NOVARTIS

SUBMISSION OF COMMENTS ON DRAFT EC PUBLIC CONSULTATION DOCUMENT: Implementing Measures in Order to Harmonise the Performance of the Pharmacovigilance Activities Provided for in the Directive 2001/83/EC and Regulation (EC) No 726/2004

COMMENTS FROM NOVARTIS PHARMACEUTICALS.
GENERAL COMMENTS
Paraphrased questions from the consultation document appear in this font for reviewer convenience.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Consult item #	**Comment and Rationale**	**Proposed change (if applicable)**
The Pharmacovigilance System Master File		
1 (pg 6)	**Should additional process be added to the content of the PV system master file?** We do not see a need for additional processes to be covered. However, we have a number of specific comments on this chapter. Section 3.1: We note that there is no INN for homeopathic formulations. The specified requirement (Section *3. Content*) creates a duplication of work and potential burden for marketing authorisation holders. The required information is quite extensive and will already be compiled in an electronic format in the EudraVigilance database per article 57(2), second sub-paragraph, of Regulation 1235/2010.	3.1 Please add appropriate exclusionary language for regulated products that do not have an INN. 3.6: Please consider limiting the requirement to a list of SOPs. We would propose limiting this document requirement to the list of medicinal products relevant for this pharmacovigilance master file including their invented names and INN.

2 (pg 7)	**With variation filings no longer required for updating the PV system master file, would it nevertheless be appropriate to notify significant changes to the competent authorities?** We agree provided the definition of "significant change" is limited in scope.	We propose restricting these notifications to changes in the MAH's designated QPPV or Deputy QPPV. All other changes should be sent to regulators twice annually and should not be considered formal variations.
3 (pg 8)	**Is it necessary to be more precise regarding delegation of certain task in the PV system master file to third parties, e.g. licensing and co-marketing partners?** We believe it is not necessary to be more precise in describing potential delegation to third parties, as these details are covered at length in the individual pharmacovigilance agreements between partner companies. To preserve the master file as a concise, user-friendly document, and to protect proprietary commercial information, we recommend inserting a list of all agreements in the master file. Individual contracts could be redacted of confidential information and produced upon health authority request. However, should regulators seek to mandate the inclusion of additional details regarding delegations, we feel there are several crucial elements of the requirement that need further clarification within the Good Vigilance Practice Guidance. • Must they include all activities performed by third parties in which an adverse event could conceivably reported, e.g. medical inquiries, patient support programs, sales calls? • Should they pertain only to activities performed in or on behalf of the EU or to those performed anywhere in the world? • Is it necessary to include copies of all signed agreements with third parties as part of the master file or will a consolidated list suffice? For a multi-national company, global and local agreements may number in the hundreds and may contain proprietary commercial information?	If inclusion of additional details regarding delegation are to be made mandatory, please clarify the scope of activities to be included in the master file. Also, please clarify the geographic territories to which the requirements apply.
4 (pg 8)	**Should copies of MAH audit reports and audit schedules be part**	Although we disagree with the requirement, we recognize that it may be

	of the master file? We believe that audit findings should not be included in the master file. Sponsors audits are an important aspect of continuous improvement. An internal audit needs to take place in a proprietary setting.	enacted in some form. In that event, we propose that the requirement to list "main findings" be amended to read "critical or major findings", both of which have established legal definitions.
5 (pg 8)	**Overall, do we agree with the requirements for content and maintenance of the master file?** We agree with the requirements with the exception of those caveats listed in the previous sections and the following	Not applicable.
6 (pg. 11)	**Is there a need for additional quality procedures in the document?** We do not believe there is a need for additional procedures at this time. However, we wish to raise an issue concerning text in Section 14.a, which immediately precedes the question posed to stakeholders for Consult Item 6. With respect to the requirements for MAH follow-up with reporters, it is not clear if the text refers to adequate follow-up of individual adverse events or to signal detection findings.	Not applicable. We request clarification of the scope of this requirement in the implementing measures or GVP guidance.
7 (pg. 11)	**Overall, do we agree with the requirements for quality systems?** In general we agree with the requirements. However, we believe that further clarification in scope and expectations is needed on the following points concerning Section 10 (*Audit*): The content and the location of the of the master file seems reasonable. It is not fully evident which types of quality system audits the document is intended to cover. Also, the expectations for the two-year audit cycle need further distinction.	We suggest the inclusion of hyperlinks to or references to the points where supporting information is stored (rather than having to create lists or duplicate files/records). A risk-based system would enable sponsors and regulators to better focus their resources on areas where systems need to be strengthened or where they face greater exposure to potential weaknesses, and is preferable to applying the same degree of oversight to all systems.We assume that 1) the types of audits to which this section pertains (i.e., provide a regulatory definition of "quality system") and; 2) the scope of the two-year audit cycle requirement will be described within the implementing measures or GVP guidance.
8 (pg. 13)	**Do we agree with the quality system requirements?** We agree in principle with the standards. We have several recommendations concerning national authorities and the EMA.	We encourage central and national regulators to develop a system that will address the current burden on sponsors created by multiple, overlapping inspections where questions are asked in duplicate. We also advocate a standardized approach to inspector training, oversight of consistency in

