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Comments to

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

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

Chapter	Consultation Item No.	Question/Topic	Comment
A. Pharmacovigilance system master file			
1. Definition		General comment to PSMF	We wish to draw attention to the definition of the pharmacovigilance system master file, (1) top of page 5, where it is stated that the pharmacovigilance system master file is a system description. In this concept paper several examples are seen where results of working with the system or detailed listings are required as part of the PSMF, this is considered to be out of scope.
2. Location		Location of Master file	The “location” of where the master file should be kept needs to be clarified. It should be specified that the QPPV should have access to the file on a server that can be positioned anywhere.
3. Content		General	As described in the introduction, the Pharmacovigilance System Master File (PSMF) contains a detailed **description** of the pharmacovigilance **system.** This means that according to the definition, detailed listings on MA’s, contracts etc. are exempt from the definition. As is now done in general they should be available for review during inspections etc. However these lists are changing daily and therefore can never be part of a “document” which has continuously to be kept up to date and should be “permanently and

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			immediate available for inspections at the storage site". In a generic medicines company with about 30.000 licenses "a list of medicinal products" is outdated the moment it is printed. Therefore to have this continuously annexed to a document makes no sense, since it would require the log to be updated with every change in license/contract etc. All licenses in the EU of a MA holder are available in the EudraVigilance database as of July 2012, following art 57(2), so there is no need for separate provision. The list of MAs should therefore NOT be part of the PSMF. See also under "general".
		(1) list of medicinal products	A list of medicinal products is requested to be provided with the master file. This is already available in the Member States, as it will also be provided with all information on the products via the database following art 57(2)
		(3) the local QP	The reference to the Directive should be corrected in article 104(4) of the Directive 2010/84/EU. The PSMF should only state in which countries contact persons for pharmacovigilance were nominated at the local level; it is not necessary to mention individual persons as these persons are registered at the national level.
		(4): Description of organisational structure	The proposed description of the organisation structure is too detailed with regard to a list of sites covering an individual case safety report collection; we propose a broader description giving the main division of activities between sites and listing main sites involved.

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		(6) description of the process, data handling and record	Please clarify "a description of the process, data handling and record…" As mentioned below the PSMF should be succinct. Proposed change: Replace "*a description of the process, data handling and record…"* by "*a list of the procedures related to PhV activities"*, similar to what is done in the DDPS.
		(7-c): records of qualifications	To avoid misunderstanding with this item. Training records should not be appended to the PSMF, nor should the location of the training record for every individual working in PhV be noted. Sentence should be changed to: "*It should be indicated whether full training files and qualifications are kept locally or centrally*".
		(7-d): Documentation arrangements	Clarify "documentation arrangements". Is this related to archiving procedures? If so, sentence should be changed to: *"Archiving policy of paper documents should be described".*
		(7-e): location of audit trails	It is unclear what is meant with this item. This is a too detailed reference to the location of audit trails of the monitoring of performance and compliance. This sentence should be deleted since it is part of the QMS and will be further detailed in the GVP.
	1	**Should additional processes and pharmacovigilance tasks be covered?**	No. The PSMF document describes the PhV system of the MA holder. The mentioned items without the listings of MA's, agreements etc. as described above do describe the <u>system</u> sufficiently.
4. Maintenance		General	As described here "*The description should be accurate and reflect the system in place".* This again explains there is no need for <u>detailed</u> listings and overviews of documents since they will change daily so the QPPV can never confirm it is accurate at that moment in

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			time.
	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 no longer be 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?**	There is no need to notify changes to the PSMF to the competent authorities. Changes of the QPPV are notified to the EudraVigilance database separately. The PSMF will contain a date in the logbook as referred to in chapter 5 of the Concept Paper ("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 alteration"). We would like again to point out that to achieve the second point of the intentions as mentioned in the "*aim of the PSMF*", the guideline/regulation for variations has to be updated. As long as that is not done the second aim will not be achieved.
5. Documentation		General	It states here that "…*a clearly arranged printed copy can be made available for audits and inspections*." Printed copies are only possible if the requirements for all the appendices as mentioned above in the content of the PSMF have been deleted. The requirement that current deviations from the pharmacovigilance procedures, their impact and management should be noted until resolved, is too extensive and should be phrased as in the Directive: PSMF should include audit notes of main findings until resolved The logbook, as part of the PSMF, should be kept and updated indicating main changes to the system. Contents of deletions with

