CONCEPT PAPER

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

EFPIA COMMENTS

EFPIA welcomes the opportunity to review and comment upon this Concept Paper. We appreciate that the draft implementing measures are being considered within a single paper, emphasising the need for an integrated approach to pharmacovigilance within Europe. However, we suggest that consideration be given to providing many of the details currently specified within the four annexes of the Concept Paper as part of the intended Good Vigilance Practice guideline rather than as part of the implementing measures. Due to the legally-binding nature of the implementing measures, with consequent limited opportunities to change thereafter, provision of such details within the GVP guideline would allow for flexibility concerning the formats of the documents in question, desirable for the benefit of future worldwide discussion and implementation processes.

In addition to the provision of specific responses to the 17 consultation items presented within the Concept Paper, EFPIA welcomes the opportunity to provide further comments on parts of the document, as invited by the concept paper - these generally follow the responses to the specific consultation items.

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?

No additional processes and pharmacovigilance tasks need to be covered in the pharmacovigilance system master file.

It should be clarified in section 1 that the definition of “marketing authorisation holder” is consistent with Commission Communication 98/C 229/03, which defines the phrase “same marketing authorisation holder”. Only one pharmacovigilance system master file should be required for all MAHs belonging to the same ‘mother company’, or group of companies, where the same pharmacovigilance system is applied.

With regard to the list of medicinal products (section 3(1)), such a list may become extremely extensive if produced in accordance with the current wording, especially if it has to list all national translations of the full product names and the full registration numbers (for centrally approved products, the last digits in the registration numbers reflects the actual strength, formulation, package size etc). For example, a list of the dual acting insulin products (‘Mixtard’) reveals 513 different ‘products’ within the EU alone. Hence, we propose that the information should be limited to that simply needed for the identification of the products, namely a list of short product names used in the EU, INN names and the countries where they

are authorised, noting that detailed information will already be provided to the EMA via XEVPRM.

In addition, the concept paper indicates that the pharmacovigilance master file should be kept continuously up-to-date. The information in the list of medicinal products and all the details requested could change frequently, particularly if all individual EU marketing authorisations need to be included (e.g. some countries issue new authorisation dates on renewal of a product licence). We suggest that consideration should be given to updating this list on a regular (e.g. quarterly) basis, as well as when a pharmacovigilance system master file is requested by a competent authority.

It is unclear why information relating to the contact person for pharmacovigilance at a national level is required in the master file (section 3(3)). Our understanding is that each national competent authority is notified with this information (including contact details and description of responsibilities) according to the appropriate national legislation, thereby making this information redundant within the master file.

As regards section 3.6(e), this seems to be mixing two concepts in one, namely the variations procedure for updating the product information, and the communication of product information to patients/health care professionals (whether urgent or routine). We suggest that the implementing measure addresses the two aspects separately, i.e.:

(e) Process for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet.

(f) Process for communicating urgent safety concerns to patients and health care professionals.

Location of Pharmacovigilance System Master File

Section 2 indicates that the master file shall be located at the site where the qualified person for pharmacovigilance (QPPV) operates. Unfortunately, this provision appears to have overlooked the fact that the QPPV may not be based at a site that operates as the headquarters or the main EU pharmacovigilance site for that company, as is the case in some EFPIA member companies and likely to be the case with many small companies that have engaged QPPV contract services (some of whom may even work from home). This is important as Regulation (EU) No 1235/2010 Article 18.3 stipulates that the 'supervisory authority' should be "*the competent authority of the Member State in which the pharmacovigilance system master file is located*", with implications as to which member state authority will then take on responsibility for audit of the company's pharmacovigilance system.

EFPIA agrees that, regardless of where the master file is compiled and maintained, full access should be provided to this document at the main EU site where pharmacovigilance activities are performed and, if different, the site where the QPPV is located.

However, in contrast to the provision current presented within the concept paper, EFPIA considers that the location of the master file should be determined by the main EU site where

pharmacovigilance activities are performed (as specified by the MAH within the master file itself). In the event that key pharmacovigilance responsibilities are spread equally across a number of EU sites (i.e. a main EU site cannot be identified), then the location of the master file shall be the site where the QPPV is located.