		inspection practices, standards, findings, and issue resolution.
9 (pg. 15)	**With respect to HA work sharing for signal detection and risk identification, do we see a risk for cumulating tasks (e.g. authorisation, PSUR scrutiny, EudraVigilance monitoring) to be done in a single Member State?** We agree in principle with regulator work sharing for signal detection and risk identification	We recommend extending the work sharing procedure to all medicinal products approved in more than one EEA country, with a lead Member State appointed in addition to the EMA. It would be prudent to name a rapporteur and co-rapporteur to achieve balance. We envisage that this will be driven by the organizational structure of the PRAC and the competencies of individual experts representing Member States on the PRAC.
10 (pg. 15)	**Are the proposed revisions for signal detection clear or should they be more detailed?** The proposed revisions lend an increased degree of clarity to the process. We believe there are elements for which transparency could be improved. We note that some areas of responsibility may necessitate a considerable amount of lead time for sponsors to adapt their policies, workflows, data systems and to identify appropriate resources.	We recommend that the following areas be addressed within the implementing measures or GVP guidance to further clarify requirements for MAHs: • In general, specific details on the timeframes, search parameters, statistical methodologies. Communication processes and other criteria for signal detection in EudraVigilance, including use of the EMA signal tracking system. • Description of how the PRAC committee will synchronize medical event terms with those of the sponsor (section 21) • Clarification on the level of public access to the signal tracking tool (if any) and description of how sponsors will be notified of signal resolution (section 23). • The specific mechanism for informing MAHs in advance of the PRAC discussion when EMA detects a signal.
11 (pg. 16)	**Do we agree with the proposed terminology?** We agree in principle with the terminology.	Implementation of these standards into national labelling (assuming they will need to be used in these documents) will require a phased approach synchronized to other planned or ad hoc labelling updates in order to manage the resource burden on MAHs. We request that the implementing measures or GVP guidance specify that these standards can be phased in simultaneously with other planned or ad hoc labelling changes provided they are done in a reasonable timeframe.
12 (pg. 18)	**Do we agree with the list of international formats and standards?** We agree with the standards and formats with the exception of item	We are committed to working with the Agency through EFPIA to determine the minimal data fields necessary for compliance with Article 57(2) of Regulation EC No. 726/2004.

	(a) concerning the extensive scope of data requirements for the EudraVigilance Medicinal Product Report Message.	
13 (pg. 18)	**Is there a need for transitional provisions for transmission and submission requirements?** We believe there is no need for additional requirements.	Significant clarifications for some topics, such as RMPs and PSURs, are needed in the Good Vigilance Practice guidance to enable MAHs to update their internal processes and make an optimal transition to the new regulatory formats.
14 (pg. 21)	**Do we agree with the proposed format for electronic ADR transmissions?** We agree in principle with the caveats listed in the Proposed Change column.	We request the following changes and thae provision of clarification as below: Section 1.2: The definition of an incomplete case should be included. Section 3.4.g: Reference to interacting products should be expanded to include, for example, food, alcohol, tobacco, supplements and homeopathic remedies. Section 3.4.h: Expiry date should be included for biologics. Section 4.b: Clarify what is meant by a "comprehensive" English summary of a literature article (would an English abstract be adequate?). Section 4.i: Clarify if the same level of detail is expected for information regarding concomitant products.
15 (pg. 23)	**Do we agree with the proposed format for Risk Management Plans?** The lack of detail concerning RMP content and responsibilities prohibit us from fully agreeing with the proposed format.	We request that the Agency address in the implementing measures or GVP guidance. detail concerning RMP format, content, responsibilities, transitioning, versioning and publication. Such detail is critical for the standards to be applied consistently and for MAHs to have confidence in developing a core RMP template, especially if work sharing is implemented. Content issues need to be clarified for multi-ingredient drugs. We have had divergent feedback from Member States concerning the need for a combination product RMP vs. separate plans for the individual ingredients. A clear definition of when an RMP is legally deemed a new submission is required to enable appropriate versioning, as draft RMPs are often negotiated between MAHs and regulators and are often amended before final approval. The current approach is inconsistent and should be

		harmonized. We request verification that summary, rather than full-text, RMPs will be published on regulator websites.
16 (pg. 26)	**Do we agree with the proposed format for electronic PSURs?** We request that the proposed format, is fully aligned with the format being developed by the ICH E2C R2 Expert Working Group.	Implementation of standards should be fully aligned with ICH guidelines and implementation timetables. We believe that the QPPV should not be required to sign off on the efficacy component of a PSUR and ask for verification that multiple signatures are allowed for the document or evidence of review by QPPV.
17 (pg. 34)	**Do we agree with the proposed format for PASS protocols, abstracts and final study reports?** 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 "Content of the study protocol", thereby allowing MAHs and study researchers some flexibility in format. Many PASS studies do not have a principle investigator.	We request amendment of the text to address the situations where there is no principle investigator for PASS.