Concept Paper on 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

Section	Comment and Rationale	Proposed change (if applicable)
A1	Under the definition of the Pharmacovigilance System Master File (PSMF) the second paragraph allows for different systems for authorized products.	Could the paper clearly state the intent, i.e. different systems if a company has pharmaceutical vs. consumer or vaccine divisions then a single PSMF may be inappropriate.
A2	Change in location of PSMF to be notified to EMA.	Details of how the notification should occur would be useful.
A3 (1)	Requirement to include a listing of all authorized products, yet the PSMF is the system that is generic for all products – the need for the listing is unclear and for some MAHs will be extensive. As it requires authorization and if placed on market will require frequent status updates of information to the PSMF and such information will be available in other documents such as marketing status in the PSUR.	Clarity as to why such a listing is required in the PSMF- this seems unnecessarily burdensome and should not be required if the Master file is not product-specific but generic.
A3 (3)	It is unclear why national responsible person's listing is required. Each CA is notified per current requirements and responsibilities are usually defined in national regulations.	Clarity as to why such a listing is required in the PSMF.
A3 (5)	The location, functionality and **operational responsibility** of systems and databases and their assessment of **fitness for**	Please clarify the difference in functionality and operational responsibility. Clarify fitness for purpose relates to validation of PV systems and associated

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	purpose.	documentation.
A3 (6)	For defined processes the PSMF should describe the process, **data handling and records.**	Clarification on what detail is expected with regard to data handling and documentation would be helpful.
A3 7a	A list of documented procedures – as with other requests, procedural documents change –. The reason for the location is unclear.	It would be preferable to require the MAH to produce a listing of procedural documents upon request within seven days as with the PSMF rather than maintain such a listing in the PSMF.
A3 7b	Description of resource management for performance of Pharmacovigilance activities. We do not believe this information is relevant.	Details of what is required here would be helpful. Clarify why this information is required.
A3 7e	Reference to the location of audit trails for monitoring performance and compliance of main outputs of the pharmacovigilance system.	Details of what is required here would be helpful.
Consultation 2	Consultation item 2: question regarding significant changes or modification to the master file to be notified and how. We agree master file should contain a date when last reviewed	If the PSMF has to be available within 7 days upon request additional requirements regarding updates seems unnecessary, especially as a log of changes is required to be maintained per A5.
A5	Current deviations, impact and management noted in the PSMF	Clarity on the intent as MAHs maintain separate deviation processes and this requirement seems

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	until resolved.	duplicative and unnecessary.
	A log book of any alteration in content within the last five years.	Clarification if this is separate to the PSMF itself. And level of details with regard to changes required – major process vs. administrative.
A6	The requirement that copies of signed agreement shall be included in the PSMF is burdensome.	It would be preferable to require the MAH to produce a listing of agreements upon request within seven days as with the PSMF rather than place such documents in the PSMF. The CA could request applicable agreements within seven days on receipt of the listing.
A7	All completed audits of the PV system recorded in an annexe to the PSMF, including date and scope.	Clarity as to what additional information is expected beyond date and scope, given the following paragraph details the corrective and preventive action plans (CAPAs) as a note to file.
Consultation 4	Should the audit reports be retained n the PSMF and require documentation of audit schedules.	The audit schedule could be added annually to the PSMF but adds to the administrative burden of changing the PSMF and requires tracking and logging. The inclusion of the audit reports seems unnecessary if the CAPA process as defined is applied and given that they are used internally to highlight areas for improvement having to disclose them in the PSMF may result in impacting their effectiveness.

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Consultation 5	Agreement with the requirements for content and maintenance of the PSMF – some additional requirements as detailed above which go beyond the current DDPS requirements seem burdensome and will require frequent updates. Note: Several additional requirements for data in the PSMF are in sections B & C.	
B10	Audit of the quality system – not less than every two years.	Clarity that this is the PV system vs. the quality system as often quality processes form part of process audits. Clarity as to why every two years vs. risk based approaches.
B11	Performance indicators – annexed to the PSMF. Possible publication of performance indicators post PRAC.	Define performance indicators in this context. Preferable to produce upon request rather than annex to the PSMF as will require regular updates, logging and tracking per PSMF log book of changes. Clarity as to where for access by whom .
C13	Resource management to be documented in the PSMF.	Clarity as to what is required here.
C14d	MAH to review conclusions of assessment and recommendations re product information made public by	Clarity required as to the expectations of MAH use of the portal. Expectation that MAH will check web portal daily

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	assessing EMA we b portal daily for relevant updates, consultations and notification on procedures. It is unclear what this means – consultation and notification of what procedures – will the EMA or CAs not submit assessments to the MAH directly?	is too onerous and should be removed. EMA and CAs should alert MAH to relevant updates, etc.
Consultation 6	Communication on PV to patients and HCPs, management of duplicates in Eudravigilance.	The MAH would expect close consultation with EMA and CAs prior to any HCP communication and is unclear as to its position with regard to direct to patient communications – further regulatory guidance would be required. The MAH would not be in a position to manage duplicates in Eudravigilance.
D17	Training plans and records shall be kept and made available for audit.	Clarify if this is internal audits within EMA or CAs. What about inspections? Would EC do these?
E20	MAH to monitor Eudravigilance with respect to signal detection and risk identification as part of broader monitoring. MAH shall inform EMA and NCAs of new risks or changes to benefit risk.	Clarity on data MAH can access and expected frequency of access would be helpful. See response to E21.
E21	A signal is defined as that which justifies verificatory action. Reference to use of statistical analysis within Eudravigilance is made.	Clarity that statistical analysis within Eudravigilance only relates to EMA and NCAs is required.

