**European Society of Toxicologic Pathology (ESTP)**

***Division of Dockets Management (HFA-305)***
***Food and Drug Administration***
***5630 Fishers Lane, Rm. 1061***
***Rockville, MD 20852***
***USA***

October 18, 2019



*Docket number 2019-16361*

Dear Madam or Sir,

The European Society of Toxicologic Pathology (ESTP) is a non-profit organization with a membership of over 300 pathologists and other scientists whose principal aim is to support the scientific interests of toxicologic pathology, to aid in the research of spontaneous and toxic changes, and to further promote the importance of toxicologic pathology as an independent, specialized area. The ESTP is mainly European in extent and has members in industry, government and academia. We are currently one of the largest professional associations of study pathologists and peer review pathologists for nonclinical toxicology studies worldwide. We closely collaborate with the American Society of Toxicologic Pathology (STP) , as well as other co-existing European professional societies of toxicologic pathology (e.g. British Society of Toxicologic Pathology (BSTP), French Society of Toxicologic Pathology (SFPT)), and further international professional societies of Toxicologic pathology.

The ESTP and its membership has been actively involved in correspondence with the OECD Working group on Peer review during the establishment of the first OECD Advisory document No.16 between 2010 and 2014, and has also contributed in STP expert working groups, publications and commentaries on the scientific and compliance aspects of peer review (Fikes *et al.*, 2015; Morton *et al,* 2010).

The ESTP Committee of Scientific Standards has reviewed the FDA's Draft Guidance for Industry: *Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers (Docket ID: FDA-2019-16361)*. This committee includes members from the biopharmaceutical

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industry, chemical industry, contract research organizations, and consultants working as study pathologists and peer review pathologists.
In this document we provide the comments and concerns raised by our ESTP Committee of Scientific Standards (CSS) and ESTP Executive Committee and suggestions for your consideration in tabulated form.
We sincerely hope that these comments and suggestions will be considered and would like to thank the FDA for the opportunity to provide comments on this important guidance.

Yours sincerely,

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**Table 1:** Comments/Concerns on Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers, FDA Guidance for Industry, July 2019

| Lines | Draft Guidance text | Comment |
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| *General* | | Overall, we would recommend to clearly distinguish, and separate paragraphs referring to consensus and non-consensus scenarios in peer review, their definition and documentation. |
| 37-39 | *Pathology peer review can be particularly useful in situations where unique or unexpected findings are noted or when the peer-review pathologist has a particular expertise with a class of compounds.* | Pathology peer review is rather a tool of quality control and generally enhances the accuracy and consistency of diagnoses and terminology, as well as the quality of the interpretation in the report narrative. |
| 45-46 | *This guidance is intended to provide information to sponsors and nonclinical laboratory staff who choose to undertake pathology peer review during the conduct of a GLP study.* | **OECD Guidance document 116** on the conduct and design of chronic toxicity and carcinogenicity studies states a clear expectation for the conduct of peer review on GLP studies from 3 months of duration for a wide range of chemicals, whatever their field of application, including pesticides, industrial chemicals and pharmaceuticals. |
| 67-69<br>**A2** | *...the peer-review pathologist should have experience with the route of administration of the test article, species and strains of animals being tested, and duration and design of the study* | More flexibility should be given here, as a peer review does not necessarily require experience with all aspects mentioned here. |
| 78-79<br>**A3** | *Pathology peer review that occurs before finalization of the study pathologist's report is considered prospective peer review.* | Harmonization with OECD Advisory document No. 16 recommended (prospective = contemporaneous). |

