AESGP Position Paper on the European Commission's Consultation on Implementing Measures in order to harmonise the performance of the Pharmacovigilance activities

We appreciate the opportunity to take part in this public consultation on the pharmacovigilance measures. As an important principle the pharmacovigilance legislation was revised with the goal to promote and protect public health and to rationalise and streamline existing systems. This file part of the so-called "pharma package" was aligned with better regulation principles, and the notion of proportionality and risk-based approach inserted in the legislation. These critical aspects should be reflected in the implementation of the file in its entirety and in particular in the implementing measures (general / introductory part).

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

No, to our mind the list is complete.

However we have the following more specific comments on:

1- Section *2. Location*:

It is correct that the legislation requires that a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union be posted on the EMA web-page however the correct reference is article 26, not article 57(2)(c).

2- Section *3. Content*:

- Item (1): To avoid duplicating work, it should be allowed to cross-refer to an already existing list from the required e-submission of the product information via XEVPRM (cf. Article 57 of Regulation 726/2004).

- Item (2):
  - We propose to replace *"experience and registration relevant to pharmacovigilance"* by a Curriculum Vitae of the Qualified Person for Pharmacovigilance (QPPV).
  - There is no INN for example for homeopathics, hence it should be added 'where applicable' to the sentence.

- Item (3): it seems reasonable to have a list of contact person(s) for pharmacovigilance where a nomination at national level has been made. However, to have to provide a description of their responsibilities in the PSMF seems unnecessary. These may vary depending on the country and should only need to be maintained at local level.

- Item (6): listing and cross-references to relating SOPs should be sufficient.

- Item (7)(b): it is not clear what 'a description of the resource management' for performance of the pharmacovigilance activities means (vs. the resources themselves).

- Item (7)(e): It is not clear what 'audit trails' refers to in this context.

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?

No, the Marketing Authorisation Holder (MAH) should not be obliged to notify any significant changes to the Authorities (beside change in QPPV). The word 'significant' may be subject to different interpretations which may create different requirements from different authorities. The Authorities have the means to contact the QPPV, to ask questions and to ask for the pharmacovigilance system master file (PSMF) within 7 days; hence there should not be an additional requirement to notify here.

The PSMF would only contain the date of the last review and each different version would get a different internal number.

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.

We understand the need to be precise on delegation e.g. co-marketing of products but we think that first of all, this document should remain a high level document; further details would be more appropriately dealt with in the Good Pharmacovigilance Practices guide.
Secondly, the MAH should only have to list third parties involved in pharmacovigilance activities and their roles, and NOT to include copies of the actual agreements; having access to them should be sufficient. To keep copies of up-to-date signed agreements within the PSMF represents an unnecessary administrative burden.

Section *6. Delegation*: the term 'delegated activities' is unclear.

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?

No, a copy of the audit report should not be retained in the master file; this should remain an internal document. In addition, the requirement to provide copies of audit reports could affect the performance of internal auditing as findings would be issued taking into account that all details would be disclosed to the competent authorities. We think it is sufficient to place a note concerning the main 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.

The term ‘main findings’ is not qualified and we would prefer ‘critical’ findings with *‘critical’* being defined as in the guidance for conducting pharmacovigilance inspections requested by the EMA i.e. *“a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety and well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines;”*

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, we overall agree but we refer to various comments made to the above consultation items on detailed aspects.

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, the stated quality procedures are quite sufficient and burdensome enough; there could be the risk that carrying out excessive quality measures may detract resources from actual pharmacovigilance activities.

In addition, the requirement for the MAHs to check the European medicine web-portal for relevant updates each working day is unnecessary detailed for a high level document. The appropriate timeline should be left to individual companies. It should also be made crystal clear in the GVP document what part of the website should be monitored. Any new information should be dated and appear in the order of posting (the most recent one on top). The possibility for MAHs to be notified of new posting (e.g. RSS feeds) should need to be explored.
The monitoring of sites should also not replace and obviate the link between authorities and companies on safety issues.

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

We think some of the requirements for MAHs are too extreme, and it should be sufficient for companies to have basic quality control measures and compliance monitoring in place e.g. for accuracy /completeness of adverse events data capture, reporting of serious and non-serious adverse events and submitting PSURs, as well as having regular internal audits of their pharmacovigilance system (together with robust documented processes for all pharmacovigilance activities and documented training of those personnel carrying them out). All other tracking and monitoring referred to in this paper would probably require an unfeasible level of pharmacovigilance resources for many companies, and in any case represents what pharmacovigilance system audits would typically cover.

Section *14. Compliance management*, Item (a): *"The marketing authorisation holder must follow-up such information independent of its source, including information spontaneously reported by patients or healthcare professionals, or occurring in the context of a post-authorisation study"*: Our understanding is that this sentence is simply referring to adequate follow-up of AE case reports with patients or healthcare professionals whereas the term "monitoring" (in the first sentence of item (a)) refers to signal detection activities. This is a bit confusing and we would appreciate clarification on both sentences.

Section *15. Record management* seems common to both authorities and MAH and we wonder whether it would not better fit in part B.

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, we agree. It should also be mentioned that authorities may delegate their pharmacovigilance tasks to another Member State. There also does not appear to be mention of the Member States and Agency collaborating and sharing information regarding inspections and inspection reports, to reduce the burden on Industry with having repeated inspections. This would be extremely useful to see reflected in the paper.

