BARQA COMMENTS ON CONCEPT PAPER

IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED IN DIRECTIVE 2001/83/EC AND REGULATION (EC) No 726/2004

The Research Quality Association (BARQA), as a stakeholder association representing marketing authorisation holders and health professionals involved in research, appreciates the opportunity to review and comment on this concept paper.

Please find responses from BARQA members to the specific consultation items as well further comments on other parts and aspects of the concept paper.

Consultation item 1 - Should additional processes and Pharmacovigilance tasks be covered?

Should also include Contracts oversight Compliance
Does this include the new requirement for the production of Development Safety Update Reports?

Consultation item 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?

We disagree with the need to notify significant changes as the log book referred to under section 5 could fulfil this role. As the logbook will record all significant changes and would in effect summarise the changes/modifications to the Master file.

To keep an amendment log would be advisable giving dates/nature of amendment and date of last review. We would recommend the log book to be used for this purpose. And suggest minimum frequency to then be annual.

The documents/sections within the PV Master file can be versioned appropriately identifying when it was last updated. As with any essential document, good documentation practices should be employed.

The MHRA compliance questionnaire can be used for the agency to keep track of what is happening by the industry. Perhaps the EM can do something similar and have it electronically captured on an annual basis. The changes which the EMA find interesting, can be collected and processed as appropriate. Or annual summary of changes prepared from

the log book could be submitted to the CAs as a means of alerting them to significant changes.

Consultation item 3 - Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

Would this require copies of all agreements (distribution, manufacturing, etc) globally (where the products is also available in the EU) be held with the PV Master File, or can reference be made to where these agreements are kept (Central contracts group etc.). We would prefer that reference can be made to where the agreements are kept and retrieved on request.

Also, what about clinical trials involving marketed products? Should those agreements also be placed within the Master File (copied) as they also form part of a TMF?

More details would be needed about what is required and how it should be presented. Would a table of responsibilities be sufficient per region, country etc. If License partners, etc. are included than this could be a very large part of the file.

Consultation item 4 - Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

BARQA does not believe a copy of audit reports should be retained in the master file. There needs to be some sensitivity between the independents QA's ability to report objectively audit observations, without inducing censorships of the reports or the finding ratings.

If this stays as a requirement how many years worth of audit activities should be kept on the PV Master File?

Would the audits include the whole system where a product authorized in Europe may be affected? For example would you want information from GLP, GCP, GMP audits that related to patient safety would corporate audit departments' audits also need to be included? Please see additional comments later on.

Will inspection reports from CAs also be required to be summarised and placed in the Master File? Who will prepare the summary?

We agree a copy of the schedule would be fine and updated schedule confirming that the audits occurred should be sufficient but only supplied as requested.

Audit schedules (historical and planned) would be an appropriate means by which audit activity can be clearly shown, although it would also be necessary to summarise any deviations from planned audit schedules, which may be resisted if failing to complete a planned audit lead to inspection findings.

Consultation item 5 Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment

In general we agree with the requirement as it will help the MAH with inspection readiness. Additional comments later on

Consultation item 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?

BARQA does not believe there is a need for additional quality procedures.
However, In addition to providing information to prevent duplication between healthcare professionals and the MAH, consideration for submissions by CROs should also be taken into account. In circumstances where the responsibility of PV may be delegated to the CRO from the Sponsor, the CRO are obligated to report SARs/SUSARs in accordance with the Regulations, and may also be required report the same events to the MAH (who then duplicate the report at the level of EVWeb)

Consultation item 7 Do you agree with the requirements for marketing authorisation holders? Please comment
BARQA agrees with sections 12-14. Archiving section is also ok if this is the section the question relates to.

Consultation item 8 - Do you agree with the quality system requirements? Please comment, if appropriate separately as regards for marketing authorisation holders, national authorities and EMA.
BARQA disagrees with section 10 audit - stating that "audits of quality system shall be performed at regular intervals and not less than every 2 years, to assure that the quality systems is in compliance with the established quality systems requirements and to determine its effectiveness" BARQA believes a risk based approach should be utilised in implementing audit programmes.
BARQA also would like it to be agreed that a risk based approach to audits should be accepted by Competent Authorities and as this concept is already applied to inspections by Competent Authorities.

Consultation item 9 - For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medical 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
A peer review system is always beneficial as information can be missed. Also, if one member state is involved all the time, they may become too familiar with the product and

may miss some things that an independent person/group would not miss. We think this should be considered.

Consultation item 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
It would also be interesting to see how EMA and other authorities are working together to identify signals. There are international programs for inspections between the EMA, FDA, PMDA, why not include Signal detection and validation activities in this as well?

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

Consultation item 12 Do you agree with the list of internationally agreed formats and standards? Please comment
Terminology and format are fine.
ICH-E2F "Guidance on Development Safety Update Report" should be included.

Consultation item 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
No comment

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

Consultation item 15 Do you agree with the proposed format and content? Please comment.
We agree, there should also be a version history as well as a version number.

Consultation item 16 Do you agree with the proposed format and content? Please comment.
We agree.

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

<u>Additional points</u>
There appears to be no instruction for MAHs to relay signal detection / emerging safety information to non-commercial research partners / CROs in this document. Should this be included?
Although this legislation is aimed at MAH level, there is no equivalent for non-commercial

level, is this due to be developed?

Section 1 definition:
Page 5
Do we need one PMF per MAH? In that case will Affiliate offices be required to have their own as a local MAH when they are MAH for local registered products?

