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

Pharmacovigilance System Master file

Consultation item no. 1:

Should additional processes and pharmacovigilance tasks be covered?

In our opinion, no additional tasks and processes need to be covered in the Implementing Measure. Additional clarifications will be included in GVP guidance.

Section 3, point 7 (a) states that the master file should contain a list of "documented procedures and processes related to pharmacovigilance activities and interfaces with other functions, with reference to their location". The meaning of "location" is unclear and it may be more appropriate to state "with details of how the procedures can be accessed".

Section 3, point 7(e) states that the pharmacovigilance system master file should contain: "Reference to the location of audit trails concerning the monitoring of the performance and the compliance of the main outputs of the pharmacovigilance system".
The meaning of the term "audit trails" is unclear in this context. It may be better to state "A description of the system for monitoring the performance of the pharmacovigilance system and compliance of the main outputs of the system".

Consultation item no. 2:

Notification of changes to pharmacovigilance system master file

In our view, a requirement should not be introduced for MAHs to notify significant changes to the content of the master file to national competent authorities (NCAs). NCAs have other mechanisms by which they may receive information concerning changes to the system e.g. changes to QPPV details and master file location details in variations/list of products updates; changes of ownership of authorisations; review of changes in the logbook when the master file is requested e.g. by inspectors prior to an inspection. If NCAs wish to obtain an overview of changes to the system, a copy of the master file can be requested at any time for this purpose (in accordance with Article 23.4) Therefore, it is unnecessary to introduce an additional legal obligation for notifications.

Section 2 (Location) requires changes to location of the master file to be notified after its implementation by updating the information contained in the list of products. However, it does not require the initial registration of the location of the master file in the list of products (see above comment). It would be useful to include this legal obligation in the Implementing Measure Regulation.

Consultation item no. 3:

Is it necessary to be more precise on potential delegation?

Section 6 (Delegation) states that the MAH may "delegate certain tasks". The MAH may delegate any pharmacovigilance task, including the compilation of the master file. It may be useful for the first paragraph to be amended to state this. It may be more appropriate for additional details relating to delegation e.g. to co-marketing partners to be covered in guidance.

Consultation item no. 4:

Should a copy of the audit report be retained in the master file?

In order to help to preserve the independence of the audit function, copies of full audit reports should not routinely be stored in the master file (although the reports can be requested by inspectors, if considered appropriate). Copies of audit schedules (containing details of planned and conducted audits of the pharmacovigilance system) should be included in the master file, as this enables the QPPV and competent authority representatives to confirm that audits have been conducted in accordance with the legislation. It would be useful to include this in the Commission Regulation.

Consultation item no. 5:

Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance system master file?

Inspectors require information on lists of ongoing post-authorisation studies in order to assist with inspection planning and checks of compliance. This has been omitted from the Concept Paper, but we would wish to see this included in the contents and this should be described in guidance.

Other comments relating to this implementing measure

Section 5 (documentation) adds the concept of a logbook. It may be a resource-intensive task for the MAH to keep the logbook updated with details of every change in the organisation (relevant to pharmacovigilance), changes to relevant procedures, changes to resource, changes to study details (initiated, ongoing and completed) etc. We consider that the logbook should record significant alteration only and clarification could be provided in guidance on what constitutes a significant alteration.

Additional provisions to be included to aid transition

The Directive states that all MAHs in the EU will have to produce a pharmacovigilance system master file by 21st July 2015 or on renewal of a marketing authorisation (whichever is earliest)). However, the Directive does not state that for authorisations granted before 21st July 2012, MAHs who have not submitted a pharmacovigilance system summary (containing details of the QPPV and the location of the master file) in an application or variation by 21st July 2015, will be required to submit such a summary (e.g. as a bulk variation for applicable authorisations). Article 104(3) requires MAHs to submit

the name and contact details of the QPPV to the authorities. However, for those MAHs who have not submitted a pharmacovigilance system summary, there may be no legal obligation for the MAH to provide updates of QPPV details or to provide details of changes to the location of the master file. This is a gap that could be addressed by introducing a requirement for the pharmacovigilance system summary (in addition to the master file) to be implemented for existing authorisations by July 2015.

Many MAHs will wish to transition from the DDPS to the pharmacovigilance system summary (and master file) at the earliest opportunity e.g. soon after July 2012, for all of the products covered by that pharmacovigilance system (even if no renewals are due). It would be helpful if the Implementing Measure Commission Regulation could state that MAHs may transition to the pharmacovigilance system summary (and master file) as soon as they wish to after July 2012, as long as this happens by 21st July 2015. Early transition would require the MAH to submit a bulk variation containing the pharmacovigilance system summary to cover all applicable authorisations. Early transition to the master file (for existing authorisations) could reduce MAH and NCA costs and resource involved in maintaining existing DDPSs.