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| 80-81 | *…,the pathologist should complete the analysis of all slides and prepare a draft pathology report before the prospective peer review occurs.* | We agree that it is preferable and optimal for a peer review pathologist to see a Draft pathology narrative and data tables before the start of the peer review. However, there are study scenarios (carcinogenicity studies, review of unscheduled sacrificed animals, etc.) for which more flexibility is necessary, in order not to hamper the fluidity of the collaboration between study and peer review pathologist, and pathology scheduling. Therefore, we would recommend to provide more flexibility in the guidance wording and replace "draft pathology report" with "draft pathology narrative and data tables (as possible)" and remove wording that suggests that all slides need to be evaluated. |
| 88-104 **(QA/A4)** | *Can pathology peer review be conducted at a non-GLP-compliant site for a GLP compliant study?* | Alignment with OECD Advisory Document 16 should be considered with regards to the details of the requirements, in order to avoid inconsistencies and confusion. |
| 98-100 | *…the name, qualifications (incl. GLP training), affiliations, and address of the peer review pathologist should be documented in the study file* | Instead of study related documentation in each study file, a centralized process of the test facility could be considered (as part of an internal SOP). Such a centralized repository of the respective documentation should allow access for test facility study directors and quality assurance and would avoid repetitive documentation. |
| 118-120 **(Q5/A5)** | *These procedures should be documented and available to the peer-review pathologist before initiation of the peer review and should be clearly described in the study protocol or study protocol amendments and in SOPs pertaining to the GLP studies.* | Detailed procedures for peer review are generally documented in a dedicated SOP, which should be referred to following OECD Advisory document 16. |

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| 126-129 | *An SOP and GLP study protocol (or protocol amendments) should include a description of the peer-review procedure, including selected target tissues, the dose groups to be examined, the number of specimens to be examined in each group, and whether the peer review should be conducted in a blinded fashion. Relevant SOPs can be referenced where appropriate."* | The wording around documentation of target tissue, dose group and specimen selection appears misleading. Details of the selection will not be known prior to the peer review, and are an intrinsic part of the peer review memo document. General recommendations for Peer review conduct should be described in a respective SOP providing a framework of how to approach a prospective/contemporaneous or retrospective peer review, and clear procedures to resolve non consensus.<br><br>Blind reading is not a technique routinely used in peer reviews, but rather a general tool to confirm suspected lesions vs controls or to refine grading if deemed necessary. Therefore we would recommend to dismiss the specific reference to blind reading. |
| 131-146 | *The peer-review statement should include….: - when, where, and under what conditions (GLP/non-GLP) the peer review was conducted.* | More clarity is needed on the documentation of the exact timing of the peer review, unless this refers to the date of signature of the peer review memo/statement. A peer review can extend over a certain period of time until consensus is reached. For documentation purposes the date of signature of the peer review memo/statement is most relevant.<br><br>The site of peer review and indication of the GLP-status is generally part of the general protocol/protocol amendment information regarding the study peer review, and the GLP status is most appropriately documented in the compliance statement provided by the study director as part of the overall study report. |

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| 148-152 | *If the peer-review pathologist concurs with the study pathologist's diagnoses and interpretations, the peer-review statement might not include a comprehensive analysis of the outcome of the peer review. Under these conditions, a statement that a peer review was conducted and that the final pathology report reflects the consensus opinions of the study pathologist and peer-review pathologist would suffice.* | We agree with this statement, but would recommend to add slightly more flexibility regarding minor differences with the study pathologist's diagnoses and interpretations, which would not impact the overall interpretation of the data set and safety assessment (i.e. NOAEL, adversity/non-adversity of findings). Harmonization with the **OECD Advisory document No. 16** should be considered and would add clarity for a more workable approach, based on current best practice: **2. GLP requirements**, ***2.10.*** *"In most cases where there are no significant differences of opinion it will not be necessary to report in detail the outcome of the peer review in the pathology report of the final report. A simple statement that it was conducted and that the pathology report presents the agreed findings would usually suffice".* |
| 154-156 | *Any changes to the overall study interpretations by the study pathologist because of a prospective peer-review process should be documented in the peer-review statement and discussed in the final pathology report, as applicable.* | In a prospective/contemporaneous peer review, discordance between the peer review pathologist and study pathologist on the overall study interpretations (i.e. NOAEL, adversity vs non adversity of findings), should only be documented in case of unresolvable non-consensus, which should trigger a defined procedure of resolution of non-consensus (e.g. consultation with further Pathologists or Pathology Working group). We consider the peer review statement as appropriate tool to document such non-consensus, in addition to subsequent documentation regarding the solution of non-consensus (additional peer review statement or addendum). Otherwise, as long as the peer review pathologist and study pathologist reach consensus at the end of the peer review process, any changes to diagnoses and interpretations of any kind should be treated as working notes and intrinsic part of the peer review. Documentation and discussion of such changes in the final pathology report would conflict with the overall and sole responsibility of the study pathologist for the pathology phase report (line 170/171 and 187-188), unless this paragraph partly refers to a situation of unresolved non- |

