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

COMMENTS FROM AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS ON THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

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A. Pharmacovigilance system master file

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

AEMPS Comments:

- With regard to the content of the Pharmacovigilance system master file (PSMS) a description of the process, data handling and records for post-authorisation efficacy studies and post-authorisation safety studies should be covered. In particular, processes for the elaboration and submission of protocols, reports and abstracts to competent authorities in accordance with the provisions in Art 107n.1., Art 107o and Art 107p of Directive 2010/84/EU should be included.

- In the description of the content of the PSMS, a point (e) related to the description of the ***"Process for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to patients and health professionals"*** *is proposed. Directive 2001/83/EC as amended by Directive 2010/84/EU contains a provision (Art 106a.1) in relation to the responsibilities of MAHs on public announcements relating to information on pharmacovigilance concerns. Also, the distribution by MAHs of Direct Healthcare Professional Communications (DHPCs) on the safe and effective use of medicinal products may be required in order to inform healthcare professionals on relevant safety issues including safety variation to SmPCs, according to Guidelines currently included in Volume 9A. On the other hand, according to Art 88.1 (a) of Directive 2001/83/EC the advertising to the general public of medicinal products which are available on medical prescription only is currently prohibited in the Union. Therefore, in relation to description of processes for communication of safety concerns and variations, we propose to limit the content of the PSMF to those procedures actually included in the legislation, i.e.: communications referred in Art 106a.1 and procedures on DHPCs, avoiding any mention to provision of information to patients.*

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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?

AEMPS Comments:

- We consider 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.
- We consider that the master file should contain a date when it was last reviewed.

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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.

AEMPS Comments:

We think that is very important that the PSMF contains precise information on potential delegations of tasks. The different sub-contract and co-marketing possibilities should be detailed together with the distribution of all pharmacovigilance responsabilities that could be affected by the delegation.

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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?

AEMPS Comments:

Affirmative response to both questions.

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

AEMPS Comments:

No additional comments.

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B. Quality systems for the performance of pharmacovigilance activities – Common Obligations
C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

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?**

AEMPS Comments:

- *In relation to study reporting (Art 107p of the Directive) we consider that quality procedures are warranted and processes documented in the Pharmacovigilance System Master File (see also comment on item no. 1).*
- *In relation to communication on pharmacovigilance between the MAH and patients/healthcare professionals, and in line with our comment to item no.1 we consider that only aspects actually covered by the legislation should be in the implementing measure on minimum requirements for the quality systems and limited to the provisions in Art 106a.1. of the Directive, DHPCs and adopted additional risk minimization measures (i.e. educational materials) in the context of European risk management plans.*
- *In relation to processes for taking corrective and improvement actions we agree that quality procedures should be implemented.*
- *In relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database, we consider that the MAH should put in place a quality system in order to prevent the submission of duplicate cases, before entering new data into Eudravigilance.*

In addition, we consider that the quality system of the MAH should include procedures and processes in order to:

- *ensure that accurate and verifiable data are obtained for the scientific evaluation of suspected adverse reaction reports including follow-up information on these reports, in accordance with Art. 107.4 of the Directive.*
- *In the point "(c) ensure effective communication...", in addition to the references to PSMF, RMS, RMM, PSUR and PASS/PAES, reference should also be made to the following obligations of MAH stated in the new legislation: communication on new emerging data (see Art 107h.3of the Directive and Art. 28a.3 of the Regulation); and on new information which may entail the amendment of the authorised conditions of use (see Art 23.2 of the Directive and Art 16.2 of the Regulation).*

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

See comments to item no.6.

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D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

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.

AEMPS Comments:

We agree that quality systems procedures shall be in place in the NCA and EMA in order to evaluate the quality, including completeness, of pharmacovigilance data submitted (18. (a)). Nevertheless, in order to clearly clarify roles and responsibilities, the following should be added to the "pharmacovigilance data submitted by healthcare professionals and patients and by MAHs respectively".

Further comments to the text:

Regarding section 18 (d), the coordination of the content of the safety announcement should be based on coordination of the key elements of communication. There may be local issues derived from clinical practice relevant for in local communication. It is agreed that coordination should be the standard, but there are exceptional instances of local media attention which may need prompt local communication, not allowing for previous coordination of key messages.

In section 19, consideration should be given to the last paragraph. It is not clear which are the documents that the text refers to. The time for keeping documents should be in line with other legal documents (info from clinical trials, registration applications...).

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E. Signal detection and risk identification

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.

AEMPS Comments:

In theory, it seems more efficient that the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur for European PSUR assessments should be the same than the PRAC Rapporteur for signal detection activities. Nevertheless, these tasks are new, and experience may found a more horizontal distribution of work to be more efficient. For this reason, implementing measures should leave enough flexibility to adapt PRAC tasks to the experience gained. It has to be taken into account that the implementing measure refers to minimum requirements for monitoring of data in Eudravigilance, being these issues out of the scope of the implementing measure.
Work sharing should involve all medicinal products, including centrally authorised product and a lead Member State should be appointed for the latter.
Regarding authorisation, we consider that not necessarily the MS involved in the authorisation should be the same MS evaluating the benefit-risk after authorisation for various reasons. It should also be taken into account that PSUR assessments and signal detection will be performed generally based on active substances while marketing authorisation application dossiers are assessed on each medicinal product; therefore, a one-to-one relation of Rapporteurships for both assessment activities will not be the case in many instances.

