PPTA
Plasma Protein Therapeutics Association

7 November 2011 **BY E-MAIL**
Reference: DGSanco11009

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IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Deadline for Public Consultation: 7 November 2011

Reference: PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance

Dear Madam, Sir,

PPTA is the international trade association and voluntary standard setting organisation for the world's major producers of plasma-derived therapies and their recombinant analogues. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a multitude of diseases in persons with immune deficiencies, therapies for individuals suffering from alpha-1 anti-trypsin deficiency and albumin which is used in emergency room settings to treat patients with shock, trauma, burns, and other conditions.

Please find below PPTA's comments on the Consultation on the Performance of the Pharmacovigilance Activities provided for in Directive 2001/83/EC and Regulation (EC) No 726/2004. Thank you very much for the opportunity to provide our views in this important consultation process. Please note that we have no objections to make our comments publicly available on the 'public health' web-site.

We remain at your disposal for further discussions at any time of your convenience.

Sincerely yours,

Ilka von Hoegen

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Senior Director, Quality and Safety

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General comments: PPTA would urge the European Commission to reconsider the scope of the XEVMPD data base which has to be populated by the MAH/sponsor for all marketed products and products under development by 2 July 2012.

PPTA appreciates the implementation of an EU wide up-to-date data base for all medicinal products with key information including but not limited to:

1. MAH/distributor, trade name, SmPC and product information by country
2. Active ingredients/dosage
3. Strength
4. Pharmaceutical form
5. QPPV details
6. Launch dates by country
7. INN where applicable
8. Indications

However, we believe that it is not warranted to include a multitude of additional details, e.g. for N- and C-terminal modification of proteins, information on protein glycosylation, disulfide bonding etc.

We noted that it is not requested to include the SmPC for centrally authorized products, which are already included in the EPARs. However, in view of the intended global approach it would be preferred to include the same information for all products independent of the mode of licensure. It should be considered to amend the EPARs accordingly.

The PhV guidance on the required data fields was published 2 months later than initially anticipated. The guidance contains 640 pages which is a significant amount of information. There is no commercial soft ware available to process the required information and there are significant doubts even from Health authorities' own experts that the remaining time until compliance will allow to develop and validate appropriate IT systems, not to speak of populating the data base with the magnitude of data required.

We would respectfully like to propose to revisit the data requirements in light of what is really relevant in terms of information to the

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public and restrict the parameters to those that are in line with the intention of the PhV legislation.		
Consultation item No	**Comments:**	**Proposed wording where applicable**
no. 1:	**Should additional processes and pharmacovigilance tasks be covered?**	
		In section 2 '**Definition**' the following statement should be added: "*Different MAHs (e.g. MAHs who are part of the same mother company) may use a common Pharmacovigilance system*".
	Section 3 '**Content**: (Point 1) - it could be useful to better explain the meaning of "product list"; in particular, we suggest to make reference to the XEVMPD data base and only include information which is not provided there. We propose not list all national translations of the full product names and relative registration numbers, but to list only what is necessary for the identification of the product itself (e.g.: a list of short product names used in the EU, INN names where available and the countries where they are authorised) (Point 6) – among the processes to be described, the interaction between PV and QA Dept (namely, "interaction between safety issues and product defects") should be added	As a consequence, in section 3 '**Contents**' (point 1) "MAH(s)" should be added as requested information We propose to add the following to the list provided at point (6): "*process for managing information on safety issues deriving from product defects*"
	We question the rationale of inclusion of a list of medicinal products, specifically authorization numbers. These data are part of the marketing authorization. From	

