Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

This guidance provides information to sponsors and nonclinical laboratory staff regarding the management and conduct of pathology peer review performed during good laboratory practice (GLP)-compliant toxicology studies. When conducted, pathology peer review should be well-documented. However, documentation practices during pathology peer review have not been clearly defined and vary among nonclinical testing facilities. This question-and-answer document is intended to clarify FDA's recommendations concerning the management, conduct, and documentation of pathology peer review.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The histopathological assessment of tissue samples is a key component of GLP-compliant toxicology studies (referred to as GLP studies). 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. 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.

[1] This guidance has been prepared by the Office of Study Integrity and Surveillance in the Center for Drug Evaluation and Research in cooperation with the Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, Center for Food Safety and Nutrition, and Center for Tobacco Products at the Food and Drug Administration.

21 CFR part 58 (GLP regulations) includes general requirements for histopathology evaluation (for example, it requires written standard operating procedures for histopathology). While pathology peer review can be valuable when performed during the conduct of a GLP study, pathology peer review is not specifically addressed in the GLP regulations. 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.

III. QUESTIONS AND ANSWERS

Q1: What constitutes pathology peer review?

A1: Pathology peer review is the process by which the findings of the pathologist assigned to a study (study pathologist) are subjected to review by another pathologist (peer-review pathologist) or group of pathologists (peer-review pathologists). Interpretations of histopathological changes are made using expert scientific and medical judgment resulting in output that is mostly qualitative and therefore subjective. Pathology peer review can help to ensure the quality and accuracy of histopathological diagnoses and interpretations.

Casual discussions, consultations, opinion exchange, and mentoring among pathologists do not constitute formal pathology peer review and are not covered by this guidance document.

Q2: Who should conduct a pathology peer review?

A2: 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. In addition, 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.[2] 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.[3]

Q3: When can the pathology peer-review process occur?

A3: A pathology peer review can occur before or after finalization of the study pathologist's report (i.e., signed and dated pathology report).

Pathology peer review that occurs before finalization of the study pathologist's report is considered prospective peer review. When pathology peer review occurs prospectively, the study pathologist should complete the analysis of all slides and prepare a draft pathology report before the prospective peer review occurs.

[2] Morton, D, R Sellers, E Barale-Thomas, B Bolon, C George, JF Hardisty, A Irizarry, J McKay, M Odin, and M Teranishi, 2010, Recommendations for Pathology Peer Review, Toxicol Pathol, 38(7):1118–1127.

[3] Boorman, GA, DC Wolf, S Francke-Carroll, and RR Maronpot, 2010, Pathology Peer Review, Toxicol Pathol, 38(7):1009–1010.

Pathology peer review that occurs after finalization of the pathology report is considered retrospective peer review. When pathology peer review occurs retrospectively, the study pathologist should document any changes to the conclusions of the study that result from the retrospective peer-review process in an amendment to the final pathology report.

Q4: Can pathology peer review be conducted at a non-GLP-compliant site for a GLP-compliant study?

A4: Yes, it is possible to conduct a pathology peer review outside of a GLP-compliant site for a GLP-compliant study provided certain safeguards are in place to protect the integrity of study data. It is preferable that the peer-review pathologist perform the review at the GLP-compliant testing facility after receiving the appropriate training on GLP principles and relevant internal standard operating procedures (SOPs); however, if the peer review is conducted at a non-GLP-compliant site, that fact should be recorded and justified within the study protocol and final study report. Regardless of where the peer review is conducted, the name, affiliation, and location (i.e., address) of the peer-review pathologist should be clearly stated in the final study report. Also, the name, qualifications (including GLP training), affiliations, and address of the peer-review pathologist should be documented in the study file.

The portions of the study that were not conducted under GLP compliance should be explicitly stated in a study director-signed GLP compliance statement and included in the final study report.

Q5: How should the nonclinical laboratory staff document the peer review, and what should be included in the peer-review statement?

A5: When pathology peer review is part of a GLP study, the activity should be included in the study protocol or protocol amendment, and it is important that the peer-review process be well documented and transparent. The process should be guided by written procedures to establish the extent of the review and ensure the integrity of the study data. Because the study pathologist is responsible for the overall interpretation of the pathology data, the final pathology report will reflect the study pathologist's best scientific opinion and judgment regarding the diagnoses and pathological interpretations.

A formal pathology peer review should be planned, conducted, documented, and reported in accordance with established procedures. 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. The peer-review pathologist should generate a signed and dated peer-review statement (document, report, memorandum, or certificate) for inclusion in the permanent study files and final study report. All peer-review pathologists' signature blocks (identity and affiliation) should be included in the peer-review statement that is contained in the final study report.

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 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[4]
- 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

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.

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.

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.

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).

Q6: When should the peer-review statement be signed, and should the peer-review pathologist sign the pathology report?

A6: The peer-review statement can be signed by the peer-review pathologist before or after the finalization of the pathology report. The pathology report is the sole responsibility of the study

[4] Mann, PC, 1996, Pathology Peer Review From the Perspective of an External Peer Review Pathologist, Toxicol Pathol, 24(5):650–653.

pathologist, and the peer-review pathologist should not sign the final pathology report. Any changes made to a final pathology report resulting from a retrospective pathology peer review should be documented in an amendment to the final pathology report.

Q7: Should the signed peer-review statement be included in the final study report?

A7: Yes, 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).

Q8: How can the Agency be assured that the study pathologist's interpretive findings are not unduly influenced during the pathology peer-review process?

A8: As discussed in the preamble to the 1987 GLP final rule, ". . . only the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens."[5] The signed and dated pathology report (raw data) is critical in facilitating a thorough review of the histopathology data and characterizing the toxicology or toxicologic potential of a specific investigational product. The pathology report is the responsibility of the study pathologist and reflects that individual's interpretation of the histopathological findings. 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.

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 (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.

Transparency is important to protect the integrity of prospective peer review because the process occurs during the period of histopathological evaluation—which by its nature is subjective, iterative, collaborative, and open to influence. 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.

If the draft pathology report is shared with the peer-review pathologist, this should be reflected in the peer-review statement. Also, the peer-review statement should clearly identify changes resulting from the peer-review process that affect the study pathologist's interpretations.

[5] Final rule, "Good Laboratory Practice Regulations," September 4, 1987 (52 FR 33768).

Q9: How are differences in interpretation between the study pathologist and peer-review pathologist resolved?

A9: The study pathologist is the individual responsible for the overall analysis and interpretation of the pathology data. 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. 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.

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.