16 September 2019

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

Re: Comments on Docket No. FDA-2019-16361, Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers (Draft Guidance Document)

To FDA Scientists Preparing Final Guidance for Pathology Peer Review in Nonclinical Toxicology Studies:

The Society of Toxicologic Pathology (STP) is a non-profit association comprised of over 1,250 pathologists, toxicologists and other scientists whose principal aim is the advancement of toxicologic pathology as it pertains to changes elicited by pharmacological, chemical, and environmental agents, as well as the factors that modify these responses. We are a global organization, although 74% of membership is in the USA, and we have members in industry, government, and academia. We are the largest professional association of study pathologists and peer review pathologists involved in nonclinical toxicology studies.

Our Society has carefully considered the topic of pathology peer review for several decades, formed expert working groups to consider both scientific and compliance aspects of pathology peer review, and published reviews and commentaries on the topic (Fikes et al, Toxicologic Pathology 2015; Morton et al, Toxicologic Pathology 2010; Crissman et al, 2004; STP, Toxicologic Pathology 1997; and Ward et al, Toxicologic Pathology 1995). As such, the Society is in a strong position to provide insight into the pathology peer review process. A working group of The Scientific and Regulatory Policy Committee (SRPC) of the STP has reviewed the Food and Drug Administration’s recent draft Guidance for Industry: Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers (Docket ID: FDA-2019-D-2330). The working group includes members from the biopharmaceutical industry, contract research laboratories, consultants, the FDA, with representatives from Europe and British STPs serving as study pathologists and peer review pathologists.

In this letter we provide general comments and concerns raised during our review and provide specific proposals for your consideration. Our comments were guided by the principles outlined in STP best practices and endorsed by the Executive Committee of the STP. Careful consideration and incorporation of these comments into the final guidance will be essential to maintain the quality and accuracy of the toxicology study reports contributing to human risk assessment and patient safety.
In addition to our general comments, our principal and most extensive comments focus on six critical topics of the proposed guidance that have the potential to adversely disrupt the practice of toxicologic pathology as a medical diagnostic discipline. Shorter, ancillary, comments on other aspects are also included in Table 1 at the end of this letter.

The six critical topics with which the STP disagrees as they relate to prospective peer review are as follows:

1) **Question 5, Question 8, and Question 9: Documentation of preliminary differences of opinion and discussion in peer review statement and report**: The agency’s recommendation to document the changes made to the study pathologist’s preliminary interpretation because of the peer review process in the peer review statement and the pathology report.

2) **Question 5: Peer Review Planning Documentation**: The agency’s recommendation to include the specific details of the peer review in the study protocol/protocol amendments.

3) **Question 8: Testing facility tracking procedures**: The agency’s recommendation to enforce procedures to track all changes to a study pathologist’s interpretations, including changes that might result from a pathology peer review, as well as possible implementation of an audit trail on preliminary histopathology diagnoses.

4) **Question 8 and 9: Records of communication**: The agency’s recommendation to retain communications related to the peer review.

5) **Question 8 (and elsewhere): Definition of transparency**: Clarity is needed on what aspects of a prospective (contemporaneous) peer review the agency considers not transparent for reconstruction of the study.

6) **Question 9: Resolution of unresolved differences**: In the event of a disagreement, the agency recommends that the peer review pathologist documents his/her interpretation before initiating discussion with the study pathologist.

We thank the FDA staff for their considerable efforts and sharing their thinking, appreciate the opportunity to provide comments, and sincerely hope that these comments will be considered in improving this important guidance. We look forward to further dialogue and collaboration with the agency in the refinement and implementation of this guidance document.

Respectfully,

Kevin S. McDorman, DVM, PhD, Diplomate, ACVP
President, Society of Toxicologic Pathology
General Comments

While it is true that pathology peer review practices or their documentation have not been codified in US regulations, it is important to note that the toxicologic pathology community has carefully considered both scientific and compliance aspects of pathology review and published documents related to pathology peer review (Fikes et al, Toxicologic Pathology 2015; Morton et al, Toxicologic Pathology 2010; Crissman et al, 2004; STP, Toxicologic Pathology 1997; and Ward et al, Toxicologic Pathology 1995). These publications have provided a strong basis for both the scientific conduct of a pathology peer review of toxicology studies, as well as the appropriate documentation practices to allow study reconstruction.