In the pharmacovigilance system summary submitted in a new MA or in a renewal (after July 2012), MAHs must include the contact details of the QPPV and reference to the location of the pharmacovigilance system master file. In order to reduce burdens on MAHs and improve the efficiency of the process, it is proposed that the pharmacovigilance system summary in an application should contain:

- The name of the QPPV and the country location (Member State) where the QPPV operates with a cross-reference to the list of medicinal products required by Article 57(b) of Regulation 1235/2010 for the specific QPPV address details. In this manner, a variation would not be required if the QPPV and the country where they operate remain the same, but their address changes. This would eliminate the need for variations to be submitted if, for example, the telephone number of the QPPV changes.

- The country location (Member State) where the pharmacovigilance system master file is located with a cross-reference to the EVPMD for the specific address details. In this manner, a variation would not be required if the country location remains the same, but the address changes. The Concept Paper proposes that the site where the master file is located should be the same as the site where the QPPV operates. In which case, only one address will be required.

In order to implement this proposal, we propose that a legal requirement is introduced for the MAH, which clarifies that QPPV contact details and (by default) master file address details can be supplied by cross-reference to the Article 57(b) list, and which places an obligation on the MAH to update (as soon as a change occurs) the contact details of the QPPV and master file address details in the Article 57(b) list. This requirement is not

currently included in Article 57(b) of Regulation 1235/2010. We believe that the addition of these requirements to the Implementing Measure Regulation would be supported by the pharmaceutical industry as it would reduce the need for variations when address or contact details change, and by NCAs, as it would allow NCAs to have easy access to up-to-date information.

Quality systems for performance of pharmacovigilance activities by marketing authorisation holders

Consultation item no. 6:

Is there a need for additional quality procedures?

Yes, there is a need for additional quality procedures. Communication of relevant safety information to patients/consumers and healthcare professionals is equally important for MAHs and should be included in the implementing measure.

Consultation item no. 7:

Do you agree with the requirements for marketing authorisation holders?

The requirement to check the European medicines portal on each working day may be excessive and unjustified for some MAHs e.g. for some generic MAHs who only market products with well-established safety profiles. If a blanket requirement is considered necessary a weekly frequency is considered adequate

Once the system described in a pharmacovigilance system master file ceases to exist, there does not appear to be any justification for retaining a copy of the superseded master file for ten years. Compliance of the system that was previously in place can be assessed by examining the outputs from that system.

We consider that in section 13 the meaning of the following sentence is unclear and could lead to confusion: “The resource management shall be documented in the pharmacovigilance system master file”. The resource for pharmacovigilance activities should be documented as part of the quality system, but we see no reason why this should be included in the master file.

We also have noted that the text of the implementing measures refers to the obligations of marketing authorisation holders but the obligations also apply to traditional herbal medicinal product registration holders and we consider it would be valuable to have a cross-reference and further clarification in the implementing measure to reflect this.

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

Consultation item no. 8:

Do you agree with the quality system requirements?

Generally we are in agreement with the quality system requirements, with regards to the requirement for NCAs and EMA inform each other and the Commission in advance of public announcements relating to information on pharmacovigilance concerns we consider the implementing measures should fully reflect the legislation and recognise that such information sharing may not always be possible 24 hours in advance of such announcements should the MS need to make the announcement in exceptional circumstances due to an urgent public health issue.

The scope of the audits should be determined by an applicable audit strategy, which takes into account risk factors. It may be challenging for an MAH to audit all parts of its pharmacovigilance system (including interfaces, affiliates, third parties involved in pharmacovigilance activities etc) once every two years. In general, we would expect MAHs to adopt a risk-based approach to planning the scope and frequency of audits (and this should be clarified in guidance). The rationale behind the MAH audits would be examined during inspections.

Other comments relating to this implementing measure

It may be useful to include in the Quality Systems section a provision for CHMP to issue a Compliance Commitment/Infringement Notice when an MAH (with CAPs) is found to be seriously and/or persistently non-compliant with pharmacovigilance legislation. Such a notice would not be issued in every case where a critical finding is identified during a pharmacovigilance inspection, but may, for example, be issued where an MAH has failed to adhere to an agreed corrective and preventative action plan relating to serious non-compliance. The Compliance Commitment/Infringement Notice would specify the steps that the MAH must take and in what timeframe, in order to rectify the non-compliance(s) and in order to prevent a further case of non-compliance.

