Bringing medicines to *life*

ABPI response to the European Commission Concept Paper:

Implementing measures in order to harmonise the performance of the pharmacovigilance activities provided in directive 2001/83/EC & regulation (EC) No 726/2004

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The Association of the British Pharmaceutical Industry (ABPI) represents innovative research-based biopharmaceutical companies, both large and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 80 per cent of all medicines used by the UK National Health Service, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

Working with our Research Affiliate Members, leaders in pharmaceutical R&D, is vital in promoting the UK as a destination of choice for international life sciences investment.

The ABPI would like to thank to European Commission for the opportunity to comment on the implementing measures for the performance of pharmacovigilance (PV) activities provided in Directive 2001/83/EC and Regulation (EC) No 726/2004.

General question

Consultation item 1: Should additional processes and PV tasks be covered in the PV system master file?

Response: We do not think additional processes or PV tasks should be covered in the PV system master file (PSMF).

Additional comments: p.5, Section A.3 (1): This section states that a list of medicinal products should be included in the PSMF and provides a list of the required information. This data will have already been provided to the European Medicines Agency (EMA) via XEVPRM and will be in the EudraVigilance (EV) Medicinal Product Dictionary and hence it is duplicative to have this information listed again. The information required should be limited to that needed for the identification of products: a list of short product names used in the EU, the INN names and countries of authorisation.

p.6, Section A.3 (3): it is unclear why information relating to the contact person for pharmacovigilance at a national level is required in the PSMF. Each National Competent authority

(NCA) is notified with this information (including contact details and description of responsibilities) according to the appropriate national legislation.

p.6, Section A.3 (5): We think clarity on the difference in functionality and operational responsibility should be included in the appropriate module of the Good Vigilance Practice Guidance. Specifically, 'fitness for purpose' should relate to validation of PV systems and associated documentation.

Consultation item 2: The aim of the PSMF 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?

Response: We do not think it would be appropriate for marketing authorisation holders (MAH) to notify changes or modifications to the PSMF, apart from those stipulated in Article 23 of Directive 2001/83/EC such as a change to the Qualified Person for PV (QPPV). There is already the provision for NCAs or EMA to request a copy of the PSMF at any time (p.8, Section A.8) and this additional requirement would be burdensome.

Additional comments: p.7, Section A.4 states that (the PSMF) shall be continuously kept up to date. Whilst this is optimal it is not always practical.

Consultation item 3: Is it necessary to be more precise on potential delegation e.g. in the case of co-marketing of products? Please comment.

Response: It is not necessary to be more precise on potential delegation, provided this section refers only to delegation external to the MAH. Co-marketing agreements are not mentioned in the concept paper but will be documented in the appropriate Safety Data Exchange Agreements (SDEA).

Additional comments:

p.7, Section A.5: In order to ensure a pragmatic mechanism for managing deviations, we propose that the implementing measure should state that 'a system should be in place to manage deviations from the pharmacovigilance procedures'. The detail can be included as part of the PSMF module of the Good Vigilance Practice Guide.

p.7, Section A.5: Is a 'logbook recording any alteration of its content' the same as a revision history?

p.7, Section A.6: Maintaining signed copies of all third party agreements in the PSMF would be extremely burdensome and impractical. We recommend this section be amended to require a list of existing contractual agreements in the PSMF with signed copies of agreements provided on request.

Consultation item 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

Response: We do not think a copy of the audit report should be included in the PSMF. It is important to ensure that audits are as effective as possible and despite the best intentions of a company it is possible that inclusion of the audit report in the PSMF would inhibit the effectiveness of the audit process. We support the inclusion of a more top level 'note' of main findings (those considered critical or major) in the PSMF, although a standard format for these has not been developed for the EU. This note should be removed after the appropriate corrective action has been implemented. It is appropriate to require documentation of internal audit schedules.

Additional comments: p.8, Section A.7: are the audits referred to in this section local, global or both?

p.8, Section A.7: The words 'the main' in this section should be replaced with the words 'any major or critical' as it would be clearer if the wording of the implementing measure was aligned with Competent Authority inspection terminology.

p.8, Section A.8: Are the 7 days stipulated for MAHs to submit a copy of the PSMF working or calendar days?