The current draft FDA guidance references several of these publications and we appreciate that in certain questions portions of these recommendations have been adopted; however, as described below there are several key recommendations in the guidance which are in conflict with both currently accepted best practice and our interpretation of the definition of anatomic pathology raw data.

The STP considers the peer review process to be an integral component of pathology reporting ensuring the integrity of the pathology data in safety studies, and encouraging consistency of diagnostic criteria, and the use of INHAND/SEND terminology. While we appreciate the agency’s desire to be assured that primary pathologists are not unduly influenced during the peer review process, some of the processes suggested for prospective (contemporaneous) peer review in this draft guidance will lengthen and complicate the reporting process, and will likely result in pathology narratives which may be unclear, contradictory, and confusing to non-pathologists. As such, we urge caution in implementing cumbersome documentation practices that will detract from the overall quality of the peer review process and study report, may discourage some from conducting pathology peer reviews, and still not achieve the stated goal of limiting undue influence during pathology evaluations. We believe that a lack of performing peer reviews is more likely to lead to negative implications for patient safety.

As the largest industry stakeholder of professional study pathologists and peer review pathologists, the STP is very interested in working with the Agency to provide guidance that retains the definition of histopathology raw data (defined as the final signed and dated pathology report); while at the same time easing the Agency’s concerns about transparency and offering clarity on the prospective (contemporaneous) pathology peer review process. Ideally, this solution would not cause detrimental effects on report quality and processes and allow for the degree of transparency the Agency desires. We look forward to further dialogue and cooperation with the Agency in developing appropriate processes that avoid the risk of reducing pathology report quality.
**Topic #1:**

**Question 5, Question 8, and Question 9: Documentation of preliminary differences of opinion and discussion in peer review statement and report:** The agency’s recommendation to document the changes made to the study pathologist’s preliminary interpretation because of the peer review process in the peer review statement and the pathology report.

**FDA Proposals - Topic #1:**

**A5, Lines 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.”

**A5, Lines 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 (discussed further in Q8 and Q9).”

**A8, Lines 189-192:** “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 result from a pathology peer review. Such procedures can include the implementation of an audit trail”.

**A8, Lines 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. One option to ensure transparency is to fix or lock the database of pathology findings before the start of the peer-review process to ensure that changes to the pathology findings will be recorded in an audit trail.”

**A8, Lines 211-212:** “Also, the peer-review statement should clearly identify changes resulting from the peer-review process that affect the study pathologist’s interpretations.”

**A9, Lines 218-222:** “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”.

**A9, Lines 227-230:** “Depending upon the directives of the SOPs, consensus may be achieved through consultation with additional experienced pathologists. Records 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.”

**STP Proposal for Topic #1:** We submit that for those cases where preliminary differences are resolved during prospective peer review, additional documentation is not warranted. We suggest deleting these new documentation practices from the guidance. Our rationale for this approach follows.
Rationale: Changes to pathology interpretations due to prospective peer review are a part of the iterative process of refining pathology diagnoses. In the majority of peer reviews, preliminary differences between the primary and peer review pathologist are resolved during the consensus process. Because the pathology observations are not considered raw data until the study pathologist has signed the pathology report, and there is no requirement in the GLP’s for retention of pathology notes, additional documentation beyond the peer review statement is not warranted. This is in contrast to retrospective peer review, where the pathology data have been finalized and are considered raw data. In those cases, we fully agree that it is important the amended pathology report clearly indicate what, if any, changes were made as a part of the retrospective peer review.

Currently the Agency’s prescriptive process recommends multiple new levels of peer review documentation and auditing above and beyond the current definition of histopathology raw data. While these measures may provide for an element of the stated transparency the agency desires, they will not allow a determination of undue influence on the pathology evaluation process, and as described above, are anticipated to have significant unintended consequences for the pathology reporting process. Specifically, many test facilities will interpret the guidance in a conservative manner, resulting in the imposition of additional, new requirements including:

- Locking the pathology database prior to peer review;
- Retention of the peer review pathologist’s diagnoses;
- Retention of peer review documents in the study records including documenting how the two pathologists came to consensus;
- Clearly identify significant changes and “interpretations” (the guidance does not define “significant” or how “interpretations” differ from tabulated histologic findings) that result from the peer review process in the final study report.

