Submission of comments on the European Commission concept paper "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"

07 November, 2011

Comments from: F. Hoffmann – La Roche Ltd.

Executive Summary of Roche position

As part of the Commission´s implementation measures for the amended PharmacoVigilance legislation (cf. Regulation (EU) No 1235/2010 and Directive 2010/84/EU), F. Hoffmann - La Roche welcomes the publication of this concept paper describing the scope and content of the implementing measures.

Roche concurs with the Commission' s view that PharmacoVigilance activities are key in the context of public health protection but that the implementing measures to be introduced need to be optimally effective. Any unnecessary administrative burden on any of the stakeholders must be avoided. In the past we have repeatedly made the experience that, unnecessary administrative burden was caused by the accumulation of many small requirements. We would like to remind that any requested activity is likely to be performed at various levels and affecting numerous procedures in the companies Therefore we urge the Commission to critically assess whether each new requirement represents a true contribution to public health.

Within the concept paper, numerous content sections require definitions including the following:

- Quality systems
- PharmacoVigilance activities
- Resource management (for which activities)

Therefore this consultation document has been carefully constructed and aims to clarify some important issues. The key comments are summarised here and discussed in further detail below:

1. PharmacoVigilance System Master File

   The purpose of this file needs to be clearly stated to avoid inclusion of unnecessary data or having too divergent approaches by different marketing authorisation holders. The PSMF should serve as a tool to describe the overall marketing authorisation holder's

PharmacoVigilance system and the Quality System implemented to ensure compliance with Good Vigilance Practices. Currently, no information why particular pieces of information are being requested is provided. Prior to finalization, each of the requested items should be justified in order to generate a quality product / document and not impose any unnecessary burden on the stakeholders that need to address a specific requirement. In particular:

- **Contracts** should not be required to be included in the PSMF; or at least only a list of contracts covering certain delegated tasks; however clarification between delegated versus collaboration tasks is needed. Also, definitions for types of **delegated PharmacoVigilance tasks** that need to be included in the PSMF should be provided or reference should be made to the GVP guidelines the Agency will produce.
- It is unclear what benefit the **list of medicinal products** brings.
- Only date, scope of the audit and critical findings, and not **audit report** nor schedules, should be included in the PSMF.
- It should not be necessary to describe in detail where each activity in the PharmacoVigilance chain happens, nor the location of each database and/or server. In larger organisations, these activities can be based anywhere on the globe and can shift easily from one location to another.

2. Quality System

Roche welcomes the clarifications brought in this sections and this should lead to more standardisation across industry and regulators leading to consistent approaches in audits and inspections.

3. Signal Detection

- Throughout the document, different **terminology** is used: signal, risk, safety issue, signal detection, data mining etc. It is imperative that the terminology is used consistently throughout. Clarifications on the definitions of signals, risks, safety issues and signal detection as well as processes on signal management are needed. Roche recommends using the terminology and methodology described in the EudraVigilance Expert Working Group Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System, 2008, be used. Or will this Guideline be updated?
- **Communication**
  Guidance should be provided on how the EMA/NRA will communicate their findings to the marketing authorisation holder and the public and the timing of such communications as well as on how marketing authorisation holder should communicate to EMA/NRA but also to the prescribers and the patients
- **Access** to data
  It is important to include provisions that EMA/NRA are being transparent to the marketing authorisation holder on what data they have

based their signals in order for the marketing authorisation holder to reproduce the data as appropriate.

- Although the concept of **work-sharing** is being supported, a transparent process for assigning rapporteur and co-rapporteur (for peer review) is required. Furthermore, clarification is needed on whether the marketing authorisation holder would have the possibility to appeal to the rapporteur(s) opinion(s).
- It would be desirable for the PRAC to perform regular review of the **methodology** used only for signal detection in the EudraVigilance database and publish recommendations as appropriate. However, it should be considered that there are several methodologies in PharmacoVigilance and that this field is evolving. Accordingly, focusing on the principle is more relevant than supplying specifics around the methodology

4. Annex II – Risk Management Plans

Roche considers identifying or characterising the safety profile of the medicinal product concerned & describing how the safety profile will be assessed and monitored to be routine PharmacoVigilance activities which should happen for all products. The process should be documented in the Quality System, while the results/outputs of this should be documented in the audit trail, in the PSUR and should be visible to the public in the label and PIL.