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	Consultation by PRAC of medical event that have to be taken into account for a verification of a signal.	Clarification that this only relates to EMA and NCAs as MAH will do own signaling and advise EMA and NCA if new risk or changes to benefit risk as defined in E20.
E25	Methodology.	Clarification that this relates to EMA/NCAs.
Consultation 9	Use of work sharing procedure. Do you see a risk in cumulating all tasks in one Member State (MS)? No, this is what currently happens. Will need transparency to be maintained with other MSs, EMA and so on. Work sharing to all medicinal products and to appoint a lead MS – same comment as before.	Clarify how this will be decided and PRAC's role in process.
E23	Monitoring of Eudravigilance – proportionate to risk etc but in C14D daily review was required of portals.	Clarity as to frequency of Eudravigilance review vs. portals and would both be required?
	Signals communication to EMA/NCA by MAH to be validated to determine if further analysis is required If MAHs have to highlight signals to EMA/NCA and then have to wait for validation and request for further analysis/follow-up action, this could delay internal MAH work-up of signal (bottle-neck effect) and also delay in implementing/communicating	This implies any potential signal, prior to any further work up or review has to be highlighted to EMA/NCA before any internal review processes – please clarify what is required here and what MAH feedback will be on such notifications and how – see below re PRAC.

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	safety changes to labels/PILs (prescribers/patients).	
	Validated signals requiring further analysis – will be tracked and sent to PRAC to consider follow up action – seems to add additional delay and burden on internal safety review processes.	This implies any potential signal, prior to any further work up or review has to be highlighted to EMA/NCA before any internal review processes – please clarify what is required here and what MAH feedback will be on such notifications and how.
E25	EMA shall support monitoring of Eudravigilance and provide access.	Clarity as to which of these applies to the MAH vs. NCAs
Consultation 10	Are provisions clear and transparent?	Provisions are confusing and clearer definition of MAH vs. NCA roles and responsibilities would be helpful.
F27	C through G are only applicable in 2015.	Can the current measures only reference current requirements?
	MAH making request for a new term e.g. to MSSO must also inform EMA.	Clarity as to why the MAH must also notify EMA and through which route?
Consultation 11	Agreement with proposed terminology.	Can the current measures only reference current requirements?
F28	A through F are only applicable published in 2015.	Can the current measures only reference current requirements?

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G	No comments.	N/A
Annex 1 3	Facilitation of personal data through replacing with pseudonyms.	Clarity and details required as to what is acceptable.
Annex 1 4m	Confirm that no additional information is available.	Clarity that this will be an expedited report to Eudravigilance.
Annex 2 Consultation 15	Agreement with proposed format and content.	
Annex 2	Module V: Post Authorisation Experience.	In current RMP format, and overview of both clinical and post marketing experience is provided at the beginning of the Safety Specification, in the new format proposed there is no module for clinical trial experience (only clinical trial exposure) and no module for post authorization exposure (only post authorization experience).
Annex 2	Part IV: Plans for studies on effectiveness and long term efficacy.	Further clarity/guidance needed on how studies on effectiveness and long term efficacy are reflected in a 'risk' management plan.
Annex 3	Listings shall not be included routinely in PSURs.	Clarity as to when listings may be required.

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Annex 3	1.1. Content of the periodic safety update reports.	General comments: - PSURs are global documents currently written according to ICH E2C and taking into account regional requirements. MAHs will need to not only take into consideration the PSUR structural requirements for the EU but also maintain adherence to ICH requirements to ensure the PSUR remains a global document acceptable to other territories, this may lead to MAHs creating a hybrid structure for PSURs that meet both EU and ICH standards (unless plans to change ICH?). - a model/example PSUR written using this structure would be helpful as it is not clear what may be needed in some sections.
Annex 3	1.1. (2). A PSUR shall contain cumulative data …	PSURs may become large and cumbersome. RMPs already contain cumulative data summaries (Clinical, non-clinical, post marketing, exposure etc…) so this may lead to duplication as RMP updates generally submitted with PSURs …
Annex 3	1.1. (4). Results of assessments of the effectiveness of risk minimization activities ….	Already presented in RMP – duplication?
Annex 3	1.2. (5.1.) Cumulative Subject Exposure in Clinical Trials.	Already presented in RMP – duplication? Also no reference to interval CT exposure data (present for marketing exposure) which usually put the CT cases for the period into perspective and present in current PSUR model.
Annex 3	1.2. (12) Other Periodic Reports.	Guidance needed on what to include in this section,

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		which type of reports/what level of detail?
Annex 3	1.2. (13) Lack of Efficacy in Controlled Clinical Trials.	Guidance needed here given efficacy is endpoint in most studies, what type of information/threshold for inclusion.
Annex 3	1.2. (16.5) Effectiveness of Risk Minimization.	Already presented in RMP – duplication?
Annex 3	1.2. (18) Integrated Benefit-risk Analysis for Approved Indications.	Guidance on level of detail needed here - template would be useful. Also see general comment above on need for model/example PSUR.
Consultation 16	Agreement with proposed format and content.	No comments.
Annex 4	Heading – protocols, abstracts and final study reports for PASS studies - does not mention PAES studies.	Clarity as to whether PAES studies should be included.
Annex 4 8	Within 12 months, MAH shall submit final study report including public abstract to EMA.	Clarify whether this is an abstract of study report intended for the public.
Annex 4 2 13	Resources required to conduct study – does not seem relevant.	Clarity as to why this is required.
Annex 4 Consultation 17	Agreement with proposed format for protocols, abstracts and FSRs for post authorization safety studies. Refer to comments under Annex 3.	