In our society’s assessment, these will (1) conflict with existing definitions of pathology raw data while not contributing to the reconstruction of the study report by making preliminary diagnoses of the study pathologist raw data (2) decrease the clarity and quality of anatomic pathology narrative reports since both original (preliminary) and final interpretations would be reported, and (3) have detrimental impact on the efficiency and timeliness of toxicology report generation which is an important component of timely drug development. To avoid the undue burden of the proposed extensive peer review documentation and auditing, we are concerned that many organizations will discontinue the practice of peer review altogether, which will negatively impact the quality of human risk assessment and patient safety.
**Topic #2:**

**Question 5: Peer Review Planning Documentation:** The recommendation to include the specific details of the peer review in the study protocol/protocol amendments.

**FDA Proposal - Topic #2:**

*A5, Lines 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.”

*A5, Line 131:* “The peer-review statement should include the following information:…..”

**STP Proposal for Topic #2:** We propose that the underlined information in lines 126-129 not be required in a GLP study protocol or amendments, but that it be documented in the peer review statement (memo) as is already common best practice and consistent with OECD Advisory Document No. 16 (OECD 2014). Some of the information listed (e.g., selection of potential target tissues) can also not be listed in an SOP a priori for a given study, as described below. Transparency is assured by relevant SOPs detailing the peer review process, and the study protocol stating that (1) a contemporaneous pathology peer review will occur; (2) referencing the relevant SOP describing the process; (3) and that the peer review statement summarizing the details of the peer review will be issued. It is standard practice that information provided in SOPs does not need to be repeated within the study protocol.

In addition, this portion of the draft guidance suggests that peer review may be performed in a blinded fashion. We recommend deleting the wording about the blinded peer review, because this is not considered best practice for nonclinical toxicologic pathology assessments (Crissman et al 2004, Morton et al, 2010).

**Rationale:** Specific tissues and groups of animals to be peer reviewed cannot be determined a priori at the time of protocol generation and are determined based on the overall preliminary findings of the study pathologist. To assure a quality study report per best scientific practices, it is best to not limit the peer reviewer’s ability to assess as many tissues as needed to assure an adequate peer review. As outlined in Fikes et al, 2015, SOPs should define the minimal materials for an appropriate peer review and allow for sufficient flexibility in review of additional materials to achieve the peer review objectives. The peer review pathologist should be able to review additional materials as appropriate based on the findings in a study without requiring additional protocol amendments, and the specific details of the evaluation should be documented within the peer review memo.

The agency recommendation to duplicate the content in the SOP and the protocol does not reflect standard practice across GLP study areas where information provided in SOPs are not repeated within the study protocol. An unintended consequence of the proposed language would be increased volume of protocol amendments on nearly every study for procedures that are already well described in an SOP, without adding value but cause substantial administrative burden to the study director, study pathologist, peer review pathologist, and quality assurance auditors. The unnecessary duplication of
information documented in various locations (i.e., SOP, the protocol, study report and the peer review statement) will complicate the study records and makes effective auditing more challenging, increasing the chances for clerical errors arising from synchronization of disparate documents.

It is not appropriate to conduct a routine pathology peer review in a blinded fashion, and the topic is outside the scope of this guidance. Effective peer review involves review of the draft pathology report and knowledge of other relevant study data, such as organ weights, macroscopic necropsy observations, clinical signs, clinical pathology and treatment group/exposure levels.

**Topic #3:**

**Question 8: Testing facility tracking procedures:** The agency’s recommendation to enforce procedures to track all changes to a study pathologist’s interpretations, including changes that might result from a pathology peer review, as well as possible implementation of an audit trail on preliminary histopathology diagnoses.

**FDA Proposal - Topic #3:**

**A8, Lines 189-192:** “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 result from a pathology peer review. Such procedures can include the implementation of an audit trail.”

**STP Proposal for Topic #3:** We recommend omitting this recommendation from the guidance.

**Rationale:** The study pathologist is accountable for the pathology report as he/she is the only one generating raw data because he/she is the only one signing the pathology report (which constitutes the raw data). Procedures are commonly followed across the industry such as (a) use of SOPs describing procedures such as Pathology Working Groups (PWG) when there are significant differences in interpretation, and (b) retention of histopathological specimens such as blocks, tissues, and slides as indicated in the FDA 1987 GLP rule preamble. These procedures allow for resolution of disagreements and preservation of durable specimens from which interpretations and conclusions can be verified at any time in the future, as noted in the 1987 Preamble.