Consultation item 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 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?

It should not be necessary for the MAH to be required to notify the competent authorities of significant changes to the master file, other than for reasons already specifically defined in Article 23 of Directive 2001/83 amended e.g. a change to the QPPV. As stated in Section 8 (Inspection), the national competent authorities and EMA may at any time ask the MAH to provide a copy of the pharmacovigilance system master file; the MAH shall submit the copy at the latest seven days after the request.

We also suggest that only changes with an impact on the Summary of the Pharmacovigilance System included in an application for a marketing authorisation [point (ia) of Article 8(3) of Directive 2001/83/EC] needs to be notified to the competent authorities. Therefore, we suggest that the Commission classification guideline for variations should be updated to reflect the following changes in section C.I.9 that should be classified as Type IA immediate notification:

- Change in the QPPV
- Change in the contact details of the QPPV
- Change in the back-up procedure of the QPPV
- Change in the location of the PSMF

Consultation item no. 3: Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

Presuming that this section of the concept paper refers to delegation external to a MAH, it is not necessary to be more precise on potential delegation e.g. in the case of co-marketing of products, since this should already be covered in detail in the individual Safety Data Exchange Agreements.

The proposal that “copies of the signed agreements shall be included in the master file” (section 6 paragraph 2) is neither practical or necessary, and consideration is required as to

how best to keep the master file to manageable proportions and easier to maintain. Given that some companies operate a significant number of contractual agreements, each subject to change at any time, we consider that the master file should include only a list of existing contractual agreements, rather than full copies of each agreement, with individual contractual agreements available on request.

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?

A copy of the audit report should not be retained in the master file as this is not a legal requirement.

Directive 2010/84 Article 104.2 requires that the MAH holder shall perform a regular audit of its pharmacovigilance system, and place a note concerning the main findings of the audit in the master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed. EFPIA has previously suggested that 'main findings' can be clarified as those considered as 'critical' or 'major' in nature; we also suggest that the note of the main findings should be placed as an annex to the master file.

EFPIA considers that it is appropriate to require documentation of proposed internal audit schedules. However, a risk-based approach should be used for determining internal audit programmes, a principle already supported by some national competent authorities.

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please 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 rather be made available on demand, e.g. by the MAH providing detailed standard operating procedures and/or current outputs from primary data systems.

Finally, in contrast to the current proposal within the concept paper, EFPIA considers that the location of the master file should be determined by the main EU site where pharmacovigilance activities are performed. In the event that key pharmacovigilance responsibilities are spread equally across a number of EU sites (i.e. a main EU site cannot be identified), then the location of the master file could be the site where the QPPV is located. Clarification of this suggestion is provided within the 'further' comments below.

Consultation item 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?

There is no need for additional quality procedures. In addition, the EMA should take on responsibility for the detection of duplicates of suspected adverse reaction reports in the EudraVigilance database (see *EMA paper on duplicate checking*).

As regards the proposal relating to performance indicators (section 11), we agree with the proposal to document indicators used to monitor the good performance of pharmacovigilance activities. However, given that performance indicators are monitored frequently by MAHs, with multiple measurements within short periods of time, maintaining all of the results in an annex to the master file is impractical and duplicative of systems in place. We suggest that the proposed annex should contain the list of indicators only, with relevant results for specific periods of time made available upon request.

As regards the requirement for MAHs to follow-up case reports (section 14(a)), the implementing measure needs to take into account the fact that national laws in some member states either forbid MAHs from conducting follow-up of spontaneous reports, or prevent MAHs from conducting follow-up if the reporter has not consented to be contacted further. In addition, consideration should be given to follow-up being risk based, with less follow-up necessary for non-serious listed case reports, i.e. it should not be a requirement to conduct follow-up for every case report.

Aside from being unnecessary detail in the implementing measure, the requirement for MAHs to check the European medicine web portal for relevant updates each working day should be reconsidered - the appropriate timeline should be left to individual companies to determine. This is especially relevant for smaller-sized companies having few medicinal products, for which such a requirement could be disproportional.

It should also be made clear what part of the website should be monitored for updates. Any new information appearing on the portal should be dated and appear in the order of posting (the most recent first).

