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Comments

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Comments of Bundesverband der Pharmazeutischen Industrie e. V. (BPI) - German Pharmaceutical Industry Association concerning the Concept Paper "Implementing Measures in order to Harmonise the Performance of the Pharmacovigilance Activities Provided in Directive 2001/83/EC and Regulation (EC) No 726/2004

07/11/2011

BPI thanks DG Health and Consumers for having the opportunity to review and comment upon the above mentioned Concept Paper. It is appreciated to put the draft implementing measures into a single paper with the aim to have one harmonised and integrated approach concerning pharmacovigilance activities within Europe.

BPI wants to draw attention to the problems of medium sized companies. Due to the changed definition of the term adverse reaction in Directive 2010/84/EC and the changes in the reporting requirements (reporting of non-serious suspected adverse reactions as individual cases) the quantity that have to be submitted electronically to the Agency will dramatically increase. This is especially burdensome for smaller and medium-sized companies. In the past a lot of these companies did not need an IT-infrastructure as competent authorities allowed paper submissions for the very limited quantity of ICSRs due to the different definition of adverse reactions.

BPI is of the opinion that the whole European pharmacovigilance system should follow a risk-based approach and reasonable requirements. It has to be born in mind that resources at the competent authorites' and industry's side are limited. For fulfilling the pharmacovigilance tasks the resources should therefore be allocated in a way that the responsible persons can take care of really important problems and tasks. Therefore a risk-based approach is urgently needed.

Concerning the risk-based approach e. g. the following topics could be taken into account to avoid extended reporting:

- well-established products with well known and overall non-serious adverse reactions, e.g. generics, traditional herbal and other OTC medicinal products,
- generics with a variety of well established products in sum generating a bulk of volume without added value.

For companies producing homeopathic and anthroposophic medicinal products the range of essential remedies is considerably larger compared to other fields of the pharmaceutical industry. Indeed, due to the strongly individualised character of the therapeutic approaches homeopathic and anthroposophic medicine needs a large range of starting materials (in the range of thousands) and of specific medicinal products. A large number of them have a low

to very low turnover. This leads to the consequence that these companies are holders of several hundreds to more than thousand marketing authorisations. In terms of finished medicinal products the figures can cover up to 400,000 different finished products per company.

Therefore, it is of high economic importance for the homeopathic and anthroposophic industry that the regulatory and administrative burden linked to pharmacovigilance should be rational efficient and proportionate to the very low risk profile i. e. restricted to a minimum while of course guaranteeing the quality and the safety of the products. It goes without saying that the relevant fees should be fair as well.

For whole industry and especially for SME, a streamlined, clear and efficient system of pharmacovigilance which is not overloaded by purely administrative measures without added value to patient safety is needed in Europe.

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

Additional processes and pharmacovigilance tasks do not need to be covered in the pharmacovigilance system master file.

Looking at Chapter “3. Content” a list of medicinal products relevant to the pharmacovigilance master file (PSMF) should be included. Apart from the fact that such a list will be very extensive the benefit of such a list is questionable especially if a company has only one single PSMF in place. In any case the information asked for should be strictly limited to what is really needed for the identification of the products: a list of short product names. More detailed information has to be provided in the EudraVigilance Medicinal Products dictionary.

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 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?

A notification of significant changes to the master file to the competent authorities other than for reasons already specifically defined in Article 23 of Directive 2001/83/EC is not necessary and is not asked for by law. As stated in Article 23 of Directive 2001/83/EC and Section 8 (Inspection), national competent authorities and EMA may at any time ask the MAH to provide a copy of the PSMF. The MAH shall submit the copy at the latest seven days after the request.

Apart from that a provision to notify changes of the PSMF would contradict the legal differentiation between the summary of the applicant's pharmacovigilance system included in the dossier and the PSMF.

It might be useful to include the date of the last revision into the PSMF.

Further, the concept paper asks for keeping the Pharmacovigilance Master File "continuously updated". To standardise level of interpretation, a specficiation of whats understood of continuously would be appreciated, e.g.: the term "continuously" being replaced by "updated at least annually and immediately only regarding terms ..." (provide a list, could be oriented after current classification guidance part C). Apart from that it would be appreciated to use the term "revised" instead of "updated". Using the term revised it would be made clear that the PSMF has to be checked but no formal updates are necessary in the case that there were no changes during the year.

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.

It is not necessary to be more precise on potential delegation e.g. in the case of co-marketing of products, since the individual Safety Data Exchange Agreements should already cover this.

In section 6 paragraph 2) it is mentioned that "copies of the signed agreements shall be included in the master file". The aim should be to keep the PSMF manageable. The mentioned requirement is neither practical nor necessary. For companies operating a significant number of contractual agreements, each subject to change at any time, the master file should at maximum include a line listing of the existing contractual agreements but no full copies of each agreement. Apart from that the individual contractual agreements are available on request.

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?