There is also ambiguity regarding the use of “audit trail” to track changes in “interpretation” (which is not the same as diagnoses recorded in an electronic capture system). If “interpretation” refers only to the changes made to the pathologist’s narrative report, it is not captured in an audit trail. Typically, audit trail pertains to capturing any changes to any diagnostic term, severity grade, or qualifier within electronic capture systems or pathology tables, and not the “interpretation” of those diagnoses. In addition, it is not necessary for the peer review and study pathologists to agree on every diagnosis or severity/qualifier classification, and minor differences in terminology, incidence and severity grading of diagnoses are to be expected and are acceptable (Morton *et al.*, 2010). If the goal is to capture all changes to the entries originally placed into the GLP electronic capture system, we are concerned that the proposed guidance seems to shift the definition of pathology raw data (which is the final signed report as per FDA 1987 GLP rule Preamble) to preliminary diagnoses as they become defensible by having to be justified. This makes it necessary to audit the tracking of all changes to preliminary entries.
(electronic capture system) and “interpretations” (draft pathology report), which adds significant administrative burden and does not “ensure the independence of the study pathologist” beyond existing practices.

**Topic #4:**

**Question 8 and 9: Records of communication:** The agency’s recommendation to retain communications related to the peer review.

**FDA proposals - Topic #4:**

_A8, Lines 198-200 and repeated in A9 Lines 228-230:_ “*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.*”

**STP Proposal for Topic #4:** We recommend that the guidance clarifies that the meeting minutes to capture are limited to the discussion of processes, plans, and expectations linked to the peer review and not the precise discourse over the evaluation itself, as explained in Fikes _et al_., 2015 and below in the rationale.

**Rationale:** The signed peer review statement/memo authored by the peer review pathologist can concisely explain or capture the scope and extent of peer review conducted for a given study. The essential correspondence to retain are those that reflect the processes, plans, and expectations directly linked to the slides used in the peer review, especially those that are not captured in other study communications. Examples may include correspondence on the process involved in the selection of the slides for review, the selection of animals for full slide review, and the review of additional potential target tissues. Communications regarding preliminary observations (pathology diagnoses that are not locked or signed) and preliminary pathology interpretations would not be required to be maintained since these are pathology working notes (per 1987 GLP rule Preamble, these are not raw data because they do not contribute to study reconstruction).

**Topic #5:**

**Question 8 (and elsewhere): Definition of transparency:** Clarity is needed on what aspects of a prospective (contemporaneous) peer review the agency considers not transparent for reconstruction of the study.

**FDA Proposals - Topic #5:**

_A8, Lines 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. One option to ensure transparency is to fix or lock the database of pathology findings before the start of the peer-review process to ensure that changes to the pathology findings will be recorded in an audit trail.*”

**STP Proposal for Topic #5:** We recommend omitting this paragraph.
**Rationale:** We agree that transparency and integrity are critical to all datasets including non-numerical endpoints such as histopathology. We believe that the existing GLP procedures ensure the accuracy and integrity of the pathology raw data, and offers transparency as stated in the preamble of 1987 GLP rule. Unlike many other specimens, histopathology specimens (blocks, tissues, and slides) are retained and the slides are available for re-evaluation at any time, including by regulatory authority personnel, so transparency is assured. Further, the FDA has the authority to interview all contributing scientists, including the study and peer-review pathologists during an inspection, and review any histopathology specimens.

This guidance appears to imply that peer review pathologist’s and/or study pathologist’s peer review notes should be retained in the study records, which is inconsistent with the current definition of pathology raw data per FDA 1987 GLP final rule and OECD No. 16, Section 2.4 (OECD 2014 which states “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.”)

**Topic #6:**

**Question 9: Resolution of unresolved differences:** In the event of a disagreement, the agency recommends that the peer review pathologist documents his/her interpretation before initiating discussion with the study pathologist.