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| | | consensus, for which resolution should be sought prior to finalization of the phase report. Such discordance should therefore not to be documented in the final pathology report, and the process described above should suffice to ensure transparency in case of conflictual situations and non-consensus.<br>We therefore propose to change the statement to:<br>*"Any changes to the overall study interpretations by the study pathologist because of a prospective peer-review process, on which no consensus could be reached between the two, should be documented in the peer-review statement and ~~discussed in the final pathology report, as applicable~~.an unbiased and transparent process to resolve those differences should be followed.* |
| 158-159 | *Any changes to the interpretations by the study pathologist as a result of a retrospective peer-review process should be documented in an amended final pathology report.* | We would recommend to add clarity to this sentence, as the documentation of changes in a retrospective peer review is not limited to interpretations, by adding the term "findings" and change the wording to: *"Any changes to the findings and interpretations by the study pathologist as a result of a retrospective peer-review process……..".* Each single change to the pathology raw data (pathology phase report including microscopic data) needs to be documented. |
| 161-164 | *Unresolved differences in interpretation from the final or draft pathology report should be clearly identified in the peer review statement. Resolution of any differences should be discussed in the final pathology report or in an amendment to the final pathology report, and the process of resolution should be documented.* | We recommend that resolution of non-consensus should be documented in the peer review statement only, and not included in the draft pathology phase report (prospective peer review), which is under the overall responsibility of the study pathologist. Resolution of differences ultimately result in consensus, which certainly may influence findings and interpretations of the study pathologist in the pathology report. Nevertheless the study pathologist should be under full control which changes to accept or not, as long as robust non-consensus procedures are in place as regulated by SOPs. A peer review is not a second readout, which should be discussed in the pathology phase report authored by the study pathologist. |

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| 178<br>**Q7/A7** | *(see Q1)* | Reference to Q1 is unclear as no relationship to Q7 is seen. |
| 189-192<br>**Q8/A8** | *Therefore, the testing facility management should implement appropriate measures to ensure independence of the study pathologist and enforce procedures to track all changes to a study pathologist's interpretations, including changes that might results from a pathology peer review. Such procedures can include the implementation of an audit trail.* | We agree that it is the responsibility of the testing facility management and its delegates to ensure independence of the study pathologist and to implement appropriate measures to avoid undue influence of any kind, which could impact the accurate and complete assessment of the pathology phase of the study, including prospective peer review. We believe, however, that the implementation of a robust process and documentation of non-consensus and its resolution, would be sufficient and superior to tracking all changes to a study pathologists interpretations and the activation of an audit trail in the scope of a prospective/contemporaneous peer review.<br>Thus, we would recommend the following wording:<br>*Therefore, the testing facility management should implement appropriate measures to ensure independence of the study pathologist and appropriate measures to avoid undue influence on pathology raw data. ~~enforce procedures to track all changes to a study pathologist's interpretations, including changes that might results from a pathology peer review. Such procedures can include the implementation of an audit trail.~~* |
| 194-200 | *The Agency acknowledges that pathology peer review is an iterative process and the draft pathology report is subject to change until the report is signed and dated by the study pathologist. The process of conducting pathology peer review involves communication between the study pathologist, peer-review pathologist, sponsor, testing facility management, study director(s), sponsor-delegated representative, and test site management* | It is unclear whether this paragraph alludes to potential changes of the draft pathology report in the scope of communications between the different parties cited here, which also might occur independently of a peer review process. In general, the peer review phase comprises predominantly communication, correspondence or meetings between the study pathologist, peer review pathologist, and, eventually, the study director.<br>Written communications and correspondence around the draft pathology report, at any phase during reporting, even subsequent to terminated peer review discussions, have to be handled as study-related communications and as such are retained automatically in the study file.<br>We would therefore recommend to change the overall wording to clarify the context and also to allow flexibility regarding meeting summaries, which could be added to the study file only if deemed necessary and unless all aspects discussed are already covered by study related written communications. |

