
Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers Guidance for Industry

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Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
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Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information to sponsors, applicants, and nonclinical laboratory personnel regarding the management and conduct of histopathology peer review as part of nonclinical toxicology studies conducted in compliance with Good Laboratory Practice (GLP) regulations. 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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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

Histopathological assessment is a key component of some in vivo nonclinical toxicology studies. The histopathological assessment includes diagnoses and interpretations by the study pathologist and can also include a subsequent review (referred to as pathology peer review) by another pathologist (peer-review pathologist), or group of pathologists (peer-review pathologists), or a pathology working group (PWG). Pathology peer review can be particularly useful, for example,

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 Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Veterinary Medicine, Center for Food Safety and Applied Nutrition, Center for Tobacco Products, and the Office of Regulatory Affairs at the Food and Drug Administration.

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in situations where unique or unexpected findings are noted or when the peer-review pathologist has a particular expertise relevant to the study.

21 CFR part 58 (GLP regulations for Nonclinical Laboratory Studies) includes general requirements for histopathology (for example, it requires written standard operating procedures (SOPs) for histopathology); however, pathology peer review is not specifically addressed in the GLP regulations. This guidance is intended to provide information to sponsors, applicants, and nonclinical laboratory personnel who choose to undertake pathology peer review during the conduct of a nonclinical toxicology study under GLP (referred to as a GLP toxicology study). Casual discussions, opinion exchange, and mentoring among pathologists are not covered by this guidance document.

FDA acknowledges the need for interactions between the sponsor or applicant and study personnel during the conduct of a nonclinical toxicology study under GLP. Sponsors or applicants and persons² performing study-related activities should have processes in place to ensure that the studies are transparent and free from undue influence that could impact the conclusions of the studies, including during contemporaneous (prospective)³ and retrospective pathology peer review.

III. QUESTIONS AND ANSWERS

Q1: What constitutes pathology peer review?

A1: Pathology peer review is the process by which the diagnoses and interpretations of the pathologist assigned to a study (study pathologist) are subjected to review by one or more peer-review pathologist(s) or a PWG. Pathology peer review can help to ensure the quality and accuracy of histopathological diagnoses and interpretations.

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

Q2: Who should conduct a pathology peer review?

A2: A 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. It can be beneficial for a peer-review pathologist to have experience with the route of administration, contact type and duration of the test article, species and strains of animals being tested, and duration and design of the study. It can also be beneficial for a 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.

² Under 21 CFR 10.3 the term person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

³ In the context of pathology peer review the terms "contemporaneous" and "prospective" can be used interchangeably. The term "contemporaneous" will be used in this guidance.

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Q3: When can pathology peer review occur?

A3: Pathology peer review can occur before finalization (contemporaneous) or after finalization (retrospective) 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 contemporaneous peer review. When pathology peer review occurs before the finalization of the study pathologist's report, the study pathologist should prepare a written narrative that describes the diagnoses and interpretations of available slides before the contemporaneous peer review occurs.

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 diagnoses and interpretations that result from the retrospective peer-review process in an amendment to the pathology report. When pathology peer review occurs after the final study report is signed, the study director should amend the final study report as necessary to reflect changes in histopathology diagnoses and interpretations.

Q4: How should pathology peer review be documented, and what should be included in the peer-review statement?

A4: It is important that the peer-review process be well documented and transparent. When either a contemporaneous or a retrospective pathology peer review is part of a GLP toxicology study, the activity should be included in the study protocol or protocol amendment. The process should be guided by written procedures to establish the extent of the review and ensure the integrity of the study. Because the study pathologist is responsible for the overall pathology data, the pathology report will reflect the study pathologist's best scientific opinion and judgment regarding the diagnoses and pathological interpretations.

Pathology peer review should be planned, conducted, documented, and reported in accordance with established written procedures. These written procedures should be available to the peer-review pathologist(s) prior to the initiation of peer review as SOPs, or in the study protocol or study-protocol amendment.

The peer-review pathologist(s) should generate a signed and dated peer-review statement (document, report, memorandum, or certificate) for inclusion in the 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.