Section 2 Location
Page 5
Which Qualified person: the EU QPPV or/and the local QP (eg the French Pharmacien Responsable)? Can this be clearer if it means EU QPPV.
This suggests a paper file but essentially, the file will likely be electronic. If electronic, what does this mean with respect to the location of the QPPV? The servers will likely be in different locations with appropriate redundancy in at least a second location.

Section 3 Content
Page 5
What does "relevant" mean in this context? Is this any product with an authorisation in EU or EEA?
Is this only for products where the company is the MAH or would this also include license partner agreements as well?
Page 6, item (3)
For section 3 and 4: This covers only EU Territories? What about agent in others territory or LP?
Page 6, item (4)
Where tasks and responsibilities have been delegated to a CRO, would the locations of the CRO where the tasks are performed also need to be in there. Would this cover any and all cases for products authorized in EEA?
Page 6, item (5)
If several systems are used, for example for medical information, literature search databases, Websites, the Global safety database. Would all these systems need to be described?

Page 6, item (6)
Would the inclusion of the SOP references be sufficient or would these items need to be outlined. Assuming a general / high level description would be sufficient.
Page 6, item (7) (a)
Where would this stop? Do local SOPs have to be covered?
Page 6, item (7) (c)
At what level does this need to be described at global level or only EU related?
Where does this stop? Do local Training and LP /Agents training have to be covered?
Most training files tend to be electronic and can be printed or viewed anywhere, so no specific location.
Also, would CRO staff training be included in here? What is expected, only the core MAH training or others that are involved in Pharmacovigilance system Global CROs, Affiliate offices etc.?
Page 7 item (e)

Should this also include proof of system validation / validation rules?

Section 4 Maintenance
"Continuously up to date", what does this mean in practical terms? Up to date on a quarterly basis? More frequent?

Section 5 Documentation
"Any current deviations" Is that covering deviation to processes or deviation to procedures
We would suggest a modular content with revisions and revision histories for each module. This will make it easier to maintain and be compliant.

Section 6 Delegation
" a description of the delegated activities and/or service provision.." How far do we have to go until the agent?

Section 7 Audit
Would audits of license partners (LP), CROs and affiliates or just central pharmacovigilance system audits be in here too? Do you keep the LP audit of your own company and a company's audit of their LP?
What is the definition of main when used in context "main findings of the audit"? Would this 'note' be prepared by the audit function? We would suggest instead of including findings for each audit to have an audit overview across the audits and a status of the CAPAs across the findings. We would not include the categories "critical, major, minor" etc. for the findings.

Section 8 Inspection
Is it only the National competent authority in the country where the QPPV is location the only authority (besides the EMA) that will have access to the file? Can any EEA competent authority request access to the file?
Is seven days a realistic timeframe? The Master File can be maintained as paper or electronic – however, how should it be provided when requested? Will the EMA and CAs have stipulations around what format (file type) they can receive documents in (if supplied electronically)?

It would be useful to understand, where there is potential for documents to be held in duplicate locations, if cross referencing is appropriate? Also, if contracts/agreements are placed within the Master File, should financial details be redacted?

Section 10 Audit
The MAH should ensure quality oversight of the PV System, outside of audits. There should also be self monitoring activities and compliance monitoring, review by the management and continuous improvements included in the system. There should NOT be such a heavy reliance on the QA function to ensure that the PV system is in control. The function(s) also need to take ownership of this as well.

Every two years is too short an interval unless this is specific to a general systems audit. Process audits etc. general systems audits, etc. together every two years would keep the MAH in a constant cycle of audits and CAPAs. The system/processes also needs some time to stabilize.
Audits should be performed using a risk bases approach. Also important to clarity the need to effectively utilize the results from audits in strengthening and improving the PV system as a whole. There should be more emphasis put into the guidance in relation to effective CAPA management.
We would like to propose that the removal of the following text as it is not in the legislation and actually changes what is required. Fully implemented is sufficient. "… ***which is taken to mean that correction and/or sufficient improvement can be demonstrated or has been verified."***

Section 11 Performance Indicators
Need guidance on which aspects of the PV system requires performance indicators. We assume compliance metrics as currently produced is definitely included.
Should be clear if the also includes audit metrics and trends seen from audit activities.

Section 13 Resource Management
If there is a split between the QPPV and the Head of Safety department what would "sufficient authority" mean, to influence the performance of the quality system and the PV activities?
Are competencies assessments more of an HR record, as opposed to a training records?
Also, how do countries get around local privacy laws, if required to include in master file?
There is no requirement for general safety training and collection of safety data. Perhaps this should be included as it is fundamental to the PV system.

Section 14 Compliance Management
Page 11
It should be clear who is doing what when activities are delegated. If the CAs are, for example, performing literature searches and these articles are include in the database, they should make it clear which articles/journals are searches so that cases from these are not submitted, thereby preventing some duplicates.

Section 15 Record Management
Does this include audit reports and which retention period should be applicable to audit reports if included?

Section 18 Compliance Management
Item (e)
Perhaps the MAH should have a way/route of commenting on inspections conducted by the national competent authority. Perhaps this can be to the EMA, in order to avoid conflict with the local authorities. As many local authorities are just starting their inspection programs, objective feedback may be helpful for them to move their inspection process forward quickly and efficiently.

Section 25 Signal detection support

This is good. We would want to see the validation of the methods used and the effectiveness checks done to ensure that the methods are working as planned. The terminology and formats are fine

Annex I
Item 4 (b)
The original language should be sent. If a translation is required, it should be a QC'd / validated translation. There have been examples noted where the English abstract published does not match the original language abstract.

Annex II
We would expect that the implementation plan would be documented for the Risk minimization measures including methods for measuring effectiveness.

Annex IV
Item 15 Annexes
What about requirements for auditing?