The focus of the RMP should be to document a plan for data gathering for important identified/potential risks as well as important missing information in order to better characterise these risks, to identify risk factors, to allow amending the risk minimisation activities for these important risks. The second purpose of the RMP should be to document why and how certain important risks will be mitigated or minimised.

The RMP should not be a ‘laundry’ list of adverse drug reactions which are adequately described in the product information and for which no specific risk minimisation is needed, a definition for ‘important’ is needed

Specific comments			
	Section of concept paper	**Box/General**	**Comment**
	General		• A Transition period for implementing measures is needed [e.g. to new Risk Management Plan (RMP) format]. • More detailed guidance regarding the format and content of Annex II (RMP) and III (PSUR) is needed. • Marketing authorisation holders might profit from clearer requirements on collection of non-interventional programs (e.g., market research programs, patient support programs) at this level. Legal requirement would help PharmacoVigilance personnel in Europe to explain requirements to US colleagues when it comes to the collection of non-serious AEs from these programs. Collection and submission requirements need to be clarified for spontaneous, solicited, studies, patients support programs, consumer cases (follow-up needed for medical confirmation?)
A	PharmacoVigilance system master file	**Consultation item no. 1: Should additional processes and PharmacoVigilance tasks be covered?**	The list of tasks and processes reflect Roche's internal PharmacoVigilance (PV) system with 4 core processes [Individual Case Safety Reports (ICSR) and aggregate reporting, integrated signal detection, integrated safety risk management and comparative benefit/risk]; Communication is of equal importance. Therefore, Roche considers the proposed list to be adequate.

		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 be no longer subject to variation obligations.**	This step taken by the Commission leads to an increased efficiency on the part of marketing authorisation holders and is highly appreciated. We therefore agree that the changes to the content of the PharmacoVigilance system master file (PSMF) should no longer be subject to variation obligations as the PSMF is no longer included in the marketing authorisation (MA) dossier. However, if the EC would decide to require such notification, a list of what would be considered a significant change should be published to guide the marketing authorisation holders. Further comments: • The frequency of mandatory updates should be specified as well as triggers for such update such as continuously updating the PSMF is putting an unnecessary burden on the marketing authorisation holder. The PSMF should be a document that contains data that does not need continuous updates (therefore, should not contain contracts or a list of medicinal products) and should be updated regularly (e.g. six-monthly or yearly with additional triggers to be identified). • Please provide a definition for: o audit trail o main outputs of the PharmacoVigilance system (e.g. ICSR, PSUR, PASS study reports, Responses to questions from regulatory authorities, signal detection outputs) • It should be made clear that the PSMF is valid throughout the EU and that no local versions should be requested by NRAs.

		Consultation item no. 2 cont'd: 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?	Considering that the legislation requires the marketing authorisation holder (marketing authorisation holder) to make available the PSMF upon request (and within seven days), we do not consider a notification system appropriate. (Art. 104 3b). Significant modifications require definition.
		Consultation item no. 2 cont'd: Should the master file contain a date when it was last reviewed?	We agree that this is part of good record keeping practice (version control, QPPV approval, change history in logbook). The PSMF should contain information when it was last reviewed by the marketing authorisation holder.
		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.**	Roche agrees that marketing authorisation holders need to have the oversight of delegated PharmacoVigilance activities, but does not believe that such contract should be part of the PSMF as the added value of contracts / agreements within the PSMF is questionable, moreover these need continuous updates. Instead a list of vendors/outsourced activities would be considered appropriate, the contracts itself can be made available upon request. Details of delegation should be clearly documented in a PharmacoVigilance Agreement (PVA). Co-promotions and co-marketing arrangements have should have a PVA in which detailed responsibilities are included. In addition, guidance is needed on definitions for types of delegated PharmacoVigilance tasks that need to be included in the PSMF. This would help marketing authorisation holders to include references to appropriate contracts in PSMF. In particular, information is needed on what types of tasks are generally delegated and which of these should be routinely covered in the PSMF and which ones not. (e.g. GCP and PV audits, medical writing).

