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Contribution to public consultation

Comment to consultation on implementing measures for pharmacovigilance (PCIM/11/01)

November, 11 2011

Case number:
2011111654

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The Danish Medicines Agency welcomes the Commissions concept paper on the implementing measures regarding pharmacovigilance activities. We find it very important that the implementing measures are adopted before July 2012 in order to be able to prepare the practical implementation of the new pharmacovigilance legislation, and we believe that the concept paper supplements essential aspects of the new pharmacovigilance system.

From a Danish perspective, the concept paper gives rise to the following comments on key consultation topics.

Pharmacovigilance system master file

Consultation item 2:
The Pharmacovigilance system master file (PSMF) should be made available to the competent authorities and should be clearly dated and numbered with versions as appropriated. A system should be put in place to assure that the MAH, its national representatives as well as competent authorities always can get access to the latest version of the PSMF.

According to article 23(4) of Directive 2001/83/EC, as amended by 2010/84/EU, the national competent authority may at any time ask the marketing authorization holder to submit a copy of the pharmacovigilance system master file. The marketing authorization holder shall submit the copy at the latest 7 days after receipt of the request.

The marketing authorization holder should send a notification of significant changes to the document to the national competent authorities. Significant changes to the pharmacovigilance system master file could be a trigger for an inspection and information like that should be available.

Consultation item 4:
For all completed audits of the pharmacovigilance activities, a copy of the audit report should be available for inspection, if needed, and it should

be ensured that the qualified person responsible for pharmacovigilance (QPPV) has access to the audit report also.

Consultation item 5:
In the description of the PSMF it would be useful to add a sentence to specify that not only the PSMF is subject to inspections but also all documents and data needed to substantiate that the MAH has fulfilled required obligations. Requirements for documents and data should be found in the Good Vigilance Practice guideline.

Quality systems for the performance of pharmacovigilance activities

Consultation items 7 and 8:
In the descriptions of record management for pharmacovigilance system related documents, it would be useful to include a statement that 'All pharmacovigilance information should be recorded, handled and stored in a way that allows accurate reporting, interpretation and verification of the information'.

It follows from the concept paper that 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.* How should the last mentioned obligation be implemented in practice? Who is responsible for this after the marketing authorisation has ceased to exist and what if the company is closed down or the product is sold to another company?

Signal detection and risk identification

Consultation item 9:
The concept of work sharing within the area of pharmacovigilance is important for the Member States in order to focus their resources and to ensure that all medicinal products are of high priority and has special ownership in a lead Member State within the network. We believe that the concepts and procedures of work sharing are very important in relation to evaluation of applications of marketing authorizations and evaluation of periodic safety update reports.

However, we have some reservations regarding work sharing in relation to routine signal detection and monitoring of the data in the Eudravigilance database to determine whether there are new risks or whether risks has changed and whether those risks impact on the risk-benefit balance.

The roles and responsibilities of EMA and national competent authorities need to be clear to all parties. The monitoring should be done in close collaboration and working methods should be well described. The Member States may have different focus or expertise in doing the monitoring and evaluation of adverse reaction reports. A 'co-rapporteur' or a peer review

system would enhance the robustness of the monitoring of data in the Eudravigilance database.

We should also bear in mind that spontaneous case reports or scientific publications may surface on a national level before an appointed lead Member State becomes aware of new safety signals. Therefore each Member State shall react promptly to any national 'signals'. Afterwards, it may be appropriate to refer the matter to a lead Member State to prepare a common evaluation of a potential new safety problem. However, we should not forget that each Member State has an obligation to evaluate information about safety issues scientifically, consider options for risk minimization or prevention and take regulatory action concerning issued marketing authorization as necessary.

The use of the term 'experiments' in relation to signal and risk identification is not clear. If trials or studies and compassionate use are meant, using these terms would be preferable.

Consultation item 10:
The text on this item is clear, but kept in very general terms. To ensure consistent high-quality signal detection in all Member States, it could be envisaged that there will be a need for practical training and cooperation to obtain a common best practice for these tasks among member states.

Quality measures must be put in place to ensure that relevant signals would be picked up independent of an appointed Member State responsible for the particular active substance. Furthermore, access to valid data on overall drug utilization, preferably stratified on age and gender, as signals must be interpreted in the light of exposure. If drug utilization statistics based on age-group and gender is not available, sales figures, including DDD's, should be a requirement.

Transmission and Submission requirements

Consultation item 14:
We agree on the overall format and content for submissions of suspected adverse reactions. However, specific information in relation to the new elaborated definition of an adverse reaction needs to be provided in a clear structured way when reports of adverse reactions are submitted. Information on e.g. medication errors, misuse, abuse or off-label use should be specifically reflected in submission forms to ensure that the information is provided on reported cases and can be utilized in evaluation of data.

If follows from Article 107a (5) of Directive 2001/83/EC, as amended by directive 2010/84/EU, that reports of suspected adverse reactions arising from medication errors shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004, as amended by

regulation 1235/2010. The Agency shall in collaboration with the Member States develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 107a of the Directive, c.f. Article 25 of the regulation.

Furthermore, it follows from Article 108(e) of Directive 2001/83/EC, as amended by Directive 2010/84/EU that the Commission shall adopt implementing measures on the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorization holders.

It is important that the various kinds of adverse reactions are identified in the reports in order to ensure that EMA, national competent authorities and the marketing authorization holders are able to act appropriately. The standard web-based structured forms may facilitate good quality reporting of suspected adverse reactions where it is possible to distinguish clearly between the various kinds of adverse reactions.

Consultation item 16:
We agree on the proposed format and content for Periodic Safety Update Reports (PSURs) with the following comment and suggestion: It is important to describe the implications of the PSUR data on the specific Marketing Authorization, including the implications on the approved Summary of Product Characteristics (SmPC) for the product that the PSUR is submitted for. This requirement should be highlighted in the legislation and a more detailed description on the practical aspects provided in the guideline module.

The information could be placed in the section "region-specific information".

Consultation item 17:
We agree on the format and content for protocols, abstracts and final study reports regarding the non-interventional post-authorization safety studies with the following comments: The study protocol should (in bullet item 11) include both the management and the reporting of adverse events/adverse reactions and of other medically important events. Also the discussion in the final study report should include deviations to the planned study, including identification of ways in which the study as conducted differed from the study as planned in the protocol.

The Danish Medicines Agency looks forward to discussing the Commission's proposal on the implementing regulation regarding the performance of the new pharmacovigilance activities later during the process.

We are of course at your disposal, should you wish more detailed comments.

Yours sincerely

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