Consultation item 5: Overall, do you agree with the requirements as regards the content and maintenance of the PSMF? Please comment?

Response: The primary benefit of the PSMF concept over the DDPS is the reduction in burdensome and duplicative work practices and we agree with the EFPIA statement on this item, reproduced below:

EFPIA comment: EFPIA kindly requests that the master file be prepared as a modular document, in order to facilitate amendment and version control.

EFPIA understands that the pharmacovigilance system master file (PSMF) should comprise an overview of the pharmacovigilance system providing information on the key elements of the system rather than a depository for the primary data relating to individual elements of the pharmacovigilance system. Hence, we consider that the extent and detail for some of the individual elements listed in the proposed implementation measure may be in conflict with the concept of a succinct, easily-managed PSMF that facilitates an effective overview of the MAH's pharmacovigilance system.

EFPIA believes the PSMF will serve its purpose best if by presenting key information in summary form, rather than by duplicating voluminous primary information or restating information accessible or provided through other means. The PSMF should cross-reference and explain the different elements of the pharmacovigilance system, e.g. via providing lists (with titles) of core procedural documents or describing MAH-specific data inventories/ systems, and contain data sources or a list of interfacing functions, specifying the primary origin of required information.

More detailed information can be made available on demand, e.g. by the MAH providing detailed standard operating procedures and/or current outputs from primary data systems.

Additional comments: In addition, the ABPI thinks the location of the PSMF should be determined by the main EU site where PV activities are performed (which is specified by the MAH in the PSMF), this may not necessarily be the site where the QPPV is located.

Consultation item 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 PV between the MAH 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?

Response: There is no need for additional quality procedures and we think the EMA should be responsible for detecting duplicates in EudraVigilance.

Additional comments: p.9, Section A.10: The ABPI think that a risk based approach to audit frequency is more appropriate than inclusion of a minimum 2 yearly requirement in the implementing measure.

p.9, Section B.11: We are assuming 'performance indicators' are the same as the performance metrics produced by MAH which we think would be duplicative and burdensome to maintain in the PSMF. These performance metrics are produced at fixed time points and made available on request, often at inspection; they are not included in the DDPS. We propose that a list of performance indicators is included in the PSMF and that these are made available 'on request'.

p.10, Section C.14 (b): We do not agree that it is appropriate for MAH to check the European medicines web portal on a daily basis, unless this is facilitated by setting up a daily e-mail alert that will highlight changes to the MAH.

Consultation item 7: Do you agree with the requirements for MAHs? Please comment.

Response: We agree with the requirements for MAH's as detailed in section 15 (Record Management).

Consultation item 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.

Response: We generally agree with the quality system requirements.

Consultation item 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.

Response: We are in general agreement with the concept of a 'work sharing' procedure for monitoring of data in EV. There is concern among our members that cumulating all tasks under one member state (MS) is somewhat risky because of variation in practice across the EU but the right of any MS to comment or review may act as a safeguard. There could be a role for the PRAC here in ensuring standardisation of processes across the EU.

Additional comments: p.14, Section E.21: we do not understand the following sentence: '*Following consultation of the Pharmacovigilance Risk Assessment Committee EMA may publish a list of medical events that have to be taken into account for the detection of a signal.'*. Is this alluding to the use of terms like Standardised MedDRA Queries (SMQ) in signal detection?

p.14, Section E.23: '*For products authorised in accordance with Directive 2001/83/EC that validation shall be done by the national competent authorities. For products authorised in accordance with Regulation (EC) No 726/2004 validation shall be done by EMA.*' If MAHs have to highlight signals to EMA/ NCA then have to wait for validation and request for further analysis/ follow-up action, this could create a bottle-neck, delaying internal MAH work-up of signal and the implementation/ communication of safety changes to labels/ PILs. In addition, sending of validated signals to the PRAC for further analysis risks adding further delay to the process.

Consultation item 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 MAHs, 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.