			Examples of PharmacoVigilance tasks that should be covered: collaborations where one company/vendor would be fully responsible for the PharmacoVigilance system in a defined territory. These activities would be covered in a PVA Examples of PharmacoVigilance tasks that should not be part of the PSMF: vendor used for medical information as these agreements are usually local, country-specific agreements.
		Consultation item no. 4: **Should a copy of the audit report be retained in the master file?**	Reports from company performed internal audits are confidential internal documents and are not shared with external stakeholders. This concept of confidential audit reports has also been applied in other areas (e.g. Good Manufacturing Practice), where only the date and the overall outcome of audit reports are shared with authorities (cf. Directive 2011/62/EU, revised Article 8 (3) point (ha)). Consequently, we recommend that only the main findings of the company performed audits are included in the PSMF and not the whole audit report. This would also be in line with internationally agreed ICH GCP requirements. According to those, the audit certificate is retained in the trial master file as the evidence of audit conduct. A systematic inclusion of the audit report in the PSMF could be detrimental to internal transparency and reporting of audit outcomes which should ultimately be avoided.

		Consultation item no. 4 cont'd: Would it be appropriate to require documentation of audit schedules?	We do not support the inclusion of audit schedules in the PSMF, as these are subject to change and therefore very difficult to maintain in the PSMF. We consider the conclusion of the main findings is sufficient. As a further comment, we consider it important that a definition is provided for 'main' finding. Current terminology includes critical, major and minor/other findings. As critical findings can potentially have an impact on patient safety, our proposal is to include critical findings. In addition, we think it would be useful to have some guidance on responsibilities and requirements of licensing/co-marketing partners with respect to audits. In conclusion, concerning the placing of the note we propose to include the date, the scope of the audit and only critical findings.
		Consultation item no. 5: **Overall, do you agree with the requirements as regards the content and maintenance of the PharmacoVigilance system master file? Please comment.**	General Comments: We agree in general with the detailed concept for the PSMF as outlined by the Commission. However, we would like to highlight that the PSMF is a detailed description of the PharmacoVigilance system. Therefore, we recommend not including specific documents (e.g. contracts) into the PSMF but – where needed - references to their physical location.
		Concerning 3. *Content* (1):	The PharmacoVigilance System Master File should not have to contain a list of all medicinal products. Such a requirement would represent duplication as marketing authorisation holders have already been requested to register all products in the product dictionary database (EVMPD).
		Content (4), Page 6 (Description of organizational structure of marketing authorisation holder)	It should not be necessary for large marketing authorisation holders to have to describe for each and every topic separately where this particular activity is being conducted. A globally