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			regard to resolved audit findings will be made without referring to the content of the actual finding.
6. Delegation		General	The sentence should change to *"Delegation or outsourcing of general pharmacovigilance system tasks should be described in the PSMF".* Product specific delegations of PhV activities are out of the scope of the definition of the PSMF which describes the PhV system. In a generic medicines company there are numerous of product-specific pharmacovigilance agreements where, for example decisions are made on exchange of safety information, responsibilities of PSUR writing or reporting to RMS. This list changes daily and therefore it makes no sense to list them per product / country and to attach the documents. Agreements are available for review in audits and inspections and on specific request. *"Copies of the signed agreement shall be included in the master file":* Agreements contain confidential information which should not be disclosed. PV inspections and audits should serve as the main opportunity to review the existing agreements, if necessary.
	3	**Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.**	No, as described above it is not necessary to describe the delegation of PV activities in the case of product specific co-marketing. Details on data exchange and shared activities which depend on the contractual situation could be reviewed sufficiently during inspections and audits. Proposed change : Please erase "*In those cases the pharmacovigilance system master file shall contain a description of the delegated activities (…). Copies*

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			of the signed agreements shall be included in the master file."
	4	**Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?**	No, a copy of the audit report should not be retained in the master file since it is a company confidential document retained internally. The inclusion of an audit note in the PSMF with the main audit findings (as given in the Directive, article 104) is sufficient. The requirement to provide copies of audit reports could affect the performance of internal auditing because findings would be issued taking into account that all details would be disclosed to the CA directly. *"Once the corrective and preventive actions have been fully implemented the note may be removed from the PSMF. That note…… has been verified*". The following sentence should be added "<u>The actual finding can be deleted from the logbook too indicating only that the section was revised."</u> Proposed change: It does not make sense to provide a full list of audits made in the company. A limit of time should be placed: "All completed audits of the pharmacovigilance activities of the marketing authorisation holder shall be recorded in an annex to the pharmacovigilance master file, including their date and scope, <u>within the last two/three years."</u>
	5	**Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.**	The content of the master file requires a list of medicinal products of each Marketing Authorisation Holder. This information will be available at the EMA via the EVMPD/IDMP (art 57(2) requirement. The master file should rather include the names of all Marketing Authorisation Holders which are covered by the Pharmacovigilance

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			System including a statement that all medicinal products of the MAH as included in the IDMP are covered. The requirement to provide up to date listings of all products within the PV master file is therefore regarded as duplicate work. Only in case a MAH maintains more than one PV system, the medicinal product(s) concerned should be described in the respective master file, e.g. by separate listings.
B. Quality systems for the performance of pharmacovigilance activities – common obligations			
10. Audit		General	Audit of quality systems (Organisational structure, responsibilities, procedures, processes, resources – resource management, compliance management and record management) suggested to be performed not less than every two years, should rather state that frequency should be according to a risk-based approach.
11. Performance indicators		General	Indicators can be described since they are part of the system description. However, results of the compliance measurements are outcomes of weekly/monthly measurements and should not be added to the PSMF; this information is part of the QPPV day-to-day activities and will, of course, be made available for inspection. To include it here would, again, be using the PSMF as a tool for measuring/documenting effectiveness of the system rather than describing the structure of the system itself.
C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holder			
13. Resource Management		General	The requirement in the last paragraph, that resource management should be documented in the PSMF is not necessary; the text in the PSMF should describe the system but should not document system implementation. Proposed change: Remove sentence "*The resource management shall be documented in the pharmacovigilance system master file*."