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 products. 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.

Although we would in principle agree to the idea, we think that this is premature given that the system is not ready at the moment (there is not enough standards and harmonisation in place that guaranties that all authorities are working consistently).

Section *21. Changed risks/new risks*, last paragraph on signal detection: the first sentence should be reworded to state *"The detection of signal shall be based on multidisciplinary based approach and be supported by statistical analysis**, where appropriate,** within EudraVigilance."*

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.

With regard to signal detection, it should be clarified whether authorities and companies are both expected to monitor Eudravigilance. If companies are expected to do so, they should be given the technical means to do so.

In a case where the EMA detects a signal: would the MAH be informed right away before discussion takes place in the Pharmacovigilance Risk Assessment Committee (PRAC)? Other areas, which would merit further clarification, are as follows:

- How will this be done practically and to which data MAH will have access?
- In general, specific details on the timeframes, search parameters, statistical methodologies. Communication processes and other criteria for signal detection in EudraVigilance, including use of the EMA signal tracking system.
- Description of how the PRAC committee will synchronize medical event terms with those of the sponsor (section 21c)
- Clarification on the level of public access to the signal tracking tool (if any) and description of how sponsors will be notified of signal resolution (section 23).

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

It is difficult to comment on standards without the possibility of looking at them. The cost/fees for companies are not yet clear. We also lack details on the phasing in of such standards. The same questions apply for the maintenance of those standards.

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

In relation to the transitional formats and standards, we have a comment on EVPRM (a). We acknowledge that a transitional format is necessary pending the finalisation of the ISO standards. However, as expressed at the EMA meeting on 20 September, we differ on the EMA interpretation of the scope of article 57(2) which refers to the Eudrapharm database (transparency purposes) and not Eudravigilance (pharmacovigilance purposes). Hence we object to the amount of data required to be submitted to the EMA by July 2012[1] which by far exceed the requirement of article 57(2) namely SPC, PIL and labelling. The submission of data until July 2012 should be limited to those foreseen in article 57(2) and the out-of-scope data submitted afterwards.

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.

With regard to the transitional measures for the reporting of non-serious suspected adverse reactions, the legislation states that Member States 'may' require such reporting. The legislator had inserted this new provision in connection with centralised reporting to Eudravigilance hence the legislator's intent should be respected and this provision should ideally be put on hold until Eudravigilance is in place. It would be good that the Commission provides a recommendation to Member States on this point. Otherwise we fear that some Member States may indeed require reporting which would generate a massive number of reporting for well-known products and a huge workload for both companies and authorities. By focalising resources which may be needed elsewhere on these tasks, this may adversely affect public health.
Transitional measures on provisions where a new format applies (e.g. PSUR, RMP, etc) will be critically needed to enable companies to adapt their internal processes and transition smoothly to the new formats. We assume this will be addressed in the Good Pharmacovigilance Practices document.

1 See EMA legal notice: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108212.pdf

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

Submitting copies of clinical papers and their translation if required will incur costs to MAHs. In addition, it can be sometimes quite difficult and resource intensive to find a medical translator.

Section *3. Content of electronic transmission of suspected adverse reactions*:

- Point 3: It is unclear whether this section refers to reporters or patients data privacy. This should be clarified in the context of the GVP.

- Point 4(b) – 'original literature': the requirement to provide a copy of the relevant article together with electronic reporting of suspected ARs cannot be fulfilled due to copyright restrictions in Europe. We therefore propose to remove this requirement. Instead the comprehensive English summary of the article can be submitted electronically via the case narrative as outlined in the concept paper.

- Point 4(d) – *"Primary source(s), which refers to the person(s) who reports the facts: reporter identifiable information including Member State and qualification."*: we guess it must be 'country' and not 'Member State' as there is no obligation for the reporter to be located or act in an EU Member State.

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

We understand that this is the standard format but that a 'modular approach' was envisaged with some modules not applying/ not being required in the case of well-known products. Would this be clarified in the GVP?

It should be clarified that only the summary of the RMP will be published, no further details are provided in the legislation. We fear that publishing potential risks will confuse and scare patients and consumers.

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

Section *1.2 Format of the Periodic Safety Update Reports*: We note that the new format is more demanding around patients' exposure, which to our mind goes beyond what is required in the new pharmacovigilance legislation.

The required 'signature page by the QQPV' could be delegated.

As the format of PSUR was harmonised through ICH, it is important that this harmonisation remains for companies submitting reports in and outside Europe. Hence this format should be consistent with that of E2C(R2).

Other comments:

- PSURs exemptions for well-established medicines, registered homeopathics and traditional herbal medicinal products should be mentioned.

- Would the existing PSUR lists established by the HMA group on pharmacovigilance be used as a basis for the list of reference dates and frequency of submission?

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

Section *2. Format of the study protocol*:

- Point 11: it should be specified whether adverse reactions or adverse events should be reported; it is not precise enough and gives room for interpretation by inspectors.

Section *4. Format of the final study report*:

- Point 4: we propose deleting *'all coinvestigators'* since this brings no benefit and would cause a large workload for maintenance and data collection.

7 November 2011