**FDA Proposal - Topic #6:**

**A9, Lines 218-222:** “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. The difference in interpretation should be documented by the peer-review pathologist before engaging in a dialogue to resolve the interpretative differences.”

**STP Proposal for Topic #6:** We recommend deleting the underlined sentence in lines 220-222 and instead focusing on SOPs and other established processes to resolve and document disagreement as referred to in lines 227-228: “Depending upon the directives of the SOPs, consensus may be achieved through consultation with additional experienced pathologists.”

**Rationale:** The proposal to provide documentation from the peer review pathologist “before” engaging the study pathologist is too prescriptive and potentially counter-productive since this may involve documentation of incorrect preliminary interpretations which will lead to confusion. Peer review is typically a collegial exchange between medical professionals and requiring prior written communication before colleagues can speak with each other will not increase the quality of the peer review and will only add time, confusion and undue administrative burden. In addition, the proposed guidance is inconsistent with GLP 1987 GLP final rule that “notes are not necessary for the reconstruction” and OECD No. 16, Section 2.4 (OECD 2014) which states “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.”

This guidance does not seem to consider that if there is disagreement on the overall interpretation of the pathology evaluation (i.e., target organs, the no-effect level, adversity of test article-related findings)
then the prospective peer review is not completed. The overall goal is to achieve agreement, and once there is agreement (which is very often easily achieved between the study and peer review pathologists), the study pathologist will sign the pathology report and the peer review pathologist will sign the peer review statement as suggested in Answer 5, Lines 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.”

If an agreement cannot be reached, then SOPs should be in place outlining the processes used to achieve agreement along the theme outlined by the agency in lines A9 227-228: “Depending upon the directives of the SOPs, consensus may be achieved through consultation with additional experienced pathologists.” We suggest that focusing on this process may help the agency achieve the desired additional transparency. In this instance, the nature of the disagreement (e.g., individual diagnoses or overall interpretation), the pathologists involved/consulted, and how the disagreement was resolved could be documented in the peer review statement.

References:


Table 1: Society of Toxicologic Pathology: Ancillary Comments on FDA Draft Guidance on Pathology Peer Review