			operating enterprise may shift such responsibility and the burden of continuously updating this information may be larger than the resulting benefit. Alternatively, a relatively large granularity as regards the provision of this information should be accepted by EMA.
		Content (5), Page 6 (Information around system and databases including safety information)	Functionality details should be described in broad terms.
		Content (6)/(7), Page 6 (Description of process, data handling and record management for the fulfilment of PharmacoVigilance/description of quality system for performance of PharmacoVigilance activities)	There appears to be an overlap between aspects of items number (6) and (7) as in the former, the question for processes is asked in the latter; the question for quality systems is being asked. However, processes and their description is an integral part of a quality system.
		Content (7) (d), Page 7 (Description of quality system for documentation arrangements and relation of records.	The need for information within the PSMF and the administrative burden to maintain it needs to be balanced. Only key expectations should be specified. For example, documentation of location of "any records" is considered too far reaching.
		Content (7) (e), Page 7 (Description of quality system for reference to location of audit trails)	It is unclear what is meant by the term "reference to the location of audit trails" in the context of item number (e).
B	Quality systems for the performance of PharmacoVigilance activities – common obligations	General	**11. Performance indicators** We are highly supportive of EMA to make public a list of performance indicators.
C	Quality Systems for the performance of PharmacoVigilance activities by marketing authorisation holders	General	
		Consultation item no. 6: **Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p**	As there is a legal obligation to submit the final study report of non-interventional post-authorisation safety studies (PASS) within 12 months after the end of data collection; we support additional procedures to ensure compliance with this legal requirement.

		of the Directive…..	
		Consultation item no. 6 cont'd: **…….in relation to communication on PharmacoVigilance between the marketing authorisation holder and patients/health professionals**	Since it is unclear what is specifically meant by the broad term "communication", it is necessary to provide a definition on what is actually covered e.g. summary of product characteristics (SmPC), patient leaflet (PIL), Dear Healthcare Professional Letter (DHCP), or press release, etc. Depending on what is covered, we would support additional quality procedures, both for competent authorities and marketing authorisation holders to ensure that procedures are reliable. It will certainly help to manage expectations, both from regulators and from the public.
		Consultation item no. 6 cont'd: **…….in relation to processes for taking corrective and improvement actions**	In principle, yes
		Consultation item no. 6 cont'd: **……or in relation to the detection of duplicates of suspected adverse reaction reports in the EudraVigilance database?**	Roche is in favour of additional quality procedures to cover the process of duplication detection for both marketing authorisation holders and competent authorities, as soon as the EudraVigilance database becomes the single reporting database in Europe. The level of detail and scope will depend on the level of access the marketing authorisation holder will get to perform such activities.
		Consultation item no. 7: **Do you agree with the requirements for marketing authorisation holders? Please comment.**	**Retention time for documents** The legislator has decided not to specify in legislation the retention time for PharmacoVigilance system related documents. While we understand the need to retain certain high level documentation (PSMF) for a defined timeframe after the cessation of the marketing authorisation, we disagree with the similar retention

			time for case-specific documentation (each ADR/ patient documentation). We understand the need for 30 years retention time has been defined only for a highly sensitive area, namely the donation of blood and blood products with a high risk potential for infections (Directive 2002/98/EC, Article 14). We do not consider that a 1:1 transfer of such provisions from “HaemoVigilance” to “PharmacoVigilance” is justified and appropriate. **Location of records in PSMF** The added benefit of requesting information on the location of records into the Master File is unclear. For selected key records, we suggest to specify (i.e. the location for such records could be specified in the PharmacoVigilance Systems Master File). To apply this requirement for “all” records may not be value adding and impose unnecessary administrative burden. Resource Management (13) Suggest either deleting the word adequate or providing guidance what would be considered adequate. Critical processes need to be defined. Compliance management (14) Definition needed for PharmacoVigilance data; also what does monitoring mean (signal detection, safety management, risk management?)? Para (d) Should the marketing authorisation holder monitor also NRA websites? What would be the purpose of this provision?

			Record management (15) It should be indicated that both electronic and hard-copy systems are allowed but not that both are needed at the same time
D	Quality systems for the performance of PharmacoVigilance activities by national competent authorities and EMA	General	
		Consultation item no. 8: **Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA.**	Overall, we support the section on the quality system (QS) requirements. The PRAC should elaborate common standards for inspection which can be used as a basis for quality systems for Member States inspectorates. For inspections, it needs to be ensured that standards are applied and interpreted consistently by different stakeholders / Competent Authorities to avoid conflicting messages and to allow marketing authorisation holder Quality Systems to develop into one agreed direction. While companies are subject to inspections for their quality system (QS), currently competent authorities of the Member States and the EMA are not subject to independent external assessment of their quality system. We would suggest that the QS of all competent authorities and the EMA be certified by an independent accredited external party in order to ensure the good performance of the system. Alternatively, a peer review system between authorities could be installed.
E	Signal detection and risk identification	General	Signal detection vs. data mining: The term “signal detection” includes activities other than disproportionality analysis, such as the detection of signals based on review of line listings or literature. It would be beneficial to define the terms and to use them through the document consistently to convey the understanding when signal detection in general or data mining in particular is meant.