The possibility for MAHs to be notified of new postings (e.g. RSS feeds) should also be explored.

The monitoring of sites should also not replace and obviate the link between the competent authorities and companies on safety issues. Indeed, the obligation for MAHs to check the European medicines web-portal should not replace direct correspondence with the MAH on individual product issues.

Exemptions to ICSR reporting in extenuating circumstances

In relation to the adverse reaction reporting timelines stipulated in section 14(b), in certain circumstances it is very challenging for Marketing Authorisation Holders (MAHs) to comply with 15 day expedited reporting rules e.g. in the situation of a pandemic or upon receipt of a very large batch of cases arising from class action law suits (whereby up to several hundred or even thousands of potential individual case reports may be generated and sent without warning). The MAH may have a Business Continuity Plan which triages prompt data entry to cases which are serious and medically important whilst proposing to delay entry of selected and less medically important cases if they become overwhelmed by numbers.

There is currently no effective mechanism in the EU to request waivers to any aspect of the legislation. Section 5.12 of the current Volume 9A (Rules Governing Medicinal Products in the European Union), which deals with public health emergencies including pandemic flu, says that "*in the event of a public emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and appropriately notified*". However, companies' experience during the pandemic flu outbreak, and in dealing with class action reports, is that this provision is of no practical use, and competent authorities are not prepared to rely on it. Some competent authorities have been sympathetic to the issue but have indicated that EU law did not support such practice.

In contrast, waivers are possible in the USA, a recent example being to extend the timeframe for initial reports to 30 days and follow-up reports to 60 days for a company that had received a large batch of legal cases.

Implementation of the new legislation represents an excellent opportunity to introduce a provision that makes it clear that competent authorities should have a discretion to amend 'regular' reporting requirements in the case of public emergencies or where otherwise legitimately justified by the circumstances.

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

Consultation item no.7 is not clear as to whether it regards the MAH quality system in general (sections 12-15) or only section 15 (record retention). Assuming the latter,

clarification is required regarding which pharmacovigilance- or product-related documents are meant to be covered; this should be addressed in the Good Vigilance Practice guideline.

The proposed 30 year retention period is much longer than existing periods specified for other medicinal product-related documents in EU legislation. Imposing a retention period that is much longer than that applied by many companies could have significant consequences, including increased cost of retention (larger storage facilities – paper and/or electronic – for longer) and iniquity in information available between existing/recently terminated products and products for which the companies' (shorter) retention period has already passed. We propose that the retention period should be more closely aligned with the requirements in Annex I 5.2.c of Directive 2001/83/EC, relating to retention of final clinical study reports: these documents must be retained by the sponsor or subsequent owner for five years after the medicinal product is no longer authorised.

Otherwise, the European Commission should provide justification for their choice of retention period and be more specific on the documentation required to be retained. The total retention period for a given product could be in excess of 70 years assuming development, active marketing phase and 30 years post-commercialisation. Furthermore, we are not aware of any validated methodology that will allow companies to confirm compliance with such a retention period.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards for marketing authorisation holders, national authorities and EMA.

In general, we agree with the quality system requirements.

However, assuming that this consultation item refers to sections 9–19, we note that section 10 indicates that the MAH should perform an audit of their quality system at regular intervals, not less than every two years. EFPIA supports the use of risk-based approaches for determining internal audit programmes rather than basing audit programmes on fixed schedules, a principle advocated by some national competent authorities.

EFPIA supports the conduct of regular internal audits to examine processes and monitor the performance of the company's pharmacovigilance system, as a robust pharmacovigilance system ultimately promotes patient safety. However, we believe that the MAH should determine the frequency of their internal audits, based upon information on the performance of the pharmacovigilance system and/or findings arising from 'routine' audits conducted on a pre-scheduled basis. However, repetitive 'routine' internal audits on a fixed schedule could become a disproportionate effort when compared with the effectiveness of a more 'risk-based' approach.

Consultation item no. 9: For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in

several medical 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 proposed 'work sharing' procedure is rational and supported by EFPIA. There is little risk in cumulating all tasks since any member state would retain the right to comment or conduct additional review if they so wished. The work sharing procedure should be extended to all medicinal products which have been approved in more than one EEA country, with a lead Member State appointed in addition to EMA.

