Remarks froh the Federal Agency for Medicines and Health Products on : Implementing measures in order to harmonise the performance of the Pharmacovigilance activities provided for Directive 2001/83/EC and Regulation (EC) No 726/2004

Commentaren Public consultation op de Implementation Measures

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered? (is related to content of the MFile)

No remarks

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?

In the frame of performing inspections (certainly for triggered inspections and setting up an inspection planning), it is important for us, PhV inspectors, that significant changes/modifications are notified to the competent authorities.

According to us, only the requirement for submission of information and significant changes/modifications about the pharmacovigilance system master file (PSMF) to the authorities allows an appropriate coordination of inspections by the Agency, and the planning and effective conduct of inspections by National Competent Authorities, based on risk assessment.

Under significant changes may be meant (this list is not exhaustive) :

- Changes to the PhV safety databases (MAH internal changes, database mergers, validation status, transfer/migration of data,..)
- Changes to the provision of significant PhV activities, for instance new or changes to outsourced PhV activities.
- Organizational changes, such as takeovers, mergers, the sites at which PhV activities are conducted of the delegation/transfer of PSMF management.

And to answer on the last question under consultation item no. 2 : Should the PSMF contain a date when it was last reviewed? Yes, it should, the master file should include a last review date. This may for instance be under the form of a logbook, including a variation table of the master file.

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.
Not at this level (Implementation measure). However, it would be helpful for MAH and authorities to clarify this subject more in the GVP (Good Vigilance Practice)-Guidance.

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 complete copy of the audit trail report should not be retained in de Master File itself, however it is proposed that Information about quality assurance auditing in pharmacovigilance should be included in the PSMF. More details about this should be described in de GVP-guidance : it is proposed that a description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism should be provided also, with a current list of the planned and conducted audits concerning the pharmacovigilance system.
This list should describe for instance date(s), scope and completion status of audits, including notes for audits where significant findings (critical/major) are raised. For these, findings are then summarized along with a reference to the audit report and full corrective and preventative plan document(s). The note and associated corrective and preventative action(s), as well as reference to the location of the audit report is documented in the PSMF until the corrective and/or preventative actions have been fully implemented i.e. the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF must also describe current deviations from the quality management system. Deviations from the written procedures, their impact and management should be listed until resolved.

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

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?
No

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

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.
Yes.

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.

However, our opinion : we are in preference of a EU-harmonized system, and the proposal of a lead member state may be favorable, but is it possible to foresee a co-lead member for not loosing the benefit of parallel monitoring ?

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 this needs additional clarification as at this moment it is not clear which aspects are exactly needed/required.

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

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

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

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

Annex I – Electronic submissions of suspected adverse reactions (p.19-21):

1. Definitions

   a. Misuse – abuse : the difference between both is not clear. Is “abuse” more a chronic process compared to “misuse”?

   b. Medication error : is always unintentional as well as for the patient as for the health care professional. Therefore, the definition should be adapted as follows : “Medication error, which refers to unintentional and inappropriate use …”

4. For the purpose of….

   d. “Member State” should be replaced by “primary source country”. Primary source country and qualification are the minimal “mandatory” fields.

   e. the “patient identifiable information” is conditional mandatory. Not all fields need to be populated. Therefore, the listing should be adapted as follows : … last menstrual date **and/or** gestation period..

   g. add the following field : “drug role characterization”. This field as well as “active compound” and/or “medicinal product” are mandatory fields.

   h. Adapt as follows : “For biological product(s), **the active compound(s)** and the batch number(s) shall be reported.”

   j. fields to be added : “reaction originally reported by the primary source” and “reaction in MedDra-terminology”

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

Yes

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

Yes

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

Yes