			Point for consideration could be the use of terminology and methodology described in the EudraVigilance Expert Working Group Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System, 2008.
		20. general, 1st alinea (page 13)	How will EMA and national authorities communicate with the marketing authorisation holder regarding their findings from monitoring the database?
		20. general, 2nd alinea (page 13)	The first sentence states that the marketing authorisation holder shall monitor to the extent possible the EudraVigilance database. It would be appreciated if we could understand which data will be accessible, and if the marketing authorisation holder can only review the data for a given product or if data mining in EudraVigilance by the marketing authorisation holder will be possible Data mining: Ideally the marketing authorisation holder would be able to do data mining in EudraVigilance and can chose the method and define the background population for the calculation of disproportionality, e.g. all products, vs. specific indications, vs. a drug class. Hopefully this can be accomplished without providing access to detailed data of other marketing authorisation holders' AE reports. When EMA/RAs communicate the results of signal detection to the marketing authorisation holder, the methodology applied should be communicated with the results, in sufficient detail to allow the marketing authorisation holder to reproduce the results. In case EMA/RAs preform data mining in EudraVigilance and the

			marketing authorisation holder only can do data mining in the marketing authorisation holder's or other databases, how will discrepancies in case counts be reconciled? Single case level: If the marketing authorisation holder will be able to see single case information for the marketing authorisation holder's products, the marketing authorisation holder's accountability to reconcile the marketing authorisation holder safety database against EudraVigilance needs to be clarified.
		21. Changed risks/new risks (page 13)	If a drug is listed for signal detection, will the EMA share with the marketing authorisation holder the methodology applied? Will the marketing authorisation holder have access to the signal detection analysis of the EMA/RA?
		22. Methodogy (page 22)	Overall we agree with the concept. It should be considered to add that the data need to be seen in context with the underlying disease, typical co-medications, and comorbidities as well. For signals with low incidence but high medical significance like Stevens-Johnson Syndrome, the methodology may be amended to address detection of these medical significant events early. Overall, it should be considered that there are several methodologies in PharmacoVigilance and the field is evolving. Accordingly, focusing on the principle is more relevant than supplying specifics around the methodology.
		23. Signal management procedure	Will the EMA communicate signals (including the methodology applied) to the marketing authorisation holder, to allow the marketing authorisation holder getting involved in the signal validation?

		24. Work sharing of signal management (page 14)	We understand that the work sharing will apply to EMA and regulatory authorities. Within the current description it is not clear, when the marketing authorisation holder will be informed and how and when the marketing authorisation holder will get involved. See also comment to consultation item no.9
		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 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)?**	We welcome the idea of work-sharing, as this would hopefully simplify the procedures by having one point of contact for dossier submission and assessment. The concept of peer review would not necessarily be lost as the PRAC has members from all Member States and the EMA´s Committee for Medicinal Products for Human Use (CHMP) provides the opinion. Additionally, there should be a transparent procedure ensuring a control mechanism by a co-rapporteur as well as for escalation if required. It would be important to clearly define roles and responsibilities. In addition, it would be good to understand when a communication with the marketing authorisation holder on signals will start, if the methodology generating the signal will be shared, and how the marketing authorisation holder will get involved in contributing to the signal validation and assessment.
		Consultation item no. 9 cont'd: **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.**	Additional comments related to the appointment of the rapporteur: a transparent process on how a Member State is appointed as rapporteur should be provided. However, it needs to be clarified as to whether this would automatically be linked to the MA assessment rapporteur or whether the marketing authorisation holder would have the right to appeal against the appointment of a certain rapporteur.