Response: The proposals could be clearer, in particular, it is important that the relative roles of the MAH, NCA and EMA are clarified. It may not be necessary to go into detail on the roles of the MAH and NCA in the implementing measure but this could be captured in the Good Vigilance Practice Guide and these roles should be unambiguous. Diversity in the signal detection process is important because assessment by independent groups yields more robust results.

Additional comments: p.15, Section E.25: Will the outputs listed be made available to the public and HCPs as well? We need clarity on which stakeholders the data will be made available to.

p.16, Section E.26: Will MAH's get access to NCA and EMA audit trails of their signal detection activities? They could contain useful information.

Consultation item 11: do you agree with the proposed terminology? Please comment.

Response: Overall, we agree with the proposed terminology

Consultation item 12: do you agree with the list of internationally agreed formats and standards?

Response: Overall, we agree with the proposed formats and standards although we have concerns relating to item (a) at the bottom of p.17; the implementation of Regulation (EC) No 726/2004 article 52(2), second subparagraph. As discussed at EMA on 20th September 2011, the ABPI recognises that a certain amount of data will have to be submitted to EudraVigilance by 2 July 2012 in order to comply with Article 57(2) of Regulation (EC) No 726/2004, as amended by Regulation 1235/2010. Despite this, we are concerned about the extent and scope of data required for submission, as detailed in the EMA Legal Notice of the 1st of July 2011 and follow up communication in September 2011, as this goes beyond the text of the legislation. ABPI is committed to continuing dialogue with the other affected trade associations to determine the minimal data fields required for compliance with Article 57(2) by the July 2012 deadline.

Pg.17 the EudraVigilance Medicinal Product Report Message (EVPRM) should now be the Extended EudraVigilance Product Report Message (XEVPRM).

Consultation item 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.

Response: Well considered transitional provisions will be crucial in the implementation of this legislation but these are better covered in the implementing guidance.

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.

Response: The ABPI generally agree with the content and format as detailed in the concept paper and think greater detail can be captured in the appropriate module of the Good Vigilance Practice guide.

Consultation item no. 15: Do you agree with the proposed format and content? Please comment.

Response: The ABPI generally agrees with the proposed format and content.

p.23 paragraph 3: The word 'summary' should be inserted before the words 'the RMP' in this paragraph as it is only the summary of the Risk Management Plan (RMP) that should be published on the EMA and NCA websites.

p.22, Section 1.2: Module II of the Safety Specification (non-clinical part) is incorrectly labelled as Module I.

p.22, Section 1.2: Should Modules VII and VIII be reversed? It could be more logical to present the Additional EU Requirements before the "Identified or potential risks", i.e. reversion of modules VI and VII. This is because any items specifically requested in the EU might end up creating new identified or potential risks, a concise summary of which could then be presented in module VII before the Summary in module VIII.

Consultation item no. 16: Do you agree with the proposed format and content? Please comment.

Response: We agree with the format for the Periodic Safety Update Report (PSUR) in the concept paper as long as it is consistent with that agreed by ICH E2C(R2) and within the scope of the text of the legislation. EFPIA have raised concerns about the phrase below in Section 1.1.3, which is goes beyond the requirements of the legislation and is not consistent with the current draft of ICH E2C (R2) guideline:

"…accompanied by qualitative and quantitative analysis of actual use including how it may differ from indicated use based on all data available to the marketing authorisation holder".

We agree with EFPIA's recommendation that this phrase should be removed from the proposed implementing measure pending further discussion by the ICH E2C Expert Working Group.

Additional comments: p.24, Section 1.1.5: The word 'routinely' needs to be deleted as this is not in line with the legislative text on PSURs or in the revised ICH E2C (R2) guideline. All reactions are to be reported to EV and there is therefore no need for individual cases to be given in line-listings.

p.25 (top): The QPPV should demonstrate appropriate oversight of PSUR production but their sign off on all PSURs produced may not be practical and is not the best use of their time. Appropriate oversight by the QPPV can be demonstrated if they have had direct input and sign off can be performed by delegation to appropriately qualified staff. We propose this bullet is amended to read just 'Signature page' and that the above is clarified in the appropriate module of the Good Vigilance Practice Guide.

Consultation item no. 17: Do you agree with the proposed format? Please comment.

The ABPI received no comments back from its members on this consultation item.