

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

DRAFT GUIDANCE

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2 **and Answers**
3 **Guidance for Industry¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

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14
15 **I. INTRODUCTION**
16

17 This guidance provides information to sponsors and nonclinical laboratory staff regarding the
18 management and conduct of pathology peer review performed during good laboratory practice
19 (GLP)-compliant toxicology studies. When conducted, pathology peer review should be well-
20 documented. However, documentation practices during pathology peer review have not been
21 clearly defined and vary among nonclinical testing facilities. This question-and-answer
22 document is intended to clarify FDA's recommendations concerning the management, conduct,
23 and documentation of pathology peer review.
24

25 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
26 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
27 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
28 the word *should* in Agency guidances means that something is suggested or recommended, but
29 not required.
30

31
32 **II. BACKGROUND**
33

34 The histopathological assessment of tissue samples is a key component of GLP-compliant
35 toxicology studies (referred to as GLP studies). The histopathological assessment includes an
36 initial read of tissue slides by the study pathologist and may include a subsequent review
37 (referred to as pathology peer review) by a second, or peer-review pathologist. Pathology peer
38 review can be particularly useful in situations where unique or unexpected findings are noted or
39 when the peer-review pathologist has a particular expertise with a class of compounds.
40

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.

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41 21 CFR part 58 (GLP regulations) includes general requirements for histopathology evaluation
42 (for example, it requires written standard operating procedures for histopathology). While
43 pathology peer review can be valuable when performed during the conduct of a GLP study,
44 pathology peer review is not specifically addressed in the GLP regulations. This guidance is
45 intended to provide information to sponsors and nonclinical laboratory staff who choose to
46 undertake pathology peer review during the conduct of a GLP study.

47

48

III. QUESTIONS AND ANSWERS

49

Q1: What constitutes pathology peer review?

50

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

57

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

60

Q2: Who should conduct a pathology peer review?

61

62 **A2: The peer-review pathologist should have a combination of appropriate education, training,**
63 **and experience to be qualified to render opinions on the study pathologist's histological**
64 **descriptions. In addition, the peer-review pathologist should have experience with the route of**
65 **administration of the test article, species and strains of animals being tested, and duration and**
66 **design of the study.² Furthermore, it can also be beneficial for the peer-review pathologist to**
67 **have knowledge of the mechanism of action of the test article and knowledge of the results of**
68 **test article administration at other dose levels or in other species.³**

69

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

70

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

73

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

78

79

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.

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

87
88 **Q4: Can pathology peer review be conducted at a non-GLP-compliant site for a GLP-**
89 **compliant study?**

90
91 A4: Yes, it is possible to conduct a pathology peer review outside of a GLP-compliant site for a
92 GLP-compliant study provided certain safeguards are in place to protect the integrity of study
93 data. It is preferable that the peer-review pathologist perform the review at the GLP-compliant
94 testing facility after receiving the appropriate training on GLP principles and relevant internal
95 standard operating procedures (SOPs); however, if the peer review is conducted at a non-GLP-
96 compliant site, that fact should be recorded and justified within the study protocol and final study
97 report. Regardless of where the peer review is conducted, the name, affiliation, and location (i.e.,
98 address) of the peer-review pathologist should be clearly stated in the final study report. Also,
99 the name, qualifications (including GLP training), affiliations, and address of the peer-review
100 pathologist should be documented in the study file.

101
102 The portions of the study that were not conducted under GLP compliance should be explicitly
103 stated in a study director-signed GLP compliance statement and included in the final study
104 report.

105
106 **Q5: How should the nonclinical laboratory staff document the peer review, and what**
107 **should be included in the peer-review statement?**

108
109 A5: When pathology peer review is part of a GLP study, the activity should be included in the
110 study protocol or protocol amendment, and it is important that the peer-review process be well
111 documented and transparent. The process should be guided by written procedures to establish the
112 extent of the review and ensure the integrity of the study data. Because the study pathologist is
113 responsible for the overall interpretation of the pathology data, the final pathology report will
114 reflect the study pathologist's best scientific opinion and judgment regarding the diagnoses and
115 pathological interpretations.

