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Brussels, November 7, 2011

Re : PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance

Dear Madam, Sir,

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important biopharmaceutical products available today.

Merck has reviewed the above referenced document and is providing the following comments for your consideration.
As the Regulatory system gains experience during the next years with the full implementation of the new provisions, we recommend keeping the implementing legislative text at fairly high level and provide full details in the forthcoming Good Pharmacovigilance Practice (GVP) guidance to enable flexibility for necessary adaptations.

We appreciate the opportunity to comment on this document and hope that you will take our comments into consideration. Should you need additional information or wish to hold further discussions with our company experts, do not hesitate to contact me.

Yours sincerely,

A. Joos

Angelika Joos
Encl.

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

A. Pharmacovigilance system master file

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?
Merck believes this list is complete.

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. 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?
The Marketing Authorisation Holder should only need to notify the Regulatory Authorities of significant changes to the master file as per Article 23 of Directive 2001/83 i.e. for a change of EUQPPV.
This should be done by notification letter or template without any further administrative process.
The master file should contain a date of last revision and approval by the EUQPPV.

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.
Yes, a summary of the delegation agreement with the co-marketing partner or vendor should be included in the masterfile. The details will be available in the individual contracts.

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?
Merck sees no added benefit in including the entire audit report. This report would include items which are not main findings and confounds the issue of removing items from the file once resolved. The 'main findings' from each audit need to be documented as a 'note' and as such enough detail is available in the PV masterfile. A clarification as to what constitutes 'main findings' is needed in the implementing guidance.

Merck believes that it is appropriate to include the audit schedules indicating completed and planned audits.

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.
Yes, we endorse the concept as it reduces regulatory burden for cumbersome notifications through variations and centralises information. The concept will also facilitate harmonisation and simplification, assuming there will be no expectation from individual competent authorities to include detailed country level information as per the pre-inspection 'Specification of Pharmacovigilance System'.

Other comments related to section A

Please clarify what is meant by the term ‘resource management’ (ref. Content of master file 7(b))

B. Quality systems for the performance of pharmacovigilance activities – Common obligations

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

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?
Merck does not feel there is a need for additional quality procedures in the implementing legislative texts. We would however request inclusion of further clarification in subsequent Guidance.

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

D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

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.
Merck agrees.
Merck believes that the audit program (page 9, C 10) should be structured by the holder utilizing a risk based approach. The various elements of the system would be assessed for potential regulatory and patient safety risk and the audit frequency would commensurate with that risk.

E. Signal detection and risk identification

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)?
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.
Merck supports the "work sharing" concept and the role and tasks of the leading Member State.

This concept should be adopted for all products registered in the EU regardless of their registration route.

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.
We agree that the specific roles of MAH, EMA and NCAs must be clarified regarding signal detection to avoid missed signals or false positives. This can be done in the Good Vigilance Practice (GVP) guidance. A robust process for identifying and eliminating duplicate reports is a pre-requisite for applying signaling tools.
If MAHs are to be expected to utilise signal detection tools within Eudravigilance (in addition to own proceses and procedures) then MAH access to these tools must be implemented before the legal requirements are applied. Otherwise appropriate transitional measures need to be put in place through the GVP guidance.

F. Use of terminology

Consultation item no. 11: Do you agree with the proposed terminology? Please comment.
Yes, Merck agrees. However detail about the transitional mechanism between E2B and the new ISO standards needs to be established for the period between 2012 -2015 in order to avoid confusion and duplication of work.

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

G. Transmission and Submission requirements

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.
Specific transitional provisions should be provided in the GVP guideline. A discussion of realistic transition periods should be held with stakeholders to ensure practicability.

Annex I – Electronic submissions of suspected adverse reactions

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.
The format and content should more closely align or refer to ICH E2A to ensure globally acceptable ICSR forms.

Other comments related to Annex 1
Merck would suggest adding 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’. We propose to include the following definition for off-label use: "Off-label use occurs when an authorised medicinal product is prescribed 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."

Annex II – Risk management plans

Consultation item no. 15: Do you agree with the proposed format and content? Please comment.
Yes, Merck agrees and supports the public summary of Part VI of RMP.

Annex III – Electronic periodic safety update reports

Consultation item no. 16: Do you agree with the proposed format and content? Please comment.
Merck is concerned that the proposed EU PSUR differs significantly in terms of format and content from the current ICH E2C (R1) PSUR. The differences between the proposed EU PSUR and the ICH E2C(R1) PSUR presents significant challenges for the marketing authorization holder (MAH) in terms of report harmonization across the ICH regions as well as the rest of the world. Sensitivity to this issue and ongoing guidance from the European Commission on how to address these challenges is necessary.

It is important to note that upon finalization of the revisions encompassing periodic benefit risk evaluation reporting, to be outlined in ICH E2C (R2), the impact of the proposed EU PSUR will need to be further clarified. The requirements potentially impacted include at least ICH E2C, ICH E2E and ICH E2F. We encourage the Commission to consider and provide guidance on harmonizing the proposed EU PSUR with these requirements as well.

There appears to be a close relationship between the ICH E2F DSUR and the proposed EU PSUR. However, any apparent alignment between the ICH E2F DSUR and the proposed EU PSUR, and the potential benefits thereof, will remain unconfirmed until more specific guidance is provided.

Guidance on standardization of methodologies required to explore in a meaningful way population exposure would be welcome. The criteria for requiring observational studies and drug utilization studies should be scientifically valid and documented.

The requirement to submit the PSUR in a modular structure Common Technical Document (CTD) is welcomed. The modular format will permit the reassembly of PSUR components to satisfy multiple reporting requirements. Further guidance on expectations required to fulfill true electronic CTD assembly with lifecycle management would be welcomed.

Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies

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

PASS studies can be very different in nature and range from Randomised Clinical Trials to observational studies and registries.
As such, Merck believes that this section contains too much detail regarding format and content of protocols and reports which will be inflexible to address the different types of studies and make amendments to the requirements very cumbersome. Guidelines may be a better tool to define more level of detail for specific types of studies.

Merck recommends that the format and content should not generally be aligned to ICH E3 for all types of studies but rather make reference to appropriate standards such as the existing ISPE Good Parmacoepidemiology Practice (GPP) guidelines[1] and the EU Data Protection Directive.

In general, we encourage the Commission to formally consult journal editors and professional medical societies that organize conferences on the legal publication requirements, to avoid that public availability of the final study abstract (in regard to conferences) and final study report (in regard to journal articles) constitute prior publication and thereby sponsors complying with those requirements risk rejection from a conference presentation or journal article.

[1] http://www.pharmacoepi.org/resources/guidelines_08027.cfm#1