Vienna, 07 November 2011

PCIM/11/01 - Public Consultation on implementing measures for Pharmacovigilance

PHARMIG response to 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

PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank the European Commission for the opportunity to comment on the implementing measures for the performance of pharmacovigilance activities provided in Directive 2001/83/EC and Regulation (EC) No 726/2004.

Please find following our comments.

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

Response:

In our opinion it is not necessary to cover additional processes and pharmacovigilance tasks in the pharmacovigilance system master file.

Additional comments:

Page 5, A.3 (Content), item (1)

It should be sufficient to make cross reference to the EudraVigilance Medicinal Products Dictionary (EVMPD) where this information is already been given.

Page 6, A.3 (Content), item (3)
To have information relating to the contact person for pharmacovigilance where nomination at national level has been made seems reasonable. However, to include a description of their responsibilities seems to be unnecessary since this information can be different depending on the country and is therefore better maintained locally.

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?

Response:
No, we think the requirement for the MAH to notify significant changes on the PSMF to the competent authorities would be redundant since the PSMF can be requested at any time by EMA or the NCA and has to be provided by the MAH within seven days.

Additional comments:
Page 7, A.4 (Maintenance)
We suggest to include the following wording:

"....it should be continuously kept up to date, ***reviewed on an annual basis*** *and where necessary, shall be revised to take account…"*

"Continuously" should be clarified. Considering the possible daily changes in personnel, contracts, systems like E2B reporting requirements and possible CAPAs which can be resolved until the next Agency request it seems to make an unintended and very high effort for companies to update the PSMF on a daily basis as "continuously" could be interpreted in this way. The system itself will be continuously updated but the accompanying document should be handled according to the requirements for a Site Master File in GMP.

Page 7, A.5 (Documentation)
"The master file shall contain a logbook recording any alteration of its content within the last five years. This logbook should record the date, the responsible person and where appropriate the reason for the alteration."

Considering the continuous updates this would result in a very long and unreadable logbook and also extreme efforts would be necessary to handle this logbook without adding value to the document. Therefore, an annual review with identified changes mentioned in the logbook would be a favourable and realistic solution.

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.

Response:
Page 7, A.6 (Delegation)
We think it would not be appropriate to keep copies of up-to-date signed agreements within the PSMF since these can change daily and therefore this requirement represents an unnecessary administrative burden. It should be sufficient for

competent authorities to have access to these documents on request. A list of existing contractual agreements in the PSMF should be sufficient.

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?

Response:
We think the audit report should remain an internal document. The inclusion in the PSMF could have detrimental influence on the effectiveness of the internal audit. In our opinion it is sufficient to place a note concerning the critical findings temporarily in the PSMF until corrective actions/improvements are put into place. It may be appropriate to require documentation of audit plans but not detailed schedules.

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.

Response:
We agree with the EFPIA statement that the PSMF will serve its purpose best by presenting key information in summary form, rather than by duplicating voluminous primary information or restating information accessible or provided through other means.

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?

Response:

In our opinion there is no need for additional quality procedures and we think the EMA should be responsible for detecting duplicates in EudraVigilance.

Additional comments:

Page 9, B.11 (Performance indicators)

Please confirm/clarify that the use of performance indicators is optional.

Page 10, C.14 (Compliance management), item (d)

We do not agree that it is appropriate for MAH to check the European medicines web portal on a daily basis, unless this is facilitated by setting up a daily email alert that will highlight changes to the MAH.

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

Response:

Page 11, C.15 (Record Management)

"Product-related documents shall be retained as long as the marketing authorisation exists and for further at least 30 years after the marketing authorisation has ceased to exist."

What is the reason for this long timeline? We suggest the timeline to be corresponding with the local legislation on the duration of product liability but at least 10 years.

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.

Response:

Yes, we generally agree with the quality system requirements.

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.

Response:

We generally agree. Please clarify if the work sharing procedure is mandatory and how it will be ensured that all Member States are working consistently and harmonised. Does the procedure include the monitoring of biosimilars?

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.

Response:

We think the following aspects should be clarified:

Roles and responsibilities of the MAH. Will the MAH have access to the results of the health authorities? The reconciliation of signals between MAH and health authorities would be reasonable. How could this be done?

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

Response:

We have no comment on this. Nevertheless it is difficult to comment on standards which are not available in the document.

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

Response:

Overall, we agree with the proposed formats and standards, however, we are concerned about the extent and scope of data required for submission regarding the implementation of Regulation (EC) No 726/2004 article 52(2), second subparagraph, 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 above mentioned legislation.

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.

Response:

We have no comment on this.

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

Response:

We generally agree. Details regarding the patient ID shall be in line with local regulations on data protection, which can result in diverging input.

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

Response:

We generally agree. However, we suggest to take advantage of a modular approach by considering a clear differentiation in content and format between new medicinal products and well-established medicines with some modules not being required in the case of products with well-known benefit-risk profile.

Additional comments:

Page 23 (1.2. Format of the Risk Management Plan), paragraph 1

"Where a RMP covers several medicinal products, a separate Part VI shall be provided for each medicinal product."

It should be clarified what is meant by "medicinal product" as capsules and tablets could be different medicinal products but have the same administration route and should result in a similar Part VI. Therefore it should be possible that similar administration routes could have a shared Part VI.

Page 23 (1.2. Format of the Risk Management Plan), paragraph 3

To avoid confusing and scaring patients and consumers by publishing potential risks only the summary of the Risk Management Plan should be published on the EMA and NCA websites.

Page 23 (1.3. Updates of the Risk management plan)

Updates on the RMP should be free of charge. It should be possible that due to the modular system only impacted and updated Modules can be submitted for an update instead of a complete RMP. This could help to improve oversight on the submitted documentation.

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

Response:

It would be good to have a definition of the electronic format. Furthermore it should be technically possible to exchange modules between RMP and PSUR as regards to content. The required “signature page by the QPPV” could be delegated to appropriately qualified staff. Therefore we propose to amend this bullet point to read just “signature page”.

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

Response:

Page 27, Title

The title should also reflect the scope regarding “non-interventional post-authorisation … studies”.

Page 27, (1. Scope and Definitions), item 1

Could the scope of Annex IV be expanded to include also “non-interventional post-authorisation efficacy studies”?

Page 27, (1. Scope and Definitions), item 4

It should be added “End of data collection” means the date at which the analytical dataset is first **completely** available.

Page 27, (1. Scope and Definitions), item 5

To avoid duplicative work it should be ensured that the MAH does not have to provide information on the study to both, the EMA and the national competent authorities.

Page 27, (1. Scope and Definitions), item 6

“The marketing authorisation holder shall ensure that the revised study protocol is submitted immediately to EMA.”

The wording “immediately” is often subject to interpretation. Therefore it would be good to have a more specific definition.

Page 27, (2. Format of the study protocol)

The point “justification for representation of the study population for generalisation of results“ is missing which is mentioned under final study protocol. This should be a post-hoc justification.

Page 28, (2. Format of the study protocol), item 5

“Any substantial amendment…”

The wording “substantial” is often subject to interpretation. A definition according to GCP would be helpful.

Page 30, (2. Format of the study protocol), item 10

"…Information about whether study subjects will be placed at risk as a result of the study…"

The scope is focussed on non-interventional post-authorisation studies. In such a study design the medicinal product has by definition to be prescribed in the usual manner and in accordance with the marketing authorisation (approved indication, dosage, etc.). Therefore, the subjects or patients are not exposed to an additional risk as a result of the study compared to non-participating patients.