Further comments to the text:

Section 21, last paragraph, the following changes are proposed:
"The detection of a signal shall be based on multidisciplinary based approach and be ~~supported~~ complemented by statistical analysis within Eudravigilance. ~~Following consultation of the Pharmacovigilance Risk Assessment Committee EMA may publish a list of medical events that have to be taken into account for the detection of a signal~~".
The change of the first sentence is proposed because statistical analysis is complementary to other approaches for signal detection. It may or may not be supportive. Regarding the second sentence, it is not understood the concept of a public list of medical events that have been taken into account for the detection of a signal. What has to be documented is any Eudravigilance search terms, and this has to be part of the report analysing the signal.

Section 22
Second paragraph. The sentence "National competent authorities shall specifically monitor data originated in their territory"is not well understood. National competent authorities (and

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Regional centers of pharmacovigilance) have the responsibility of detecting signals, using every available data source.

Section 23
Third paragraph, last sentence: for products authorised in accordance with Regulation, the appointed rapporteur should be involved in the signal validation process.

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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.

AEMPS Comments:

According to Art 108 (d) of the Directive an implementing measure to be adopted by the Commission should state "the minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed". We consider that the implementing measure should be strictly limited to this provision and therefore should be limited to the detection of signals based on spontaneous individual safety case reports reported to the Eudravigilance database. Any reference to procedures or obligations related to other possible safety concerns (which may be also covered by the wide definition of signal) from other sources and type of date should be deleted. These other safety issued are covered in other pharmacovigilance procedures.

Regarding the role of EMA supporting the monitoring of Eudravigilance (Section 25), the access proposed should be considered as minimum. National competent authorities should have access to all data and tools for analysing them.

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F. Use of terminology

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

AEMPS comments

The proposed terminology is agreed.
Just to mention that it is stated that the terminology according to lit. (c) to (g) shall be applied as of January 2015. It may be more appropriate to state that shall be applied six months after the announcement of Eudravigilance full functionality. The same comment applies to page 17 when refers to the formats and standards according to lit. (a) to lit.(f).

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

AEMPS comments

The list of internationally agreed formats and standards is supported.

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G. Transmission and Submission requirements

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.

AEMPS comments:

There is a need for transitional provisions as regards of the format and content of periodic safety update reports, since the new ICH format may not be agreed before the implementing measures coming into force.

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Annex I – Electronic submissions of suspected adverse reactions

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

AEMPS comments:

We agree with the proposed format and content

Regarding annex 1, we have the following comments:

I Definitions
We think that definitions of misuse, abuse, medication error, overdose or occupational exposure should not be included in the implementing measure but in the guidance documents of good pharmacovigilance practices to be developed according to Art 108a of the Directive . The reasons are as follows:
- The proposed definitions are not useful for the purpose of a clear distinction of types of adverse events since the concepts are not clear-cut concepts. So, the same event can be classified both as misuse and as medication error, or as misuse and as overdose, for instance.
- The definitions are not needed for establishing reporting rules. The wide definition of adverse drug reaction including noxious and unintended effects also from the use of a medicinal product outside the terms of the marketing authorisation is sufficient for this purpose.
-Regarding the definition of misuse, is difficult to agree with this negative concept for uses outside the summary of product characteristics. There are uses outside the terms of the SPC that are supported by scientific knowledge and clinical practise.

3. Content of electronic transmission of suspected adverse reactions
3.1.- Member States and marketing authorisation holders shall make efforts to document well all individual cases, but this cannot be ensured, as proposed in the text.
3.2.-This point will not apply to medication errors, since patient safety organisations collect anonymised data.
3.3.- Overall, it is not understood the need of this point. In previous point is already stated that sufficient details have to be recorded in order to obtain follow-up information. The issue of pseudonymisation needs to be carefully considered, and is not mature enough to be mentioned in the implementing measures. It is not understood the relation between pseudonymisation of name and address and the assessment of ADRs.
3.4., firs paragraph: It should be specified that Member States and marketing authorisation holders shall provide all available information on each individual case <u>reported by the primary source</u>
3.4(d): What is meant by reporter identifiable information? Details are needed, since it may collate with national laws on data protection. Names and addresses will not be reported in any case.
3.4(m): We consider that to expedite a follow up report only to inform that "no additional information is available" creates an unnecessary burden in the receiver's system. It is understood that any report will contain the latest available information. It is clear from 3.1 that all available information has to be reported.

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Annex II – Risk management plans

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

AEMPS comments:

With regard to the proposed Part IV: It should include Plans for studies on effectiveness and long term efficacy that has been requested by competent authorities, according to the criteria to be detailed in the European Commission delegated act. Other studies which are not requested by competent authorities will be addressed in the periodic safety update reports.

With regard to the Part VI summary, which according to Art 106c of the Directive will be published in web portals, we note the relevance of the publication (and therefore the inclusion in the summary) of those risk minimization activities containing information targeted to healthcare professionals and/ or patients as Educational Materials and Direct Healthcare Professional Communications. We consider that imposing the publication of these materials in the European/national web portals along with the rest of the summary of the RMP would add great value to the publication of the RMPs. Therefore, we propose that summaries of RMPs should annex the materials and communications that the MAH has distributed to healthcare professionals and patients in the context of risk minimization activities.
The summary of the RMP (Part VI) should also include the planned studies together with a timetable.

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Annex III – Electronic periodic safety update reports

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

AEMPS comments:

The proposed format and content are agreed.

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Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety Studies

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

AEMPS comments:

The proposed format is agreed.

We have the following comments under 1. Scope and Definitions:
Points 5 and 6: Both the study protocol and the revised study protocol have to be submitted not only to EMA, but also to the Member State in which the study is to be performed or is being performed. The same applies to point 8 regarding the final study report and a public abstract

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