plans for submission of progress reports, final reports and publications**.	It is proposed to specify here that this section should address progress reports, final reports and publications.
2. Format of the study protocol 15. Annexes	*2. Format of the study protocol* 15. Annexes: **The ENCePP Checklist for Study Protocols signed by the principal investigator shall be included as an Annex. Annexes may also include a**ny additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms).	The ENCePP Checklist for Study Protocols has been developed by a group of leading European pharmacoepidemiologists to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and of writing a protocol, and to promote the quality of such studies. Its submission would facilitate and speed-up the review of study protocols by competent authorities. Some member states are already using it for the evaluation of protocols submitted by MAHs.
Annex I to Annex IV		
	The Agency may provide a detailed description of the requirements for the format and content set out in Annex I to Annex IV as part of the guidance on Good Pharmacovigilance Practice and shall make this publically available on its website together with appropriate templates.	Implementing measures are high level and more detailed guidance on content and format is in Good Pharmacovigilance Practice (GVP). At the moment there is no link between the format and content in the legislation and the more specific details in GVP and this is needed.