As there is no legal requirement a copy of the audit report should **not** be retained in the PSMF.

Article 104 (2) of Directive 2010/84/EC requires that MAH holders shall perform regular audits of their PSMF. Concerning the main findings of the audit a note should be placed in the PSMF. Based on the audit findings MAH have to ensure that an appropriate corrective action plan is prepared and implemented. When the corrective actions have been fully implemented, the note may be removed.

When a copy of the note should be retained this would mean the same as the note itself would be retained and therefore contradict the legal obligation to remove the note when the corrective actions have been fully implemented.

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

From BPI's point of view the PSMF should allow an overview of the company's pharmacovigilance system providing information on the key elements. It should not be seen as a depository for the primary data relating to individual elements of the pharmacovigilance system. Taking this into regards the extent and detail for some of the individual elements listed in the Concept Paper may contradict the efforts to have an easily-manageable PSMF providing an effective overview of company's pharmacovigilance system.

A useful solution would be to allow cross-references between the PSMF and the company's pharmacovigilance system having e. g. the possibility to provide lists (with titles) of core procedural documents or describing MAH-specific data inventories/ systems.

More detailed information can rather be made available on demand, e.g. by the MAH providing detailed standard operating procedures.

A modular structure of the PSMF would be of benefit as this would facilitate amendments and version control.

Considering the location of the PSMF it should be determined by the main EU site where pharmacovigilance activities are performed. If pharmacovigilance responsibilities are spread and a main EU site cannot be identified the PSMF should be located at the site where the QPPV is located.

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?

The need for additional quality procedures is not seen. EMA should make greater efforts to detect duplicates of suspected adverse reaction reports in the EudraVigilance database.

Although it would be acceptable for MAHs to check the European medicines web-portal on each working day regarding new information it is suggested to have a clearly defined area of the portal where pertinent information will be posted. A system with daily e-mails concerning new information being posted would be an important tool to help MAHs.

Independent from the obligation for MAHs to check the European medicines web-portal this should not replace direct correspondence of the competent authorities or the EMA with the MAH on individual product related issues.

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

It is understood that this question should be seen in the context of section 15 (record retention). The requirements for MAHs regarding record retention are agreed. However, clarification is required regarding which pharmacovigilance- or product-related documents are meant to be covered. This should be addressed in the Good Vigilance Practice guideline.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards for marketing authorisation holders, national authorities and EMA.

The quality system requirements are agreed in general.

In section 10 it is stated that the MAH should perform an audit of their quality system at regular intervals, not less than every two years. Concerning the 2-year period for audits this seems not to be appropriate. A risk-based approach should be followed allowing longer periods and occurrence-related audits.

MAH should determine the frequency of their internal audits, based upon information on the performance of the pharmacovigilance system and/or findings arising from 'routine' audits conducted on a pre-scheduled basis. However, repetitive 'routine' internal audits on a fixed schedule could become a disproportionate effort when compared with the effectiveness of a more 'risk-based' approach.

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 medical 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.

The proposed 'work sharing' procedure is supported. The feared risk in cumulating all tasks e. g. for one active substance in one Member State is little. Any member state would retain the right to comment or conduct additional review if wished. The work sharing procedure should be extended to all medicinal products which have been approved in more than one EEA country within the EEA.

A system of "Rapporteur / Co-Rapporteur" could be envisaged.

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.

An appropriate level of diversity in signal detection methods should be the aim. No single system or process will yield a perfect result. In this regard, general principles would probably be more useful to establish commonalities than selecting one single methodology to be applied in different settings.

When thinking about methods concerning signal detection it has to be kept in mind that there are medicinal products on the market with a very limited number of adverse reactions. Concerning these products it might be sufficient to evaluate the ICSRs. Therefore a certain method should not be prescribed.

The aim of the common triggers must be to eliminate false negatives (missed signals) and to keep false positives to a minimum. Thus there is merit in ensuring that the roles of MAHs, national competent authorities and EMA are clarified. Whilst the proposals are clear concerning the role of EMA, a series of process outlines and specific deliverables must be defined for MAHs and national competent authorities in the Good Vigilance Practice guideline.

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

In general we agree with the proposed terminology.

The specific aspects of homeopathic and anthroposophic medicinal products should be taken care of. Apart from that for SMEs and other companies with only a limited number of ICSRs the fulfillment of all requested IT requirements would not be proportionate. Provisions for that must be in place.

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

The list of internationally agreed formats and standards is agreed, with the exception of item (a), relating to the new Extended EudraVigilance Medicinal Product Report Message (XEVPRM).

As discussed at the Stakeholder Meeting at EMA on 20th September 2011 a certain amount of data that has to be submitted to EudraVigilance by 1 July 2012 in order to comply with Article 57(2) of Regulation (EC) No 726/2004, as amended by Regulation 1235/2010 goes beyond what is required by law. BPI is concerned about the extent and scope of data required for submission, as it is described in the EMA Legal Notice of the 1st of July 2011 and follow up communication in September 2011, as this goes beyond the legal basis.