The peer-review statement should be signed and dated by the peer-review pathologist(s) and include the following information:

- Who performed the peer-review and the date(s) it was performed
- Whether the peer-review was performed contemporaneously or retrospectively
- Whether the peer-review was conducted in compliance with GLP regulations
- What tissues were examined microscopically, corresponding animal identification number, dose/treatment group, and the basis for their selection
- What format (e.g., glass slides or whole slide images) was used

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- Whether the terminology, diagnoses, and interpretations used in the pathology report were agreed upon by both the study and peer-review pathologist(s)
- Whether a narrative report prepared by the study pathologist was reviewed either prior to or during peer review (for contemporaneous review only)
- What data and documents were utilized during the peer review (a listing)

If the peer-review pathologist concurs with the diagnoses and interpretations of the study pathologist, the peer-review statement might not include a comprehensive analysis of the outcome of the peer review. Under these conditions, sponsors or applicants can submit a statement explaining that a peer review was conducted, and the final pathology report reflects the consensus opinions of the study pathologist and peer-review pathologist(s). If no resolution of differences in diagnoses and interpretations can be reached during pathology peer review, the study pathologist and peer-review pathologist should carefully follow a transparent and unbiased process that is clearly described in written procedures (i.e., SOPs, study protocol, or study protocol amendment) for addressing diagnostic and interpretative differences during pathology peer review (as discussed further in Q9).

Any changes to the diagnoses and interpretations by the study pathologist as a result of a contemporaneous peer review do not need to be documented in the study pathology report, as contemporaneous peer review is considered part of the iterative diagnostic pathology process. Any changes to the diagnoses and interpretations by the study pathologist as a result of a retrospective peer-review should be documented in the peer-review statement and in an amendment to the study pathologist's report.

Q5: Can pathology peer review for a GLP toxicology study be conducted at a site that does not have an established quality system that complies with GLP regulations?

A5: Yes, it is possible to conduct the pathology peer review for a GLP toxicology study at a site that does not have an established quality system that complies with GLP regulations provided the integrity of the study is protected. It is preferable that the peer-review pathologist(s) perform the peer review under a GLP-compliant quality system after receiving training on GLP regulations and relevant SOPs. If the pathology peer review is not conducted under a GLP-compliant quality system, that fact should be recorded within the study protocol and final study report. The name, affiliation, and work address of the peer-review pathologist(s) should be included in the final study report. Also, the name, qualifications (including GLP training), affiliations, and work address of the peer-review pathologist(s) should be documented in the peer-review pathologist's training files and retained at the testing facility.

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

A6: The peer-review statement for a contemporaneous review can be signed by the peer-review pathologist before or after the study pathologist's report is signed. The peer-review statement for a retrospective review is by definition signed by the peer-review pathologist(s) after the study pathologist report is signed. The pathology report is the sole responsibility of the study pathologist, and the peer-review pathologist(s) should not sign the final pathology report. Any

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changes to a study pathologist's report resulting from a retrospective pathology peer-review should be documented in an amendment to the study pathologist's 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 in the final study report.

Q8: How can the Agency be assured that the study pathologist's diagnoses and interpretations are free from undue influence during the pathology peer-review process?

A8: The pathology report is the responsibility of the study pathologist and reflects that individual's diagnoses and interpretations. The signed and dated pathology report (raw data)⁴ is critical in facilitating a thorough review of the toxicologic potential of a specific investigational product.

Testing facility management should implement appropriate measures to ensure that the conduct of all phases of GLP toxicology studies, including the generation of the pathology report, is free from undue influence impacting the conclusions of the studies. Regarding pathology peer review, the independence of both the study pathologist and the peer-review pathologist(s) throughout the process should be ensured by both the management of the nonclinical testing facility and the sponsor or the applicant. Measures to ensure transparency can include, among other options, the implementation of an audit trail, or conducting contemporaneous peer review after the study pathologist's diagnoses are fixed or locked in an electronic system.

Diverging diagnoses, interpretations, or conclusions between the study pathologist and peer-review pathologist(s) should be addressed using a transparent and unbiased process that is clearly described in written procedures (see Q9).

Q9: How are differences in interpretation that result from pathology peer review addressed?

A9: If no resolution of differences in diagnoses and interpretations can be reached during pathology peer review, the study pathologist and peer-review pathologist should carefully follow a transparent and unbiased process that is clearly described in written procedures (i.e., SOPs, study protocol, or study protocol amendment) for addressing diagnostic and interpretative differences during pathology peer review.

Depending upon the directives of the written procedures, consensus could be achieved through consultation with additional experienced pathologists (e.g., PWG). Records of communications pertinent to differences of opinion relevant to the pathology peer review, including but not limited to records of meetings (e.g., meeting minutes), should be retained in the study file. Adherence to written procedures should be documented. Consensus diagnoses and interpretations should be documented in a report (e.g., PWG report) separate from the study pathologist's report and should be appended to the final study report.

⁴ The final rule, "Good Laboratory Practice Regulations," published September 4, 1987 (21 CFR Part 58).