Consultation item 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.

The aim of the common triggers must be to eliminate false negatives (missed signals) and to keep false positives to a minimum. Thus EFPIA agrees that there is merit in ensuring that the roles of MAHs, national competent authorities and EMA are clarified. The contributions of each stakeholder should be recognised and encouraged within the implementing measures. Thus, whilst the proposals are clear concerning the role of EMA, a series of process outlines and specific deliverables must be defined for MAHs and national competent authorities in the Good Vigilance Practice guideline. These outlines and deliverables should be described in sufficient detail to help ensure consistency of approach between national competent authorities.

Overall, the proposals for signal detection could be clearer, in particular, it is important that the relative roles of the MAH, NCA and EMA are clarified and unambiguous. 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 guideline. Such guidance should specify the expectations for automated signal detection, what level of access to statistical signal detection methods will be provided to MAHs, and what the EMA's expectations are with respect to usage of these tools by the MAHs. In establishing a framework for signal detection, the maximum possible transparency in terms of roles, methods and expectations is essential to establish the most productive framework.

It is also important to retain an appropriate level of diversity in signal detection methods, as no single system or process will yield a perfect result. In addition, it should be recognised that statistics may be less relevant for products with relatively low patient exposure and consequent low numbers of reported adverse reactions. In this regard, general principles

would probably be more useful to establish commonalities than selecting one single methodology to be applied in different settings.

Section 21 indicates that the detection of a signal shall be based on multidisciplinary based approach and be supported by statistical analysis within EudraVigilance. The implication of section 20 is that this shall apply equally to MAHs as well as the competent authorities. If so, EFPIA requests that the following be considered:

- This would require that MAHs have access to the statistical tools being utilized for the analysis of data from EudraVigilance
- For orphan/low volume drugs, although the data in EudraVigilance should still be considered as part of any evaluation of a potential safety signal, advanced statistical analysis may not be appropriate and, hence, should not be required.

Section 22 (Methodology) requires clarification as to whether it refers to the process of nominating associations as signals or to the process of triaging of signals already identified. Details on the methods, or at least minimum criteria, should be provided at the time of initial implementation - this would require the PRAC to publish their recommendations by the due date for implementation (presumably July 2012).

Section 23 (Signal management procedure) requires clarification with respect to the concept of 'frequency proportionate to the identified risk'. Definition of risk in this context would be needed, and clarification on whether it should be quantitative (e.g. a relative risk) or based on the clinical seriousness of the risk or a combination of both. In addition, the term 'validated signal' should be defined. The GVP guideline should provide details on the communication process to the MAH once a competent authority detects a signal. The EudraVigilance access policy should enable MAHs to download data with frequent updates, and not at prolonged intervals, so that signals can be detected before, or at the same time as, the competent authority monitoring the product.

As regards section 25 (Signal detection support), will the outputs listed be made available to the public and healthcare professionals as well? We need clarity on which stakeholders the data will be made available to.

As regards section 26 (Signal detection audit), will MAHs get access to NCA and EMA audit trails of their signal detection activities, given that these could contain useful information?

Consultation item no. 11: Do you agree with the proposed terminology? Please comment.

We agree with the proposed terminology, but not how the terminology is being applied by the EMA.

It should be noted that the scope of the ISO standards is broader than simply facilitating pharmacovigilance and signal searching. These standards were developed to provide a single format for the exchange of information in all interactions between stakeholders within the

pharmaceutical domain. It is therefore difficult to see how these standards can be implemented solely for the purpose of pharmacovigilance ahead of their application to all other interactions with competent authorities. Hence, we suggest that the ISO terminology should only be applied when these standards have been adopted and implemented via ICH. Application of these standards in isolation to pharmacovigilance, and in particular the EVMPD described in Article 57, is excessive and impractical for the intended purpose.

