4th November 2011.

EC 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)

AstraZeneca comments.

1. General comments

AstraZeneca welcomes the opportunity to provide feedback to this Concept Paper. AstraZeneca has had the opportunity to contribute to the EfPIA comments to the 17 consultation items presented within the Concept Paper and agree to those. Additionally, AstraZeneca would like to provide further comments to some of the consultation items, as well as more detailed comments asking for clarification. These follow the responses to the specific consultation items.	

2. Specific comments

Consultation item 1: Should additional processes and pharmacovigilance tasks be covered?

Comment: *Yes.* Section 6e seems to be mixing two things together – the variations procedure for updating the product information and the communication (whether urgent or routine) of product information to patients/health care professionals.
AZ suggests clarify or separate the two aspects separately, i.e. 1) one process for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet and 2) one process for communicating urgent safety concerns to patients and health care professionals.

For II. A. 3 (1) Content of PSMF we suggest to delete the requirement to list authorisation procedure, authorisation number and marketing information in the PSMF and allow the MAH to reference the full product listing EVMPD as that has to be maintained and managed. A list can be generated if needed.

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 MA. Therefore changes to the content of the master file will no longer be subject to variation obligations. Would it nevertheless be appropriate to require the MA 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?

Comment: No. AZ feels that it would not be appropriate to require the MA holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks. Such notifications would undermine the concept of moving away from regulatory variations, thereby reducing regulatory burden. A notification system implies multiple "approvals" from competent authorities which would have to be tracked and monitored separately. The master file will contain a logbook recording all changes, dates and reason for change. This should be sufficient for tracking purposes.

The MA holder is obliged to notify changes defined in article 23 to the EVMPD within 15 days, this should be adequate. The MAH will record the amendment in the master file and retain a revision log. The PSMF is not submitted as part of the MAA and not subject to the variations regulation. Future guidance should address the details of how HMA or EMA will request a copy of the PSMF.

Consultation item 6: Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Art 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to process for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reports in the Eudravigilance database?

There is no need for additional quality procedures however a web-portal notification is a broad term and could impact on product information and timelines for action by MAH. AstraZeneca therefore asks the commission to confirm that activities under the Pharmacovigilance Legislation are aligned with the Variations Legislation as relevant to the maintenance of safety information in the Product information. If product information needs to be updated a formal variation has to be provided to the RA, MAHs are not in a position to amend product information based on notification to a website of a conclusion or recommendation. The activities under the pharmacovigilance legislation must be aligned with the maintenance of product information. AstraZeneca would like to ask you to consider if the MAH be updated via email alerts instead.

Consultation item 7: Do you agree with the requirements for MA holders? Please comment.

Comment: No. The proposed 30 year retention period is much longer than existing periods specified for other medicinal product-related documents in EU legislation. Imposing a much longer retention period than many companies may currently follow will have potentially significant consequences, including increased cost of retention (larger storage facilities – paper and/or electronic – for longer) and iniquity in information available between existing/recently terminated products and products for which the companies' (shorter) retention period has already passed.

The EU Commission should provide justification for the choice of retention period and be more specific on the documentation required to be retained. The total retention period for a given product could be in excess of 70 years assuming development, active marketing phase and 30 years post-commercialisation. We are not aware of any validated methodology that will allow companies to confirm compliance with this retention period.

Proposed change: Realign the retention period with the requirements in Annex I 5.2.c of Directive 2001/83/EC, relating to retention of final clinical study reports: these documents must be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

Consultation item 11: Do you agree with the proposed terminology? Please comment.

Comment: AZ agrees with the proposed terminology but not how the terminology is being applied by the EMA. The scope of the ISO standards is broader than the facilitation of pharmacovigilance and signal searching. These standards were developed to provide a single format for the exchange of information in all interactions between stakeholders within the pharmaceutical domain. It is therefore difficult to see how these standards can be implemented solely for the purpose of Pharmacovigilance ahead of their application to all other interactions with Competent Authorities.

Proposed Change: The ISO terminology should only be applied when these standards have been adopted and implemented via ICH. Application of these standards in isolation to pharmacovigilance and in particular the EVMPD described in Art 57 is excessive and impractical for the intended purpose.

Consultation item 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

AZ agrees with the list of internationally agreed formats and standards, with the exception of item (a), relating to the EudraVigilance Medicinal Product Report Message (EVPRM). As discussed at EMA on 20th September 2011, a certain amount of data will have to be submitted to EudraVigilance by 1 July 2012 in order to comply with Article 57(2) of Regulation (EC) No 726/2004, as amended by Regulation 1235/2010. Despite this, we are concerned about the extent and scope of data required for submission, as detailed in the EMA Legal Notice of the 1st of July 2011 and follow up communication in September 2011, as this goes beyond the text of the legislation.
We would welcome the opportunity to have dialogue with the EMA and HMAs accountable for implementation on the methodology and approach for development of the database EVMPD described in Art 57 (2).