<table>
<thead>
<tr>
<th>Section or Answer: Line (s)</th>
<th>Referenced Text</th>
<th>Comment/Issue</th>
<th>Recommended Change/Solution/Language</th>
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<tbody>
<tr>
<td><strong>I. Introduction</strong></td>
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<td><strong>II. Background</strong></td>
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<tr>
<td>Background: 36</td>
<td>“...includes an initial read of tissue slides by the study pathologist....”</td>
<td>Although the term “read” is used colloquially for a pathologist’s evaluation of tissues, a better term would be “evaluation” since they do not just record what they see, but rather they use their training, experience and understanding of the range of normal tissue morphologies, incidental observations, pathophysiology and other relevant study data to evaluate what they see under the microscope and provide a considered judgement of the presence or absence and the relevance of any observations in the species and tissue under evaluation prior to rendering any diagnosis or applying any diagnostic term.</td>
<td>Change the word “read” to “evaluation”</td>
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<tr>
<td>Background: 35-37</td>
<td>“The histopathological assessment includes an initial read of tissue slides by the study pathologist and may include a subsequent review (referred to as pathology peer review) by a second, or peer-review pathologist.”</td>
<td>Only review of tissue slides has been indicated as part of routine peer review process.</td>
<td>Since peer review process includes review of the slides, other relevant study data and interpretations and often the draft pathology report, it may be best to describe this in the background section.</td>
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<td><strong>III. Questions and Answers</strong></td>
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<td>A1: 55</td>
<td>“...or group of pathologists (peer-review pathologists).”</td>
<td>It is unclear if this is referring to a “Pathology Working Group” or several individuals performing the peer review.</td>
<td>Replace the underlined text as follows: “... or group of pathologists (peer review pathologists) or a pathology working group (PWG).”</td>
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<td>A1: 55-57</td>
<td>“Interpretations of histopathological changes are made using expert scientific and medical judgment resulting in output that is mostly qualitative and therefore subjective.”</td>
<td>STP, INHAND and SEND has been making successful efforts to improve the standardization of diagnostic criteria and severity grading (which is not acknowledged in the draft guidance). Qualitative data need not be completely subjective. Objective parameters can be applied.</td>
<td>Delete: “...and therefore subjective.”</td>
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| A2: 66 | “The peer-review pathologist should have a combination of appropriate education, training, and experience to be qualified to render opinions on the study pathologist’s histological descriptions.” | Language | We would submit that the peer-review pathologist can “render scientific expertise” (as opposed to “opinions”).
Since “histological” implies analyses of normal tissues, or might refer to the technical procedures in preparation of tissue for evaluation, it would be more appropriate to refer to the study pathologist’s “histopathologic findings or descriptions.” |
| A2: 67-69 | “….peer-review pathologist should have experience with route of administration…” | Documenting experience with a particular route of administration or study design may be impractical in many cases. | Replace “experience with…” with “knowledge of…” |
| A2: 69-71 | “Furthermore, it can also be beneficial for the peer-review pathologist to have knowledge of the mechanism of action of the test article and knowledge of the results of test article administration at other dose levels or in other species.” | Ideally, the peer review pathologist should have knowledge of prior studies conducted with the test article. Line 69-71 should emphasize that it is not only beneficial but rather critical to have the knowledge of MoA/pharmacology and changes in other species, in order to put the findings in a context |
| A3: 78-79 | “Pathology peer review that occurs before finalization of the study pathologist’s report is considered prospective peer review.” | Align terminology with OECD advisory document No. 16 (OECD 2014). OECD distinguishes peer reviews as “contemporaneous” or “retrospective”. Introduction of the term “prospective” may cause confusion regarding how prospective peer reviews differ from contemporaneous peer reviews. Contemporaneous peer review starts before the final pathology report. | Revise to “Pathology peer review that initiates before finalization of the study pathologist’s report is considered contemporaneous peer review.” Alternatively, indicate in the guidance that prospective peer review is synonymous with contemporaneous peer review (i.e., prospective = contemporaneous). |
| A3: 79-81 | “When pathology peer review occurs prospectively, the study pathologist should complete the analysis of all slides and prepare a draft pathology” | The draft guidance language does not allow sufficient flexibility to accommodate study designs and study reporting processes where the pathology evaluation may occur in a phased or rolling manner. For example, certain tissues or special techniques may have | We recommend removing the language suggesting that all tissues must be evaluated prior to the start of the peer review to allow for flexibility for those studies in which the pathology evaluation occurs in a |
significant longer processing times and it may be most efficient to have all “routine” tissues processed, evaluated, and peer reviewed and then the additional tissues evaluated when they are available. In addition, for 2-year carcinogenicity studies it is most efficient for the study pathologist to begin reviewing early sacrifice animals prior to the end of the live phase. In all of these instances, neither the primary or peer review evaluation would be complete until all protocol-specified tissues have been reviewed and the various phases of peer review would be documented in the peer review statement.

**Phase manner:**

“When pathology peer review occurs prospectively, the study pathologist should generally complete their initial evaluation and prepare a draft pathology report before the prospective peer review occurs. In those cases where the primary or peer review occurs in multiple phases or in a rolling manner, the peer review pathologist may initiate the peer review prior to the availability of the draft pathology report.”

**Clarify that the scope of the guidance focuses on prospective (or contemporaneous) peer review.**

**Recommend adding:** The scope of the remainder of this guidance is limited to prospective/contemporaneous peer review.

Since the original data is not transferred to, or accessed directly by, any non-GLP-compliant site but rather retained at the site of study conduct (GLP-compliant), and only study specimens (slides) are transferred while any other data are generally “certified copies” thereof, we suggest removing the word “data”.