Consultation item no. 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

EFPIA agrees with the list of internationally agreed formats and standards, with the exception of item (a), relating to the EudraVigilance Medicinal Product Report Message (EVPRM). As discussed at EMA on 20th September 2011, EFPIA recognises that a certain amount of data will have to be submitted to EudraVigilance by 1 July 2012 in order to comply with Article 57(2) of Regulation (EC) No 726/2004, as amended by Regulation 1235/2010. Despite this, and as previously communicated to the EMA, 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. EFPIA is committed to continuing dialogue with the EMA and with the other affected trade associations to determine the minimal data fields required for compliance with Article 57(2) by the July 2012 deadline.

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.

Yes, there is a need for transitional provisions to be included in the implementing measure. Given the extent of changes in a number of provisions, especially those relating to PSURs and RMPs, MAHs will need some time to adapt the current formats to the new requirements. Hence, the implementing measure should establish a transition period (at least 6 months after coming into force) before the new PSUR and RMP formats are mandatory.

In addition, transitional provisions will be needed to allow for the use of PASS protocols, abstracts and final study reports produced prior to implementation of the proposed new formats: MAHs should not be required to reformat existing documents.

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

EFPIA generally agrees with the proposed format and content. However, we consider that the definitions cited in Annex 1 can be improved; our proposals are provided below.

In addition, clarification of requirements presented in the following paragraphs should be provided in the Good Vigilance Practice guideline:

- Paragraph 3.1: clarify that medically significant follow-up information should be transmitted to EudraVigilance;
- Paragraph 4(b): clarify what is meant by a 'comprehensive' English summary of the article;
- Paragraph 4(b): clarify possible copyright implications if MAHs are required to provide copies of relevant articles
- Paragraph 4(i): clarify whether the same extent and detail of information is expected for concomitant medicinal products, presumably <u>if available</u>;
- Paragraph 4(m): clarify whether or not a further report should be transmitted in the event that no additional information has been secured via follow-up, if only to confirm "no further information available".

<u>Definitions</u>

Annex 1 provides proposed definitions for 'misuse', 'medication error' and 'overdose'. While EFPIA recognises the challenges in formulating definitions for these terms, and acknowledge the issues in doing so, we have suggestions to make the distinction between medication error and misuse clear. In addition, we would value a definition of 'off-label use', as medically appropriate use of a product outside the terms of the SmPC is otherwise not addressed - it is not clear whether 'off-label use' is covered by 'misuse' or whether 'misuse' should be considered as part of 'off-label use' (important given that PSURs and Risk Management Plans require summarisation of 'off-label use' rather than 'misuse').

EFPIA suggests the following minor amendments to the proposed definitions and the addition of a definition of off-label-use, as presented below (changes underlined for ease of reference).

1. Definitions

For the purposes of this annex, the following definitions shall apply:

1. Adverse reaction reports include reports on noxious and unintended effects from the authorised use of a medicinal product but also from:

a) Use outside the terms of the marketing authorisation including <u>off-label use</u>, misuse and abuse. <u>Off-label use refers to the administration of an authorised medicinal product for use outside the conditions of the Summary of Product Characteristics (e.g. use for an unauthorised indication, in contraindicated circumstances, or in an unauthorised patient population), whether or not considered as medically appropriate.</u> Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or <u>(for OTC products)</u> authorised dose, route of administration and/or indication(s) or where a prescription only medicinal product was used without a prescription. Abuse refers to the sporadic or persistent, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

b) Medication error, which refers to inadvertent and inappropriate use of a medicinal product while in the control of the healthcare professional, patient, or consumer.

c) Overdose, which refers to the administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorised product information. This shall also take into account cumulative effects due to overdose.

d) Occupational exposure, which refers to the exposure to a medicinal product for human use as a result of one's occupation.

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

EFPIA generally agrees with the proposed format and content.

As regards the proposal for Part IV of the RMP, we suggest the term 'effectiveness' should be clarified. Does it refer to studies on the effectiveness of the medicinal product, or studies on the effectiveness of risk minimisation methods?

With respect to the RMP format on page 22 it would be more logical to present the "Additional EU Requirements" (module VII) before the "Identified or potential risks" (module VI), 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.

The final paragraph in section 1.2 (Format of the RMP; page 23 para 3) should be reworded, since it is not clear whether the publication on the websites refers to the RMP format or to the RMP itself. In the latter case, only the summary of the RMP is to be published on the authorities' websites, not the full RMP as might be implied by the current wording.