	an oversight perspective we recognize that some details should be presented in the master file, but we question the added value of giving the authorization numbers.	
no. 2	**The aim of the pharmacovigilance master file is two-fold: to concentrate information in one global document and to facilitate maintenance by uncoupling it from the marketing authorisation. Therefore changes to the content of the master file will be no longer subject to variation obligations. 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 it was last reviewed?**	
	In our opinion it would **not** be necessary to require that the MAH notifies the Competent Authorities/EMA of changes/modifications made to the master file since, as stated in the Concept paper: 1 – upon request by any Competent Authority/EMA, the MAH shall provide them with a copy of the Pharmacovigilance system Master File “at the latest seven days after the request” (Article 23 of Directive 2001/83/EC and Section 8 (Inspection)); 2 – the PV master file “shall be continuously kept up to date” To standardise level of interpretation, a specification of what is understood of continuity would be appreciated, e.g.: the term "continuously" being replaced by "updated at least annually and immediately regarding terms listed under classification guidance part C" 3 – “the master file shall contain a logbook recording any alteration of its content within the last five years. This logbook should record the date, the responsible person and where appropriate the reason for the alteration”. In any case, it could be very useful to add the version number and date of the last revision to the currently	We propose, with regards to the section on ‘maintenance’ to add the sentence “The currently approved PV Master file should contain the version number and date of last revision”

	approved PV master file.	
no. 3	**Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.**	
	We consider the proposal to include a copy of any signed agreement in the PV Master File as not practical (please note that the PV Master file *"should be succinct"*). Instead, the PV Master File should, if at all include not more than the list of existing contractual agreements and reference to their location; Individual contractual agreements should be made available upon request.	We propose to replace the sentence '~~*copies of the signed agreements shall be included in the master file*~~' with '*The list of existing contractual agreements and reference to their location should be included in the PV Master File. Individual contractual agreements should be available upon request by any Competent Authority/EMA" or during inspection/audit'*.
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?**	
	We do not agree that all completed audits of the PV activities of the MAH shall be recorded in an annex to the PV MF: We therefore suggest to include in the PV master file only MAH initiated audits of the (global) pharmacovigilance system (full system audits) and not to the whole set of audits of specific parts and pieces, e.g. distributors, contractors etc., It should be acceptable that these audits are covered during "inspection" (please refer to as stated in Directive 2010/84 Article 104.2). The meaning of 'main findings' should be better explained (e.g.: only 'critical' or 'critical and major'?).	
no. 5	**Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.**	
	In principle, we agree with the stated requirements.	

	As a suggestion, we would like to further stress the fact that the PV master file should be as succinct as possible and it should make reference to other documents / procedures for the detailed description of all activities it covers/mentions.	
no. 6	**Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to processes for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database?**	
	The list of quality procedures mentioned in the Consultation paper is nearly complete, except for a quality procedure for the detection of duplicate ICSRs in the EudraVigilance data base. We would like to propose that EMA develops a quality procedure appropriate for the EudraVigilance database system. Pertaining to section 14(d),web.portal we would propose a weekly screening by the MAH. In addition, the MAH should be supported by e.g. email notification if new info relevant to MA has been posted. We understand that the portal shall not replace the possibility of direct communication between authorities and MAH.	
no. 7	**Do you agree with the requirements for marketing authorisation holders? Please comment.**	
	With regards to section (13) ‘resource management’, the parameters used to determine whether the personnel of the PV system are of a sufficient number should be clarified together with MAH/PV stakeholders considering volume and scope of activities. QPPV and other supervisory PV function's hierarchical relationship shall	