In addition, where the legislation may be unclear, an EU Compliance Commitment/Infringement Notice may add clarity by documenting the expectations of CHMP. If the Implementing Measure states that such notices would be published, this may be a mechanism not only to promote compliance and clarify the expectations of the authorities, but also to deter future non-compliance. The process for issuing such a notice (which would need to be developed) may be less complex than referral under the EU Infringement Regulation (658/2007). However, if the MAH fails to adhere to the conditions documented in a Compliance Commitment/Infringement Notice, this may facilitate a referral under the EU Infringement Regulation. Introducing this concept in the Implementing Measures would provide a legal basis for such notices.

Signal detection and risk identification

Consultation item no. 9:

Worksharing for monitoring of medicinal products

Work sharing in signal detection on Eudravigilance for non-CAPs is vital for the system to work effectively. Risks associated with the concentration of all tasks in one member state need to be mitigated by ensuring the data and decision making processes are documented and transparent (through the signal management system). Peer review for signal detection and PSUR assessment will be provided through scrutiny by other member states and discussion at the PRAC. Worksharing should be applied to equally to CAPs and non-CAPs.

Consultation item no. 10:

Are the proposed provisions sufficiently clear and transparent or should they be more detailed?

We consider that regular automated screening of all new data on Eudravigilance using measures of disproportionality would be the most effective and efficient approach for detecting new risks or risks that have changed. These statistical values indicate the strength of the association between a drug and a suspected ADR in a database, the higher the score the stronger the association. A threshold can be chosen and applied so if the statistical score exceeds the threshold then this gives you a potential signal. Thresholds are commonly applied to help manage signals so we do not generate too many false signals and these need to be set carefully. Statistical tools applied to Eudravigilance will help generate a signal and bring them to the attention of staff in EU so then we can appropriately apply clinical and scientific judgement in the signal evaluation process. Discussions are ongoing between EMA and member states as to the best methodology for signal detection in Eudravigilance.

Once there are agreed methodologies for signal detection on Eudravigilance, Member States and EMA should apply common criteria and principles to signal detection so all parties can scrutinise/query the Eudravigilance database themselves. In addition we consider that the use of different data sources and methodologies are necessary to enhance signal detection capabilities in the network.

EMA support in the monitoring of Eudravigilance database through provision of access to data, analysis and evaluation of the case reports and statistical signal detection methods is vital.

Given that MS and MAHs may not be able to take advantage of all the capabilities of Eudravigilance until full functionality has been established, the implementing measures and GVP guidance should also reflect the requirements in the transition period.

Use of terminology

Consultation item no. 11:

Do you agree with the proposed terminology?

It is recommended that where a required term is not available MS or MAHs should make a request to the responsible organisation for addition of this term. Either within the implementing measures of guidance clarification should be provided as to what is the expectation in the interim – as it may be crucial, in order to meet reporting timelines etc, for the next best term to be utilised whilst a decision is being made about the addition of the specific term, this is particularly important given that for IDMP the process for updating has not yet been defined.

Consultation item no. 12:

Do you agree with the list of agreed formats and standards?

Whilst we agree with the list of formats and standard, we do have concerns regarding the requirement for the format and standards in section 28 (a) to (f) to be applied as of January 2015. We consider this may be too rigid and suggest there does needs to be an element of flexibility around this timescale, particularly since there will no doubt be a need for back and forward conversion between systems and to implement to this time frame would have considerable resource and cost implications.

Transmission and Submission requirements

Consultation item no. 13:

Is there a need for additional transitional provisions with respect to this implementing measure?

We do not think that additional transitional provisions are required for this implementing measure.

Consultation item no. 14:

Do you agree with the proposed format and content?

Annex 1 Definitions: We do not feel that it is appropriate to include the current definition with respect to adverse reaction reports in the implementing measure. This is because these current definitions have some overlap, especially those relating to abuse, misuse and medication error. We consider further work is needed to better define these areas to provide the clarity required. Hence it may be premature to include them at this stage until this further work is complete.

Consultation item no. 15:

Do you agree with the proposed format and content?

We agree that this adequately covers the key requirements.

Consultation item no. 16:

Do you agree with the proposed format and content?

Annex 3: According to the Directive, the QPPV is no longer personally responsible for the preparation of PSURs. The QPPV should be able to gain assurance that PSURs are being produced in compliance with the legislation. This assurance can be gained from the QPPV's knowledge of the quality system and from review of compliance/QC and audit/inspection data. In our view, it is unnecessary for a QPPV to have to sign every PSUR produced by an MAH. In some major pharma companies, this would mean that the QPPV would have to sign over 300 PSURs a year and very few QPPVs will sign a PSUR without reviewing the document (as such a signature would have little meaning). Reviewing all PSURs is not always practical for a QPPV and if the MAH has implemented sufficient controls (and an adequate quality system) this may be unnecessary.

Consultation item no. 17:

Do you agree with the proposed format and content ?

We agree that this adequately covers the key requirements.

Medicines and Healthcare products Regulatory Agency
November 2011