**Remove the word “data” and change the underlined phrase to the following:** “…to protect the integrity of the study.”

We propose omitting the word “internal”
<table>
<thead>
<tr>
<th>Q4:97-100</th>
<th>“Also, the name, qualifications (including GLP training), affiliations, and address of the peer-review pathologist should be documented in the study file.”</th>
<th>It is redundant for the GLP training-status and qualifications of the peer review pathologist to be retained in the study file.</th>
<th>We recommend omitting <strong>GLP training</strong> as part of what is included in the study file or the “<strong>should</strong>” could be changed to “<strong>can</strong>”.</th>
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<td></td>
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<td>It is common practice to include the name, credentials (qualifications), and address (if this is the site they are associated with) either directly or indirectly in the study file. The GLP training and affiliations are not typically listed in the study file, as these exist in the peer review pathologist’s CV and/or their training record. This is not a typical expectation for other contributors to GLP studies and therefore should not be a special request for peer review pathologist, especially given that peer review pathologists do not generate raw data.</td>
<td>Remote or home addresses of peer-review pathologists that could conduct a portion of their work from a home office are not appropriate for inclusion in study reports. In this instance the pathologist’s address should be their company office address or affiliation. The sponsor can have on file where the peer reviewers are physically located.</td>
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<td>A5: 123</td>
<td>“All peer-review pathologists’ signature blocks...”</td>
<td>“Pathologists’” should be changed to singular form to match singular form elsewhere in guidance.</td>
<td>Replace “pathologists’” with “pathologist’s”</td>
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<td>A5: 131-146</td>
<td>“The peer-review statement should include the following information: Who performed the peer review; When, where, and under what conditions (i.e., GLP- or non-GLP-compliant) the peer review was conducted; What tissues were examined microscopically; A statement on whether the terminology and findings used in the pathology report were agreed upon by both the study and peer review pathologist; For prospective peer review, a statement of whether the draft pathology report was shared with the peer-review pathologist; Peer-review pathologist’s dated signature”</td>
<td>Something that is notably absent in this section is a statement on whether the interpretations in the pathology report/narrative were agreed upon by the study and peer review pathologist. The underlined recommendation on lines 140-141 only considers if diagnoses in tables are agreed upon. Arguably, the interpretation is more important than complete agreement in the pathology tables.</td>
<td>Modify the underlined recommendation on the following statement:</td>
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<td>“A statement on whether the diagnoses, terminology, and interpretations in the pathology report were agreed upon by the study pathologist and peer review pathologist.”</td>
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<td>A5: 135-136</td>
<td>“When, where, and under what conditions (i.e., GLP- or non-GLP-</td>
<td>It is not necessary and may be confusing to document when and where the peer review was conducted. The test facility affiliation of</td>
<td>Delete this sentence.</td>
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<tr>
<td>Section</td>
<td>Notes</td>
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<td><strong>compliant) the peer review was conducted”</strong></td>
<td>the peer review is more important. However, it is important to document when the peer review was completed (e.g., by a dated peer review memo).</td>
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<td><strong>A5: 143</strong></td>
<td>“For prospective peer review, a statement of whether the draft pathology report was shared with the peer-review pathologist”</td>
<td>Align terminology with OECD advisory document No. 16 (OECD 2014). Using “shared with” does not strongly indicate whether or not the pathology report was reviewed by the peer review pathologist. Stating “reviewed by” automatically means that it was shared and reviewed by the peer review pathologist. Revise to “For contemporaneous peer review, a statement of whether the draft and/or final pathology report was shared with and reviewed by the peer-review pathologist”</td>
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<td><strong>A5: 148-152</strong></td>
<td>“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.”</td>
<td>Though conceptually we agree, this statement is not clear. Does this mean “if the PRP does not request any changes to be made to any recorded observations, in addition to the overall interpretation”? For example, would this apply when only changes to severity grades and/or terminology used to record an observation across the board without any impact on criteria or “diagnosis”, or only if nothing is changed at all? Clarify the meaning of “diagnoses and interpretations” vs. recorded observations.</td>
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<td><strong>A7: 177-178</strong></td>
<td>“… the signed peer-review statement should be included as an appendix to the final study report and should also be included as part of the study file (see Q1).”</td>
<td>We do not think the peer review statement needs to be retained in both the report and the study file. Suggest change to “be included as an appendix to the final study report.”</td>
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<td>A9: 222-225</td>
<td>“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.”</td>
<td>We are concerned that the sentence in lines 222-225 would restrict the SOP to be used for resolving differences of interpretation to that of the testing facility. Peer reviews are routinely conducted by sponsors or third-party pathologists using their own peer review SOPs, which is an acceptable practice, as long as it is stated in the study protocol and agreed to by the testing facility. We fully support the concept that regardless of who’s SOP is used for the peer review or resolving differences, it should include a clear and unbiased process for resolving differences of opinion (Morton et al, 2010).</td>
<td>We propose substituting the word “relevant” for the words “testing facility” in line 224.</td>
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