	not get into conflict of interest.	
no. 8	**Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA**	
	We agree with the stated requirements, except that (section 10) a standard interval of not less than 2 years for the conduct of system audits may be inappropriately small, and shall be replaced by a risk based approach e.g. depending on observations and relevant developments.	
no. 9	**For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medicinal product. However, do you see a risk in cumulating all tasks (for the authorisation, PSUR scrutiny and Eudravigilance monitoring) in one Member State, as thereby the benefits of parallel monitoring may be lost ("peer review" system)? Additionally, it may be envisaged to extend 'work sharing' to all medicinal products (including all centrally approved products) and to appoint a lead Member State in addition to EMA (Article 28a(1)(c) of Regulation (EC) No 726/2004). Please comment.**	
	We strongly agree with the proposal to extend the work sharing procedure to all medicinal products. We also agree with the proposal to appoint a lead Member State in addition to EMA.	
no. 10	**In the Commission's view the aim of this part is to establish common triggers for signal detection; to clarify the respective monitoring roles of marketing authorisation holders, national competent authorities and EMA; and to identify how signals are picked up? Are the proposed provision sufficiently clear and transparent or should they be more detailed? If so, which aspects require additional considerations and what should be required? Please comment.**	
	We would like the role in monitoring for MAHs to be better clarified depending on the company's size. There may be limitations caused by the pattern of products as well.	

	An adequate combination of signal detection methods should be the aim. e.g. ADR/ICSR evaluation may be sufficient for many products on the market that cause only very small number of ADRs. Either more general principles should be applied or a risk based approach should be pursued. We would also like to point out limitations for small companies or companies without significant mix in products (low variability pattern). These companies usually do not have a database adequate for data mining. Experience with the Eudravigilance data base will show whether these limitations will be overcome or will persist.	
no. 11	**Do you agree with the proposed terminology? Please comment.**	
	We agree with the proposed terminology.	
no. 12	**Do you agree with the list of internationally agreed formats and standards? Please comment.**	
	We agree with the proposed list of internationally agreed formats and standards.	
no. 13	**Is there additionally a need for transitional provisions as regards certain aspects of this implementing measure, especially in relation to the specifications on format and content? Please comment.**	
	There is no need for transitional provisions, provided that each Member State will adopt the same measures at the same time.	
no. 14	**Do you agree with the proposed format and content? Please comment.**	
	With regards to literature cases (Paragraph 4(b)) clarification about the timelines of submission of the full translation of the article should be provided. An	

	appropriate timeline could be 15 calendar days after request? With regards to information about the batch number (Biological Medicinal Products; Paragraph 4(h)), clarifications how many attempts should be made in order to obtain this information. We suggest to use the Final Report of CIOMS Working Group V - 2001 as a reference.	
no. 15	**Do you agree with the proposed format and content? Please comment.**	
	We recommend adjusting the RMP format to ICH provisions to provide a globally accepted format. In section 1.2. Part IV the expectations pertaining to studies on effectiveness and long term efficacy should be specified. In paragraph 1 of section 1.3 (Updates of the Risk Management Plan) the content of the updated RMP should be better explained.	
no. 16	**Do you agree with the proposed format and content? Please comment.**	
	In general we suggest that clarifications for the requirements reported in section 1.2 should be provided in the Good Vigilance Practice guideline, e.g.: Sections 1.2 –5.2 “Cumulative and interval patient exposure from Post-Marketing experience” and 6.2 6.3 “Cumulative and Interval Summary Tabulation from Spontaneous Data Sources”. Some medicinal products have been on the market for decades (e.g. Human Albumin). It should be possible to provide data from a well definite (and duly justified) date onward.	

	Section 1.2 –6.2 “Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials”: it should be clarified whether all events are required or only those with a suspect of correlation. Section 1.2 - 12. “*Other Periodic Reports*”. It should be stated what type” of other periodic reports has to be provided (e.g.:DSURs, others). A rationale would be helpful to avoid redundancy between DSUR and PSUR, for example that a DSUR should only be provided when a PSUR is not yet available, ie. pre-authorisation state. We would also like to point out that the PSUR format is no longer consistent with the respective ICH format.	
no. 17	**Do you agree with the proposed format? Please comment.**	
	Clarifications about the content of both the study "protocol" and the Study "report(s)" should be provided in the Good Vigilance Practice guideline. With growing experience with the requirements of the guideline MAHs and regulatory authorities should cooperatively develop a common understanding in which settings a PASS would be required.	