From: Franzen Wilhelm MD TPDE
To: SANCO PHARMACEUTICALS
Subject: PCIM/11/01 - public consultation on implementing measures for pharmacovigilance

Dear ladies and gentlemen,

following the invitation of the DG8 to comment on the process and conditions for implementation of the new PV legislation the chapters below contain comments on particular aspects of the concept paper.

PV System Master File
In times where media become more and more relevant to our day by day business it seems questionable whether there is a need to define the location of the PVSMF – as long as the QP PV has access to it and has control over the changes of the documentation. It seems more relevant to define a structured release process by the QPPV – to ensure appropriate authorization.

Further the PV System is nothing limited to the EU (as defined in the EU treaty) – and national authorities may require the access to the system from their local point of view – therefore it should be avoided to have multiple copies to be controlled but to have a valid electronic system – for which the "location" is less important than it permanent accessibility.

In the concept of the introduction of the EU QPPV it has to be understood, that the authority given to this function is limited by the area to which the legislation applies. Not rarely there are situations where national legislation even contradicts to the settings in the EU directives / regulations. As this is beyond the legislative influence of the EU parliament and governments there is also a limitation to the required authority of the EU QPPV – this has to be clearly addressed and understood.

The concept paper implies the existence of an electronic database for PV (no. 3 (5)) – which in fact is not required by the legislation. Further there is a question whether the Eudravigilance database may be used as the MAHs reference system – in case all the cases are entered into the Eudravigilance database via the web-interface- including the requirements to fit for the intended purpose?

According to topic 4. "maintenance" the EU commission qualifies the PVSMF as "one" global document. In fact this is not a single global document as long as there is no international agreement on it's structure. It would be welcomed if there is an initiative on this to develop such common approach.
When there is a proper and adequate versioning it should rely in the responsibility of the PVMSF owner to update it appropriately and authorities will have a look into it at the time they deem it necessary – an update process to authorities without an actual reason seems senseless because at the time of submission the authorities may not have the time to look into it and when they decide later on to have a look into it for preparation of an inspection for example they will ask to the MAH to ensure to have the latest actual status.

The inclusion of audit reports needs to be further defined – otherwise there will be a flood of audits included into the documentation. Multinational companies have usually audit activities on their corporate and local level, further audits may not only come from PV directly but may touch onto it – like GCP audits, GMP audits or even compliance audits or IT QA audits. Further in case of license partners also these relations are accompanied by audits which usually include PV aspects.
It is questionable if all these activities will add a beneficial information to the PV System Master File – therefore it should be considered that only these audits which are planned under the guidance of the QPPV to understand the function of and the adherence to the processes in the PV system are included in this documentation.

Topic 8. Inspection – as for all local inspections it should be considered whether it makes sense that an inspection in Sweden is conducted with a reference to the PVMSF available for inspection in Spain. This aspect contributes to the discussion earlier in this chapter.
Also the requirement to have the PVSMF available within 7 days (not defined as calendar or working days) may be challenging with regard to the different religious and cultural conditioned bank holidays in the EU. Therefore these limits should be reconsidered.

Quality Systems – common obligations
The article on audits describes a regular audit of the quality system – but not less than every two years. With regard to the extent of such a PV system – including the fact that licensees are also part of these activities the requirement should be more concrete with regard that not the entire system needs to be audited – but only parts of the system in a two years interval and within the plan for auditing the PV system it should be defined that within 3 audit cycles for example all relevant sections have been audited.

Quality Systems – MAH obligations
The introduction for this chapter talks about the QMS at the MAH site in general and the relevant processes – from the scope of the legislation it is understood that this refers to PV processes and therefore it should be also mentioned here. QMS systems may also be established in finance or HR departments – but it is assumed they are not in the focus of this concept.

The compliance management ideas refer to the process of updating product information, including assessments published on the European medicines web-portal. It is not understood why the MAH is obliged to check this site on a daily basis – the legislation requires that a QPPV contact is registered at the EMA site and why is this information not forwarded accordingly to the QPPV contact.

Record-Management: The archiving of PV information is totally different across the EU as this was in the past mainly controlled by national legislation. Further there was no adaptation to the possibilities electronic archiving offer in the current legislations – with regard to the authenticity and reputation of documents which have been transferred from a paper file to an electronic document.
The records referred to in the concept paper are understood to include also the basic information of a single case report. Under these conditions the time limits described in the concept paper in fact add up to a situation of indefinite storage – as long as the company exist – as also a PV system will exist in this case. It is not feasible to align storage durations to the layout and setup of the PV-system at a certain time.
There should be a consideration on an EU level how to accept electronic storage of documents and how long paper documentation should be available – if still required. With regard to the defined periods of storage in the concept paper one has to acknowledge that even today there is no guarantee the paper based documents can be read (without further handling)at any time in the future. In addition handling of electronically received information (Emails, Websites) must be included in this concept.
If the intention of this chapter is not the one described above – in this case the expressions “PV system related documents” and “product related documents” need to be clearly defined.
Also a situation of closing down a company may be considered – as there is no longer a legally responsible person – and therefore the conditions may not be applicable.
Most importantly – with regard to the current different requirements for archiving it needs to be defined from which date or for which approvals the new requirements become valid

Quality Systems – CA and EMA obligations
There should be no difference for the submission timelines of cases between authorities and MAHs. The compliance management as described under topic 18 should include submission or publication

of single cases according to the timelines as defined for the MAHs. With the concept of providing access to PV information to the public and to enhance the reporting by using public sites maintained by the CAs, there will be an increasing number of cases which are relevant for all signal detection activitiers performed by the MAH.

Signal detection and risk identification
Principally the idea of work-sharing is a valid approach to strengthen the processes in PSUR assessment and risk-management. With regard to the selection of the leading CA it should be considered that the CA should have experience with the compound – or one of the same class – from an approval application process, as this includes back-up and experiences from the clinical data review and their assessment.

Annex I: Definitions
For the sake of clarity the wording for inclusion of adverse reaction reports for cases received from use outside the approved indication should clearly state that it refers to the reports of adverse reactions reported – and not as the wording could be interpreted for reports outside the terms of the market authorisation in general even without adverse reaction.

I hope that I understood the intention of the proposed concepts appropriately and that therefore my comments are useful for the further assessment process. In case further clarification is needed I would be happy to answer any question you may have.

With kind regards

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