		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.**	Access to the EudraVigilance database remains a difficult issue: what level of access is needed to fulfil the requirements as set forth in the (legislative) text (Art. 24(2) paragraph 5) of the Regulation? The PRAC shall perform a regular review of the methodology to be used for signal detection in the EudraVigilance (EV) database only. If not, this should not be prescriptive as there are different methodologies with each methodology having its own merits in certain situations. It would be difficult to have common recommendations as the data sources may be different (different levels of access to the EV database, different company safety databases, different characteristics of these databases depending on the size of the company, the type of portfolio, etc). It would be better to share the methodologies used by each of the stakeholders involved. In general, this section needs more clarification, particularly regarding definitions on signals and signal detection and data mining. Furthermore, processes on signal management need to be clarified. Audit trails for signal activities require further definition. A specific procedure for how marketing authorisation holders are to retrieve signals from EudraVigilance is necessary. Further specifications for how to submit signals is required. What is currently not addressed in this concept paper is the process for risk communication to the public. Is it intended to follow the established processes, or is there any intention to publish reports, like e.g. during the influenza pandemic by EMA and MHRA on signal detection, on dedicated EMA or RA webpages. In case of

			the latter, it would be highly appreciated if the marketing authorisation holder would be informed prior to publication and would have the possibility to investigate and provide input/data analysis or background data if required, unless there is a public heath impact requiring immediate action. Communication of risks to the public must be balanced in such a way that the risk reduction from communicating the signal is not outweighed by the benefit reduction from discouraging appropriate use of the product.
F	Use of terminology	General	
		Consultation item no. 11: **Do you agree with the proposed terminology? Please comment.**	Overall yes
		Consultation item no. 12: **Do you agree with the list of internationally agreed formats and standards? Please comment.**	Overall yes. However, please find suggestions for improvement below.
G	Transmission and Submission requirements – Annex I + general (p.18)	General	
		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.**	There is a perceived need to have additional transitional provisions for these topics. Guidance on the implementation of the new requirements would be welcomed; especially the RMPs and Periodic Safety Update Reports (PSURs). Also, further clarification needs to be provided on transition to the new format of the RMP (e.g. current RMPs are in the template of the current requirements as outlined in volume 9a). Is the new template to be used immediately, only with updates, or only upon specific request from the PRAC?
		Consultation item no. 14:	Overall yes. However, please find a suggestion for improvement

		Do you agree with the proposed format and content? Please comment.	below.
		Annex I.1.1.(a), pagepage.19	Instead of using the word misuse, we recommend to use the current MEDRA term: “intentional drug misuse”. Using this term will allow following the additional information provided by this term to set up the coding rules. Same for abuse, we recommend changing to “drug abuse”.
		Annex I.1.1. (c), pagepage. 19	For overdose, the meaning may be clarified in the RMP, so that the marketing authorisation holder and the EMA/CAs can agree on what would constitute for an overdose for a products, or the term may be revised to unintentional overdose, however this would come closer to medication error.
		Annex I.1.4. (o), last sentence, page. 21	The narrative should conclude with a statement if follow-up information is sought or if it is confirmed that no further information is available.
G	Transmission and Submission requirements – Annex II	General	
		Consultation item no. 15: **Do you agree with the proposed format and content? Please comment.**	In general, yes. However, more detail and guidance would be needed around section VI of the RMP (summary for public), e.g. who is responsible, what will be the format, what will be the content, what language should be used, will it be tested, etc. The current terminology appears in the penultimate paragraph of section 1.2., without further definition. A similar sentence as for PSURs should be included here: EMA may publish appropriate (annotated) templates on the individual modules.
G	Transmission and Submission requirements – Annex III	General	
		Consultation item no. 16: **Do you agree with the proposed format and content? Please comment.**	In general, yes. However, there is insufficient guidance presented to make a full impact assessment for some of the proposed sections of the PSUR. Notably, defining which trials should be considered when estimating clinical trial exposure and when preparing cumulative tables of Serious Adverse