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14. Compliance management		(14-d): up to date information l	The EMA holds and maintains a list of QPPVs active in the EEA through EudraVigilance. It is an obligation of the European authorities to inform the general public and the MA holders actively when urgent and important safety information has become available. The QPPV should be actively contacted For minor notifications/changes the web portal should be constructed in such a way that feeds can be generated and it is easily visible what sections are updated where and when. Change :"*To this end, the marketing authorisation holder shall check…….on each working day*" into "*The EMA will inform the marketing authorisation holders directly by phone or email when an urgent safety restriction is needed for one of the products of the MAH. The European medicines web-portal will be constructed in such a way that the MA holders can prescribe to a "RSS feed" leading to relevant updated sections of the portal."*
	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?** General	No, there is no need for additional quality procedures in the system of the Marketing Authorisation Holder. However it should be communicated more clearly to the Health Care Professionals that they have an obligation to cooperate with the MAH as well as the MS in order to collect and clarify safety-related issues without any request for financial compensation. There is a need for additional quality procedures regarding the quality of the information received from reporters through the Member States and directly to EudraVigilance without follow-up or proper description or clarification of the cases. Since the new legislation's aim is to receive more cases through the Member States the quality of those cases should be improved. The first sentence after the consultation should have Marketing

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			Authorisation Holder in the singular instead of plural
15. Record Management	7	**Do you agree with the requirements for marketing authorisation holders? Please comment.**	Firstly the definition of "pharmacovigilance-system-related documents" should be defined. It should be described clearly that document retention can be done in electronic format and there is no need for paper archiving or retention of originals. Furthermore it should be understood that with the current speed of IT development the documentation may no longer be readable after 10 to 15 years. The validity of 30 years is therefore questionable.
D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA			
overall	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.**	See the comments provided below: • Chapter 18. Compliance Management (c): please confirm that *"effective communication with…marketing authorisation holders"* encompasses timely and *direct* communication to these parties • Chapter 18. Compliance Management (last paragraph): we look forward to publication for comment of draft detailed guide regarding monitoring of medical literature.
E. Signal detection and risk identification			
20. General		General	Occupational exposure without adverse events is not in the scope of pharmacovigilance as described in the Directive or the regulation. No additional requirements should be introduced through this chapter.
23. Signal management procedure		General	The pharmacovigilance legislation was introduced with the main concept to simplify procedures, minimise bureaucracy and maximise the safety of patients. In this chapter, MA holders, CA as well as EMA are directed to do signal detection on the same data through the same methods in the same database. This outcome of the new legislation is in absolute contradiction to the initial intention and this duplication of efforts should be deleted. Proposed clarification: MA holders should statistically review the

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			data as received by the MA holders directly, CA should statistically review data on actives from their countries and the EMA should statistically review the complete picture of actives and MA holders. In this way the signal detection is not duplicated, but has a different scope per stakeholder.
24. Work sharing of signal management	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.**	The work sharing concept avoids multiplication of signal management tasks for the same products by MAH, NCAs and EMA. It also facilitates the availability of "product experts" in the NCAs, which can be an advantage in the assessment of efficacy and safety. Please ensure that well-established medicinal products are included in the Work Sharing project. As long as decisions as made by the reference RMS can be referred to the PRAC and the outcome of the PRAC is binding to all MSs, we have no comments.
	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**	It is stated that "any validated signal that requires further analysis.....shall be transmitted to the PRAC. It is not clear what kind of validated signals qualify and which validated signals do not qualify for transmission to PRAC. Furthermore it should be stated that signal detection and follow up should be risk based making sure that a signal of "nausea and vomiting" does not get as much attention and priority as a "sudden death".

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		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.	The responsibilities of the different stakeholders should be more clearly described. It should be stated that the MA holder checks the safety data in the MAH database, the Member States check the data originating from the relevant country and the EMA does the signal detection in the EudraVigilance database and publishes this (including supportive details) to avoid duplication of effort? .
F. Use of terminology			
27. Use of internationally agreed terminology	11	general **Do you agree with the proposed terminology? Please comment.**	Under (a) the abbreviation ICH is mentioned in the wrong place. EGA agrees to a common terminology. However, we would note that for reporting of a suspect product for many adverse drug reactions, only the active substance name (and not product name) is available. In this regard, the many fields proposed for the MPRD would be irrelevant. Will it be possible to submit reactions giving only the active substance as the suspect product? It is stated that *"In the event that a required term is not available, Member States or MAH shall make a request for the addition of a new term to the organisation [...] and inform EMA accordingly.*" The additional information to the EMA is considered as redundant and should be deleted.
28. Use of internationally agreed formats and standards	12	**Do you agree with the list of internationally agreed formats and standards? Please comment.**	EGA agrees with a list of internationally agreed formats and standards, however, there are far too many unnecessary details included, e.g. ISO EN 11238. See comment Item11.