Below are more detailed comments asking for clarifications in the PV Guidelines

Consultation item 1 II.A.3 (6) (a)	Comment: What does "…and the result of evaluation" mean in this sentence? In the PV Guideline we ask you to clarify whether this means that a process for the evaluation of results should be included. Otherwise which "result" is referred to?
Consultation item 2	In the PV Guideline we ask you to clarify "It shall be continuously kept up to date", i.e. regular review, weekly /monthly.
Consultation item 6	In the PV Guideline we ask you to clarify what level of detail is needed for Resource Management - "The resource management shall be documented in the pharmacovigilance system master file"
Consultation item 9 II.E.24	In the PV Guideline we ask you to clarify if the MAH can make a request to the coordination group for a lead Member state for work sharing? Presumably the coordination group will also take into account where the product(s) is/are registered under the Centralised Procedure and already have a Rapporteur assigned, as well as RMS for MRP etc.
Consultation item 14 Annex I Electronic submissions of suspected adverse reactions	Comment on Annex I Definitions: Abuse – abuse may not be accompanied by harmful physical or psychological effects. AZ would like to recommend to remove this statement to ensure all cases of abuse is included within the definition Company Clinical Comment (CCC) is not specifically mentioned as required within the content of electronic transmission of suspected adverse reactions. In the PV Guideline AZ ask you to clarify if CCC is out or scope for this kind of reports or if this is an actual change in requirements?

Consultation Item no 15	Comment: The last paragraph of section 1.2 seems to suggest that RMPs may have to be submitted twice and possibly in two different formats – in the CTD, and electronically to national competent authorities or EMA. To avoid duplication and additional work, AZ would like you to clarify in the PV Guideline if the format of the electronic version is acceptable for inclusion in the eCTD. In cases where the MAH has submitted the electronic version in the eCTD, no separate submission should be required.
Consultation item 15 Annex II Risk Management Plans	In the PV Guideline AZ ask you to provide further guidance on production of RMPs for generic products, in the context of not having access to the complete product information kept by the IMP originator. In the PV Guideline AZ ask you to provide more detailed guidance on the content required for an Abbreviated RMP. In the PV Guideline AZ ask you to provide guidance on how to approach a situation where an active substance used in separate products have different indications and thereby might have dissimilar risk profiles. In the PV Guideline AZ ask you to provide further guidance on principles for how to monitor the outcome of risk minimisation effectiveness if only the product information as per SmPC etc is used as risk minimisation measure. In the PV Guideline AZ ask you to clarify whether generic products are within scope of the monitoring requirements for products that do not have a RMP. In the PV Guideline AZ ask you to provide guidance for any specific format or content requirements regarding Part VI of the RMP.
Consultation item 16 Annex III, 1.1, 2	In the PV Guideline AZ ask you to clarify if there will be allowance for how cumulative data is presented for older products.
Consultation item 16 Annex III, 1.1.3	This section needs clarification, especially concerning the data relating to volume of prescription and also concerning the qualitative analysis in relating to indicated use. Please clarify in the PV Guideline what kind of data is expected.
Consultation item 16 Annex III, 1.1, 5	In the PV Guideline AZ ask you to clarify what will be the criteria for including listings and how this will be communicated? In e.g. addendum reports, listings have been included as essential part.
Consultation item 16 Annex III, 1.1, 6	AZ asks you to clarify in PV Guideline if existing lists for synchronisation and worksharing will be adapted. Even though frequency may change we hope that reporting periods already established can be maintained as we have done a lot of work with other countries to align to the dates used for EU.

Consultation item 16 Annex III, 1.1, 6	AZ asks you to clarify in PV Guideline whether MAHs will have any opportunity to request multiple product PSURs, or if this will be presented to us as a pre-determined list. To have all products in one PSUR could result in a very large document.
Consultation item 16 Annex III, 1.1, 7	AZ asks you to clarify in PV Guideline whether both options will be available to an MAH to choose and if we need to decide this in advance to be included in lists.
Consultation item 16 Annex III, 1.2, 1	Currently PSUR is presented in module 5.3.6. AZ asks you to clarify if the intention is that it is presented in the same place as one document, but comprising modules that may be extracted by reviewers. We also ask you to clarify in the PV Guideline How much is expected concerning Effectiveness Information.
Consultation item 16 Annex III, 1.2, 6.3	AZ asks you to clarify in the PV Guideline if there are specific requirements for the content and format of the Cumulative and Interval Summary Tabulations from Spontaneous Data sources.
Consultation item 16 Annex III, section 7 of PSUR	AZ asks you to clarify in the PV Guideline definitions of ongoing and completed Clinical Trials. As this information may be common to both PSUR and DSUR we need to ensure that it is clear.
Consultation item 16 Annex III, section 12 of PSUR	Presumably we can use this to refer to other reports e.g. for a combination product. AZ asks you to clarify in the PV Guideline if this section also requires information on e.g. generics. Could DSUR also be cross-referenced here?