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BPI urges the Commission and the EMA to continue the dialogue with industry about the mandatory and not mandatory information and data fields for compliance with Article 57(2) of Regulation (EC) No 726/2004 by the July 2012 deadline.

In any case a limitation of public access to certain fields, in particular details on the QPPV must be ensured.

The aim should be to allow the Agency the fulfillment of its pharmacovigilance tasks by submitting really necessary pharmacovigilance related information about medicinal products. All information that is not directly related to this task should be not mandatory especially all information that is related to the ISO IDMP projects. Under the prerequisite that the legal basis is clear the IDMP related information could be included into the system at a later stage when the ISO process is finished.

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.

Related to PSURs and RMPs transitional measures co-ordinated across the EEA will be necessary. The transitional measures shall aim at not modifying processes into an "interim hybrid" and thus complicating the situation for MAH, but rather allow to use those processes existing for as long as necessary. In addition, different transition specifics by country or region should be avoided.

Regarding the requested time frames for the implementing measures it should be born in mind that the changes will especially affect SME.

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

The proposed format and content is agreed in general. However, the proposed definitions for ‘misuse’, ‘medication error’ and ‘overdose’ should be clearer. It is challenging to find clear and distinguished definitions for the first two terms, as they may be interrelated. Particularly a more elaborate interpretation/definition of ‘off-label use’ would be of value – as off-label use may be a justified scientifically sound treatment and need not necessarily being put into a negative context, where "mis"use clearly implies an incorrect, potentially adverse, situation. Currently it would not be clear whether ‘off-label use’ is covered by ‘misuse’ or whether ‘misuse’ should be considered as part of ‘off-label use’ (important given that PSURs and Risk Management Plans require summarisation of ‘off-label use’ rather than ‘misuse’).

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

Although the format and content for products with new active ingredients is agreed in general, in section 1.2 “Format of the RMP” it should be clarified that only the summary of the RMP has to be published on the authorities’ websites. In the moment it could be understood that the full RMP should be published – that would cause problems concerning confidential data.

RMP are also regularly submitted with marketing authorisations applications across the world and international Safety Departments suffer from adapting to various formats already. Thus the EMA shall not further increase this burden.

It should be made clear that medicinal products that have a low risk profile or a well-established active substance where no risk minimisation measures are necessary “routine pharmacovigilance” is possible. Concerning those medicinal products that build up a very big part of the whole market the format of the RMP should be adjusted following a risk-based approach. Additional bureaucracy that does not lead to a relevant improvement of patient safety should be avoided.

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

Periodic safety update reports (PSURs) are often submitted to regulatory authorities outside the EU, too. Format and content should be in accordance with ICH E2C (R2). The timeline for finalisation of this guideline will be after the implementation date of the pharmacovigilance legislation, but the alignment of the implementation measure with the ICH E2C (R2) outcome should be envisaged.

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

The whole draft is too much orientated in the way studies in accordance with GCP have to be conducted. It has to become clearer that there are different requirements concerning studies that have to be GCP-compliant (interventional studies) and those PASS that are non interventional.

Inter alia the following aspects should be reviewed for PASS that are NIS:

1. Scope and definitions
Nr. 5: „*study protocol*“ is a definition stemming from GCP. The term „observational plan“ would be better to distinguish PASS from GCP studies.

2. Format of *study protocol*
Nr. 3: The naming of the main author of the protocol is not necessary, a principal investigator and co-investigator are not part of all NIS. It should be avoided to use terminology stemming from clinical trials. This is again the character of NIS. The doctor taking part in an NIS does

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not take part in a clinical trial, he or she treats patients in a way he/she would do in normal daily practice. He/she then documents the results of the therapy (e. g. ADRs, outcome etc.).
Nr. 4: Naming of main author is not necessary.
Nr. 7: It is agreed to provide a description of the actual safety profile and an explanation what the aims of the NIS are. All other information goes beyond what is necessary. In addition this information has to be shown in the context of the marketing authorisation procedure.
Nr. 8: All NIS mentioned in Annex I are asked for by competent authorities. Having this in mind it would be logical that the competent authority in question should give the reason for conducting the NIS and not the MAH.
Nr. 9: 9.1 to 9.9: Again it should be made clear that these points are too much related to requirements in the context of GCP. It might be that this is not intended, but the wording implies very complex answers having the GCP system in mind. Hence the wording should be reviewed in this regard or it should be made clear that the distinction between GCP-compliant clinical trials and NIS is seen and the answers can be kept short and simple.

3. Format of the abstract of the final study report und 4. Format of the final study report
Again it should be made clearer that there is a distinction between NIS and clinical trials in accordance with GCP.

A PASS as a non-interventional study has to reflect the medical routine and reality. Hence it is not possible with a prospective NIS to look over the doctor's shoulder on the one hand side and to expect data in GCP quality on the other hand side.