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		EVPRM	*"Although the EGA may support the EVPRM format as a transitional to provide the information to the EMA in accordance with the Art 57, however the EGA members do not agree on the content of data to be provided to the EMA by July 2012 as defined in the EMA Legal Notice 505633/2011.* *The EGA is of the opinion that MAHs can only be legally obliged to populate by July 2012 the EMA database with summaries of product characteristics, the patient or user package leaflet and the information shown on the labeling as mentioned in Art 57 in the format published by the EMA. Any extent of data may be only requested at the moment of implementation of the international standards (what is foreseen not earlier than by 1 January 2015).* *The new legal obligation introduced by Regulation (EC) No 1235/2010 imposes on the EMA to publish a format for the electronic submission of information by July 2011, without extending the scope of data to be provided.* *Legal reference:* ***Regulation (EC) No 1235/2010 requires via Art. 57** that the Agency undertakes the following task:* *1.* *.....*

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			(l) creating a database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database shall facilitate the search for information already authorized for package leaflets; it shall include a section on medicinal products authorized for the treatment of children; the information provided to the public shall be worded in an appropriate and comprehensible manner. *2. The database provided for in paragraph 1(l) shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labeling. The database shall be developed in stages, priority being given to medicinal products authorized under this Regulation and those authorized under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to include any medicinal product placed on the market within the Community.* *For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorized in the Union. To this effect the following measures shall be taken:* *(a) the Agency shall, by 2 July 2011 at the latest, make public a format for the electronic submission of information on medicinal products for human use;* *(b) marketing authorization holders shall, by 2 July 2012 at the latest, electronically submit to the Agency information on all*

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			medicinal products for human use authorized or registered in the Union, using the format referred to in point (a); *(c) from the date set out in point (b), marketing authorization holders shall inform the Agency of any new or varied marketing authorizations granted in the Union, using the format referred to in point (a).".*
G. Transmission and submission requirements			
	13	**Is there additionally a need for transitional provisions as regards certain aspects of this implementation measure, especially in relation to the specifications on format and content? Please comment.**	To get real benefit from the introduction of the PSMF all related regulations/directives/guidelines should be amended to reflect that variations are no longer needed when there are changes to the QPPV, safety database, etc. As long as this is not arranged there should be a transitional provision described and put in place. Transition of processes may vary from one MS to another MS; overarching transitional guidance should be provided by EMA.
Annex I – electronic submission of suspected adverse reactions			
	14	**Do you agree with the proposed format and content? Please comment**	<u>Definitions</u> The definitions of off-label use, misuse, abuse and medication errors currently overlap which gives rise to a lot of "double coding" and lack of clarity. The EGA supports the definitions as stated in the position papers as Proposed by EFPIA. Regardless of the above we are of the opinion that these definitions should be part of the GVP and not of these implementing measures, in order to make needed changes when the definitions should be clarified further. Item 1(b) It should be clarified that only medication errors that have lead to an adverse reaction are collected in the view of

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			pharmacovigilance.
		Content – Item 2:	The reference to the Directive should be corrected to article 107a(1), (2) and 107(4) of the Directive 2010/84/EU.
		Content – Item 3:	Pseudonymisation of ICSRs should be standardised within the EU, this is not up to requirements of member states.
		Content - Item 4b: comprehensive summary in English for literature	In individual case processing there is no requirement to translate the full source documentation into English. The MA holder or MS should make sure that the source (i.e. literature case) is correctly coded and all relevant fields in the E2B are filled. A relevant summary is placed in the narrative. Therefore a comprehensive summary of the full article in English should not be required and cannot be justified. The EMA requirement for the MAH to translate a complete article into English should only be valid for articles which are initially submitted by the MA holders and not articles which result from research done by the EMA. As for the requirement for the MAH to submit a copy of the relevant literature and provide translation if needed: for the many companies having same substances, all being responsible for a world-wide literature search, will this mean x numbers of the same article being paid for and submitted to the authorities, or which of these x number of companies will be requested to provide the full article?