In addition, the final paragraph of section 1.2 seems to suggest that RMPs may have to be submitted twice and possibly in two different formats – in the eCTD, and electronically to national competent authorities or EMA. To avoid duplication and additional work, the format of the electronic version should be acceptable for inclusion in the eCTD. In cases where the MAH has submitted the electronic version in the eCTD, no separate submission should be required.

EFPIA suggests that the new template for RMPs should focus more on identifying and mitigating risk, with a more logical, efficient, and risk-focused structure. It is also desirable to see less repetition and duplication throughout the document, and a more thoughtful positioning of certain sections (e.g. risk of medication errors, off-label use, etc is currently located in section 1.9, after presentation of important and identified risks in section 1.5). Currently a single risk is discussed separately in multiple sections and separate tables, and it would be easier and less error prone for both author and reviewer if each risk and its associated minimization activities (if applicable), were only discussed once in detail.

In evaluating the effectiveness of risk minimization actions, it is important to recognize that surrogate measures of effectiveness should be acceptable, since direct measurement of effect on preventing risk realization may not be feasible.

We also recommend that the Good Vigilance Practice guideline specifies that partial updates to RMPs (one or more modules) should be possible, and that MAHs should be allowed a delay (e.g. 1-month) between a PSUR submission and the submission of the RMP update so as to capitalise on PSUR conclusions to set up or adjust risk minimization measures, while keeping the same PSUR data lock point.

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

As periodic safety update reports (PSURs) may also be submitted to regulatory authorities outside the EU, it is important that the format and content should be consistent with that agreed by ICH E2C (R2). Even though the timeline for finalisation of the ICH E2C (R2) guideline will occur after the implementation date of the pharmacovigilance legislation, alignment of this implementation measure should be co-ordinated with the ICH E2C (R2) outcome.

In this respect, EFPIA is concerned to see that certain concepts neither included in the legislation nor discussed or currently included in the draft E2C (R2) guideline have been introduced into the proposed implementation measure. In particular, section 1.1.3 introduces a new mandate for the estimation of patient exposure to be "*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"*.

This provision goes well beyond the requirements for patient exposure stipulated in the new pharmacovigilance legislation as regards PSURs and is not consistent with the current draft of the ICH E2C (R2) guideline. Furthermore, by requiring, without caveat, such analyses to be included in all PSURs, it may be implied that the provision is effectively mandating drug utilisation studies or other quantitative measures on all products when this is not necessarily warranted on a scientific basis. Moreover, the proposal does not have a legal basis and is inconsistent with the risk proportionality principle advocated in the pharmacovigilance legislation for these reports. As a result, EFPIA considers that this sentence should be removed from the proposed implementing measure, pending further discussion in ICH E2C (R2) Expert Working Group.

As regards section 1.1.5, we suggest that MAHs should be allowed an option to summarize cases, highlighting the information relevant to the signal or safety concern in question and allowing the most user friendly presentation of case narratives, rather than providing case narratives in full. We suggest that this section could be modified to: "Detailed listings of individual cases shall not be included routinely. Case narratives ~~shall~~ **may** however, be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR."

As regards section 1.1.6, clarification is needed concerning whether the expectation that a single PSUR shall be prepared for all medicinal products containing the same active ingredients will be applied to biological vaccine products as well as to drug products.

The proposed PSUR format (section 1.2 bullet #1) includes a 'Signature Page by the qualified person responsible for pharmacovigilance'. Such a requirement would mandate that QPPVs in all MAHs will have to review and approve all PSURs compiled by their companies which, for a number of large MAHs, will amount to in excess of a hundred reports each year. This would be an onerous task which would ultimately detract from the numerous other responsibilities of the QPPV. It should be noted that article 23(b) of Regulation 726/2004 does not stipulate QPPV signature of PSURs. Furthermore, many QPPVs may review and approve PSURs within an electronic document management system which does not necessarily include a signature page per se. It is important that QPPVs can demonstrate that they have appropriate oversight of the quality and content of PSURs but it should not be necessary for them to sign off on all PSURs compiled by their company. Appropriate input can be demonstrated either through direct input or through delegation to appropriately qualified staff.