			Events (SAEs) from clinical sources. For example, it is not clear how these data relate to the current Development Safety Update Report (DSUR) definitions. • Section 9 'Other Clinical Trial/Study Information' is ambiguous and needs further explanation • Expansion of the depth of information in Section 10 'Non-clinical data' is required • The specific criteria in Section 12 'Other Periodic Reports' should be provided. For example, does this refer to documents prepared by the marketing authorisation holder, other parties using the same IMP or both? • Section 13 'Lack of Efficacy in Controlled Clinical Trials' is ambiguous – which trials are being referenced? How does this relate to the current DSUR section regarding lack of efficacy and what are the data presentation requirements (overall summary, case level descriptions)? • Section 15 may be best embedded in Section 16 (i.e. within 16.2 'Signal evaluation) rather than as a standalone section. The effectiveness of risk minimisation is a worthy inclusion and appropriate guidance for this section would be welcomed. • Also threshold for inclusion of signals needs to be determined • Section 17 'Benefit Evaluation' is a significant and worthy expansion to the PSUR format and guidance for the marketing authorisation holder and its content should be elaborated.
G	Transmission and Submission requirements – Annex IV	General	
		Consultation item no. 17: **Do you agree with the proposed format?** **Please comment.**	In general yes, however please find below some suggestions for improvements (all marked in yellow).
		Scope and Definitions page 27 1. "This annex applies to non-interventional post-authorisation safety studies"	A clear definition of non-interventional post-authorization safety studies would be required. Sometimes a pilot study is necessary to understand of the overall

		study feasibility (not limited to the test of instrument as indicated in the context) before moving forward to the full study. How should a pilot study be incorporated to the current format of proposal?
	1. Scope and Definitions page 27 4. 'End of data collection' means the date at which the analytical dataset is first available	We would suggest adding –**complete**- the date at which the complete analytical dataset is first available
	1. Scope and Definitions page 27 7. The study protocol shall follow the format included in point 2 of this annex.	Should it be mentioned that this applies only to the new protocols?
	2. Format of the study protocol page 27-30	It should be also recognized and indicated somewhere that not all the specific points mentioned in this proposal could fit into all different study designs
	2. Format of the study protocol page 27-30 3. Responsible parties:	All the information listed should go on the protocol? (Investigators, co-investigators, study sites)?
	2. Format of the study protocol page 27-30 7-8. Rationale and background – Research questions and objectives	If applicable, study results from previously conducted pilot study may be presented between “7” and “8”
	2. Format of the study protocol page 27-30 9.2 Setting: *“the rationale for any inclusion and exclusion criteria ad their impact on the number of subjects available for analysis should be described”,*	This statement seems to more fit in to the “point 4, format of the final report” (may be addressed in combination with sensitivity analysis), as in many occasions, this may not be addressed until the data is collected and analyzed. 9.9. Limitations of the research methods: Any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias (e.g., patients selection bias), generalisability, and random error known before start of the study.

	2. Format of the study protocol page 27-30 9.9:Limitations of the research	We would recommend to add the words shown in **bold**: Any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias **(e.g., patients selection bias),** generalisability, and random error **known before start of the study.** Suggest adding "strengths" in addition to limitations, it is also important to state the strength of current study design
	4. Format of the final study report *9.6 Bias*	We would recommend to add the words shown in **bold**: Any efforts to assess and address potential sources of bias **known before start of the study (see 2/9.9) and those which appeared during the study** (the same also for discussion 4/11.2)
	4. Format of the final study report *11.2 Limitations*	Same as before, we suggest adding: limitations **known before start of the study.**