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		Content - Item 4k Content - Item 4m Content – Item 4o	Only results of tests and procedures relevant to the adverse reaction should be recorded, not all tests and procedures relevant to the patient. "It should be confirmed that no additional information is available" If this is to be included in the narrative for all cases as they become closed, it will involve unnecessary use of resources to re-roll all cases through the safety database at MAH and EMA site. There should be no reporting to EudraVigilance in other languages than English, whether or not the event originated within or outside the EU.
Annex II – Risk Management Plan			
	15	**Do you agree with the proposed format and content? Please comment**	<u>General</u> A provision should be added to waive the request for a full RMP when the product as such is known to have a favourable safety profile and when there are no additional Risk Minimisation Measures required. The list of exempted products should be synchronised with the list of products exempted for the regular PSUR writing which has been defined by PRAC as a list of "safe products". RMPs should not be misused for market protection and only contain marketing triggered obligations. <u>Format - general</u> The EGA strongly advises not to specify the modules in the implementation measures. We have seen with the past guidelines on RMPs that there is a need for change with the changing circumstances and developing knowledge on the subject. If the format is detailed in the Implementing measures there is no

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			possibility to change in the near future. The content should be given on a higher level and the actual naming of parts and modules should be detailed in the GVP. <u>Format – Part IV</u> For an RMP without any risk minimisation measures it makes no sense to have a separate part IV for every medicinal product. There should only be a requirement as such "if relevant" because of different safety profiles following, for example, formulation or route of administration. For established products which are not exempted from an RMP there should be an abbreviated template, focussed on current identified risks.
Annex III – Electronic periodic safety update reports			
	16	**Do you agree with the proposed format and content? Please comment**	<u>General</u> PSURs shall follow the agreed template of the ICH E2C, which is also accepted in non-EU countries. The format should not be detailed in the implementing measures, since then there is no possibility for the EU to adopt ICH changes. Details should be given in the GVP. The intention of the new legislation was simplification and less bureaucracy, therefore it should be made clear that the PSUR should be submitted only ONCE to a central repository at the EMA in eCTD format <u>without sequences</u> specifically for CAPs or MRPs/DCPs. Point 1 under 1.2 "format of periodic safety update reports" should be changed to indicate that. There is no legal requirement to keep the procedure specific PSUR submissions as mentioned currently. 1. *Without prejudice to the requirements to submit a PSUR as part*

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			of …….modular structure:" should be changed to "*PSURs shall be submitted by electronic means in a format following ICH E2C which does contain the following information*:" Regarding the exact format and content which will have to be described in the GVP the following comments can already be of assistance. <u>1.2 Format</u> <u>Signature page by the QPPV</u> The PSMF does describe the role of the QPPV in PSUR writing, therefore a signature of the QPPV is not needed per PSUR. The PSUR should be signed and dated, but not by the QPPV. 7: summaries of significant findings…. It should be stated that this concerns company-sponsored clinical trials. 9: Other clinical trial/study information What information is referred to other than that already included in 7, 8 or 13 10: non clinical data Should the preclinical expert report be cross-referenced? Duplication of work should be avoided in the new legislation. 12: What *"other periodic reports"* (1.2-12) are considered here: DSURs, Periodic reports to FDA? 15: Overview of signals ongoing and closed

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			Why is this not included in 16? 16: Signal and risk evaluation It is suggested to move 16.2, 16.3 and 16.4 into one section.
Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies			
	17	**Do you agree with the proposed format? Please comment.**	This Annex is far too detailed to be adopted as part of the legislation. Therefore the description should be less specific and should make clear it is only relevant for PASS studies as conducted in the light of EU approved RMPs. The format as given serves as a start for the GVP on RMP and PA(S/E)S with practical examples and descriptions. To add this to the regulation and directive limits the MA holders, MS and EMA in the future evolution and development of the conduct of PASS studies. It needs however a lot of further discussion on the content and the format to ascertain protocol and deliverables are consistent.