In this context, we note that a current 'Question & Answer' document on the EMA website makes provision for the QPPV to *"delegate the task of preparation of the PSUR to an appropriately qualified and trained individual. That individual may sign the PSUR provided that there is a letter of delegation signed by the QPPV and attached to the PSUR cover letter"*.

Hence, EFPIA considers that this bullet point is either removed from the proposed implementing measure or changed to '*Signature Page*', to allow for some flexibility in how the signature is managed. We also recommend that the Good Vigilance Practice guideline clarifies that the QPPV needs to be able to demonstrate appropriate oversight of and input to PSURs either directly or through appropriately documented delegation.

The first paragraph of section 1.2 seems to suggest that PSURs may have to be submitted twice and possibly in two different formats – in the eCTD, and electronically to national competent authorities or EMA. To avoid duplication and additional work, the format of the electronic version should be acceptable for inclusion in the eCTD. In cases where the MAH has submitted the electronic version in the eCTD, no separate submission should be required.

As regards section 1.2.20 (Region-specific information), further clarification is needed regarding the contents of this section so that there are clear expectations by both MAHs and competent authorities concerning the information to be included in this section.

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

As regards the proposed format for a post-authorisation safety study (PASS) protocol, the content of a study protocol is more important than its format, therefore we suggest that Annex IV Section 2 be revised to "Format and Content of the study protocol", and that a paragraph

is inserted to allow MAHs and study researchers some flexibility in format, if required by the type of study to be conducted.

The format/content of the study protocol, abstract, and report should be modified to help the flow of the information. We recommend that several of the sections can be grouped into one section under "methods", which would include and follow the following order: study design, data source/setting, study population, exposure measurement, outcomes of interest, and covariates. In addition, the statistical analysis can include data transformation (if applicable), data analysis methods and sample size justification.

Some of the descriptions of sections are only applicable to field studies, not to electronic medical record or insurance claim database studies. While it is explained as such in some sections, it is not specified in a couple other sections.

Scope and definitions

4: Clarification is required as to which 'analytical dataset' this refers to. With the secondary use of data, and especially if repeated interim study reports are required, there may be several versions of the analytical dataset such that the dataset for the final study report may be several years after the datasets used for the interim reports. Hence, the 'end of data collection' should apply to the date at which the final dataset is available in support of the final study report.

6: As written, this indicates that any revised study protocols should be submitted 'immediately' to EMA. Article 107o of Directive 2001/83/EC, as amended by Directive 2010/84/EU, requires that "*any substantial amendments to the protocol shall be submitted, before their implementation*". We suggest that the implementing measure is reworded to be consistent with the Directive. For non-substantial amendments, it may be more appropriate to submit the revision at the next RMP update or as part of the PSUR in some circumstances, as per an agreement with the relevant competent authority.

8: Some studies may require interim reports. If so, we suggest that these should be submitted as per specific agreement with the EMA.

11: The EMA should open a public consultation before publishing the protocol template.

Format of the study protocol

6: This section indicates that the timelines for important steps of the study conduct should be presented. It is not clear what additional steps should be presented in addition to what is already specified above (start of data collection, end of data collection, etc.); we suggest either that this sentence is either deleted or amended to specify "*Timelines for any other important steps of the study conduct should be presented*."

9.2: For secondary database analyses, the impact on the number of subjects for analysis may not be known until analysis starts. We suggest that the impact of inclusion and exclusion criteria be described in the study report, not in the study protocol.

9.3: The selection criteria for study subjects should be presented in the section for study subjects e.g. data source/setting.

9.8 & 10: The implementation measure should specify that these sections are applicable only to studies that require primary data collection.

13: We question the value of providing details on the resources being required to conduct a study, in particular information on the personnel required, and suggest that this level of detail is unnecessary and should not be required. Alternatively, it could be included if available.

Format of the final study report

9.6: The bias is more appropriate to be put in the discussion section.

10.3: It is not relevant to put exposure in the section describing outcomes; we suggest putting exposure data in the exposure measurement section.