Responses from the GCP-Records Managers Association on the 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 The Concept Paper Submitted for Public Consultation (dated 8th September 2011)

The GCP Records Management Association supports processes that will genuinely harmonise the performance of pharmacovigilance activities. It is to be welcomed that this should lead to increased transparency in regulation and avoidance of overlap between different implementing acts. However there are some points in the Consultation Document that the GCP-Records Management Association feels should be clarified and these are represented in the responses below.

A The pharmacovigilance system master file

Consultation Item No. 1: Should additional processes and pharmacovigilance tasks be covered.

The document does not appear to clearly define the meaning of the Pharmacovigilance System Master File, and whether it is intended to describe the processes solely or include records (outputs) of pharmacovigilance activity. If it is the latter then there would be extensive overlap with GCP Trial Master File documentation already collected to support Marketing Authorisation Applications.

We feel that the document would benefit from an Annex, similar to ICH Good Clinical Practice (E.6; R1), to present what are regarded as essential documents to describe the pharmacovigilance system and master file. Such an Annex could also indicate which documents should be available pre- and post-marketing authorisation and the location where these should be held. If the pharmacovigilance system master file is intended to cover a controlled and approved description of processes as well as records of activity then there should be some qualification in respect of the Essential Document list defined in ICH Good Clinical Practice (E.6; R1) for the Trial Master File. Such clarification would help avoid the confusion often associated with duplicate filing.

However if the intention of the pharmacovigilance system master file is to cover post-market products only, then it is unclear what mechanisms should be adopted for pre-market clinical trial investigational medicinal products. In this case there would be a risk of operating dis-jointed dual quality systems, unless the pharmacovigilance system master file is considered a sub-system of the Trial Master File.

Furthermore, we consider that the location of the pharmacovigilance system master file at the site where the Qualified Person operates may not be practical. It may be better to state that the system master file must be accessible at all times to the Qualified Person. This is particularly important as electronic records systems are increasing in use.

The comment in section (5) Documentation (p7. Para. 2) would seem to imply that auditors and inspectors will be reviewing paper copies of electronic files, even if the system is completely electronic with data having been captured directly or digitised.

We would suggest that fully electronic systems should be audited or inspected by review of the electronic files. Best practice should be to audit data at or as close to the source as possible.

For the comment in section (5) (p7. Para. 4) we recommend that the master file logbook be made available in an electronic format rather than creating additional paper records.

For the comment in (7) (p8: Para. 1) we presume that "all completed audits" covers internal and external audits as well as regulatory inspections, but request that this be explicit to avoid any ambiguity. The comment (7) (p8: Para. 2) should recognise that the CA PA systems are generally external to the PV system; these should be integrated into company-wide processes, including pharmacovigilance systems, within the overall Quality System. It would not be good practice for companies to operate dual corrective / preventive action systems, merely in order to separate pharmacovigilance activities from the rest of the Quality System.

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.

We suggest that audit reports should not be kept in the Master File. We consider that placing the audit report in the master file would compromise the independence of the audit process and may deter effective process and quality improvement initiatives.

ICH GCP requires that only the audit certificate is retained in the Trial Master File as the evidence of audit conduct. This would be the preferred practice for audits of pharmacovigilance. Furthermore, as audit schedules are used as planning tools of audits to be conducted, these would not seem to be appropriate documentation of audit conduct.

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

We think that it needs to be recognised that as a practical matter the physical location of the pharmacovigilance master file may change during the course of the clinical development programme from pre- to post-market. Furthermore, to insist that the system master file available located at site where the QP operates may not be practicable. It might be preferable to expect that the pharmacovigilance master file is accessible to the QP at all times irrespective of the physical location of the Master File and the QP. Where the PV master file is electronic, in a validated system, the key issue will be access (rather than physical location).

C. <u>Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders</u>

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

Retention times of 10 years beyond the lifetime of the pharmocvigilance system for pharmacovigilance system related documents; and 30 years after the cessation of the marketing authorisation for product-related documents would seem incompatible with the legal limitations applicable to the reason why the records are being kept, i.e. to protect patient safety. It must be considered that PV records are not unitary but consist of multiple records. Furthermore, Directive 95/46/3C on the protection of personal data requires that personal data (both directly and indirectly identifiable data) must not be retained for longer than necessary to achieve the legitimate purpose of its collection. A 30 year time-span appears to be incompatible with the Directive and Member State data protection laws in this respect.

We refer back to our earlier comment that an essential document-type description for pharmacovigilance system records would be helpful. Such a list will introduce standardization across industry and will make it possible to identify overlap with ICH-GCP Trial Master File essential documents. We feel that further clarity and definition is needed on what is covered by the term “product-related documents”, and how these relate to the system.