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British (BSTP), French (SFPT), Indian (STP-I), Japanese Societies (JSTP)
and the International Federation of Societies of Toxicologic Pathologists (IFSTP)

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Comments to "Draft OECD Guidance on the GLP Requirements for Peer Review of Histopathology"

Dear Mr. Gray,

The community of Toxicologic Pathologists has recently been informed of a new draft version of an OECD advisory document "Draft OECD Guidance on the GLP Requirements for Peer Review of Histopathology." It is our understanding that the OECD considers the current document to be a near final version of the document elaborated by the OECD Working Group that was previously shared with the various international societies of Toxicologic Pathology (STPs) in July, 2010. The respective STPs and the IFSTP (International Federation of Societies of Toxicologic Pathologists) had previously provided comments on this document (gathered from their memberships) to the OECD Working Group in October, 2010. It was anticipated that the pathology community would have additional opportunity for comment once the document had moved to a more mature state. We have several important concerns regarding the guidance document. We believe these concerns must be addressed before such guidance is finalized if it is to be effectively instituted. Also, it is our understanding that it is common practice for subject matter experts (in this case, practicing toxicologic pathologists) to be included on any Working Group generating such guidance documents, and we think that the inclusion of such individuals would be of great benefit.

We appreciate that the OECD Working Group has significantly modified the previous 2010 draft document. We recognize that part 1 (Background) of the current draft document adequately presents the context of a peer review as proposed in the recent "Recommendations for Pathology Peer Review" (Morton et al.,Toxicologic Pathology, 2010). The Morton et al. publication has been endorsed by all major toxicologic pathology organizations including the American Society of Toxicologic Pathology (STP), the European Society of Toxicologic Pathology (ESTP), the Japanese Society of Toxicologic Pathology (JSTP), the British Society of Toxicologic Pathologists (BSTP), the French Society of Toxicologic Pathology, the Italian Society of Toxicologic and Experimental Pathology, the Society of Toxicologic Pathology— India, the Korean Society of Toxicologic Pathology, the Latin American Society of Toxicologic Pathology, and the American College of Veterinary Pathologists.

The subsequent paragraphs 2 and 3 (GLP Requirements and Compliance) also largely refer to existing best practices as described in the aforementioned Morton et al. publication and other documents listed in the Reference section at the end of this letter (e.g. Peer Review Statement document, clear

designation of a Peer Review pathologist in the Study Plan, appointment of an expert group (PWG, Pathology Working Group) etc.). However, the OECD document goes on to list additional expectations in the main body of the text which do not comply with recognized peer review best practices. These specifications have raised significant concerns in toxicologic pathology and quality assurance communities, as well as GLP-compliant pharmaceutical and chemical toxicology test facilities and contract research organizations. Some of these additional expectations lack clarity, seem contradictory within the document, or dramatically change major aspects of conducting and documenting peer review activities for GLP studies. It is uncertain if this was the intention of this document, but compliance with this draft OECD guidance document will require substantial alterations in internationally accepted peer review processes. It is important that the expectations in the guidance document are more clearly defined so as to be better understood by the groups responsible for implementing the final OECD guidance. We also feel that it is important that any expectations in the final guidance remain consistent across all international regulatory agencies. Below we list some of our points of concern; note that this list is not comprehensive.

Major points of concern are:

- Lack of clear distinction between prospective and retrospective peer review and clear acknowledgment of different types of peer review during the reporting life-cycle.

- Requirement to appoint the peer reviewing pathologist as Principal Investigator if working remotely from the Test facility (irrespectively of the peer review type and despite the fact that the peer review pathologist does not generate raw data or a contributor report (QC character of a peer review) prior to finalisation of the Study pathologist's report (2.3.)).

- Definition of histopathology slides as raw data, in contrast to current understandings and practices communicated by authorities (FDA GLP Regulations, 21 CFR Part 58, 1987) (2.4.): Histopathology slides are archivable specimens, according to the FDA GLP Regulations.

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/NonclinicalLaboratoriesInspectedunderGoodLaboratoryPractices/ucm072706.htm

- Inconsistencies and lack of clarity regarding both general expectations and the precise nature of documentation during the peer review and reporting life cycle. For example, section 2.10 indicates that "In most cases it will not be necessary to report in detail the outcome of the peer review"; however both sections 2.7 and 2.10 indicate that "…if changes are required these are clearly documented and explained in the final report;") . These statements are seemingly contradictory. Due to the iterative and collaborative nature of peer review as summarized in Morton et al, the majority of pathology peer reviews result in some modification of either the preliminary study histopathology data tables or the draft study pathologist's report prior to its finalisation. In the majority of peer reviews, the primary and peer review pathologist reach consensus on the histopathology findings and their overall interpretation before finalization of data and contributing scientist report. Therefore, the requirement to include in the final study report a listing of all changes made to draft data/reports does not add value and has the potential to create confusion in the final study report.

- Capability of the study director to assess expertise of the reviewing pathologist and the quality of the peer review process (3.2.) without involvement of the Test Facility/Test Site Study pathologist's management.

The practice of peer review is strongly endorsed by the international Toxicologic Pathology community, and we agree that for GLP compliance it is essential that "…peer review procedures are planned, conducted, documented, and reported such that the integrity of the regulatory study is not compromised and activities can be fully reconstructed and verified."(4.1). However, we consider that the current document will not achieve this objective, given the number of shortcomings (mainly in part 2 and 3), and the lack of acknowledgment of the variety of situations under which a rigorous peer

review can be conducted and regulated in test facilities and test sites. In our opinion, this guidance should be revised before final approval to provide clarity on expectations, and so as not to create confusion for pathologists, study directors, quality assurance auditors, and test facility/site management if this draft is implemented in its current form.

In order to strengthen the histopathology peer review process in the pharmaceutical and chemical industry and contract research organisations, we strongly recommend that the OECD Working Group assign recognized subject matter experts (practicing Toxicologic Pathologists) representing international toxicologic pathology societies to assist in the preparation of the OECD Guidance on the GLP Requirements for Peer Review of Histopathology. We feel important modifications to the guidance must be made to ensure effective institution and added value in the pathology peer review process and report quality.

The Presidents of the ESTP, STP, BSTP, SFPT, JSTP and IFSTP thank you for the opportunity to review these draft guidelines and hope that suggestions provided will be taken into consideration by the OECD Working Group. The point of contact for this matter is: Annette Romeike, Dr med.vet., D.A.C.V.P. , ESTP Committee Chair for Scientific Standards (Tel. +33 6 22 16 58 87, email: annette.romeike@covance.com).

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