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| | *(if applicable). Records of communications pertinent to the process of slide evaluation and meeting summaries (e.g., meeting minutes) relevant to the pathology peer review should be retained in the study file.* | |
| 204-208 | *To best ensure transparency, documents (e.g., worksheets, electronic files) that record peer-review events and changes to the study pathologist's findings should be retained in the study records.* | In our experience from peer reviews by peer review pathologists working in industry and contract research organizations, an appropriate level of transparency and control of undue influence is ensure by strengthening the study pathologist's independence, which should be supported by the respective test facility management, and a robust process in case of non-consensus on differences in opinion on findings or interpretations. Retaining further worksheets and notes, apart from the peer review memo/statement would inappropriately increase irrelevant data to the study file and not avoid the rare cases of attempts of undue influence. **OECD Advisory document No. 16** states: **2.4.** ....*Notes made by the peer review pathologist which are used to record observations during the histopathological examination of individual slides do not normally have to be retained in the study file.* However, documentation on resolution of non-consensus should be retained in the study file and is in our opinion an appropriate tool to ensure full transparency on the conduct of peer review. |
| 211-212 | *Also, the peer review statement should clearly identify changes resulting from the peer-review process that affect the study pathologist's interpretations.* | As stated above, for prospective/contemporaneous peer review, such documentation in the peer review memo/statement should be limited to unresolved discordance and its resolution. A robust procedure for documentation and resolution of discordances strengthens the independence of the study pathologist and helps to resolve conflictual situations through involvement of further independent pathologists. |

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| 214-230<br>**Q9/A9** | *If the peer-review pathologist does not concur with the study pathologist's interpretations then changes to the interpretations might be made by the study pathologist to reflect consensus with the peer review pathologist.*<br><br>*The difference in interpretation should be documented by the peer-review pathologist before engaging in a dialogue to resolve the interpretative differences."*<br><br>*If no resolution can be reached, the study pathologist and peer-review pathologist should carefully follow a transparent and unbiased process that is clearly described in the testing facility's SOPs for resolving interpretative differences during pathology peer review.*<br><br>*Depending upon the directives of the SOPs, consensus may be achieved through consultation with additional experienced pathologists. Records* | We would recommend to reconsider wording, since "to reflect consensus" seems not to reflect a voluntary action from the study pathologist. However, changes to interpretations resulting from aspects brought up during a peer review are to be made only in case the study pathologist fully concurs with the changes based on further reflection about the data set. Therefore, we would recommend: "*....then changes to the interpretations will be made by the study pathologist only when he/she fully concurs with the changed data set.*<br><br>Documentation should therefore only occur in a case of unresolved non-consensus, following a transparent an unbiased process clearly described in the test facility's or test site SOPs.<br>The most appropriate document to document such differences in interpretation, remaining unresolved after the consensus discussion between study pathologist and peer review pathologist, is the peer review memo/statement. Therefore we would recommend a change in wording of the second paragraph to: "*The unresolved differences in interpretation should be documented by the peer-review pathologist before engaging in a clearly defined process to resolve the interpretative differences.* |

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| | *of communications pertinent to the process of slide evaluation and records of meeting summaries (e.g., meeting minutes) relevant to the pathology peer review should be retained in the study file.* | |

References:

**Fikes JD, Patrick DJ, Francke S*, Frazier KS, Reindel JF, Romeike A*#, Spaet RH, Tomlinson L and K Schafer* (2015)** Review of the Organisation for Economic Co-operation and Development (OECD) Guidance on the GLP Requirements for Peer Review of Histopathology. Tox Path, vol. 43, 7: pp. 907-914.

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