116
117 A formal pathology peer review should be planned, conducted, documented, and reported in
118 accordance with established procedures. These procedures should be documented and available
119 to the peer-review pathologist before initiation of the peer review and should be clearly described
120 in the study protocol or study protocol amendments and in SOPs pertaining to the GLP studies.
121 The peer-review pathologist should generate a signed and dated peer-review statement
122 (document, report, memorandum, or certificate) for inclusion in the permanent study files and
123 final study report. All peer-review pathologists' signature blocks (identity and affiliation) should
124 be included in the peer-review statement that is contained in the final study report.

125
126 An SOP and GLP study protocol (or protocol amendments) should include a description of the
127 peer-review procedure, including selected target tissues, the dose groups to be examined, the

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128 number of specimens to be examined in each group, and whether the peer review should be
129 conducted in a blinded fashion. Relevant SOPs can be referenced where appropriate.

130
131 The peer-review statement should include the following information:

- 132
- 133 • Who performed the peer review
- 134
- 135 • When, where, and under what conditions (i.e., GLP- or non-GLP-compliant) the peer
136 review was conducted
- 137
- 138 • What tissues were examined microscopically
- 139
- 140 • A statement on whether the terminology and findings used in the pathology report were
141 agreed upon by both the study and peer-review pathologist⁴
- 142
- 143 • For prospective peer review, a statement of whether the draft pathology report was shared
144 with the peer-review pathologist
- 145
- 146 • Peer-review pathologist's dated signature

147
148 If the peer-review pathologist concurs with the study pathologist's diagnoses and interpretations,
149 the peer-review statement might not include a comprehensive analysis of the outcome of the peer
150 review. Under these conditions, a statement that a peer review was conducted and that the final
151 pathology report reflects the consensus opinions of the study pathologist and peer-review
152 pathologist would suffice.

153
154 Any changes to the overall study interpretations by the study pathologist because of a
155 prospective peer-review process should be documented in the peer-review statement and
156 discussed in the final pathology report, as applicable.

157
158 Any changes to the interpretations by the study pathologist as a result of a retrospective peer-
159 review process should be documented in an amended final pathology report.

160
161 Unresolved differences in interpretation from the final or draft pathology report should be clearly
162 identified in the peer-review statement. Resolution of any differences should be discussed in the
163 final pathology report or in an amendment to the final pathology report, and the process of
164 resolution should be documented (discussed further in Q8 and Q9).

165
166 **Q6: When should the peer-review statement be signed, and should the peer-review
167 pathologist sign the pathology report?**

168
169 **A6:** The peer-review statement can be signed by the peer-review pathologist before or after the
170 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.

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

174

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

176

177 A7: Yes, the signed peer-review statement should be included as an appendix to the final study
178 report and should also be included as part of the study file (see Q1).

179

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

182

183 A8: As discussed in the preamble to the 1987 GLP final rule, “. . . only the signed and dated final
184 report of the pathologist comprises raw data respecting the histopathological evaluation of tissue
185 specimens.”⁵ The signed and dated pathology report (raw data) is critical in facilitating a
186 thorough review of the histopathology data and characterizing the toxicology or toxicologic
187 potential of a specific investigational product. The pathology report is the responsibility of the
188 study pathologist and reflects that individual's interpretation of the histopathological findings.
189 Therefore, the testing facility management should implement appropriate measures to ensure
190 independence of the study pathologist and enforce procedures to track all changes to a study
191 pathologist's interpretations, including changes that might result from a pathology peer review.
192 Such procedures can include the implementation of an audit trail.

193

194 The Agency acknowledges that pathology peer review is an iterative process and the draft
195 pathology report is subject to change until the report is signed and dated by the study pathologist.
196 The process of conducting pathology peer review involves communication between the study
197 pathologist, peer-review pathologist, sponsor, testing facility management, study director(s),
198 sponsor-delegated representative, and test site management (if applicable). Records of
199 communications pertinent to the process of slide evaluation and meeting summaries (e.g.,
200 meeting minutes) relevant to the pathology peer review should be retained in the study file.

201

202 Transparency is important to protect the integrity of prospective peer review because the process
203 occurs during the period of histopathological evaluation—which by its nature is subjective,
204 iterative, collaborative, and open to influence. To best ensure transparency, documents (e.g.,
205 worksheets, electronic files) that record peer-review events and changes to the study
206 pathologist's findings should be retained in the study records. One option to ensure transparency
207 is to fix or lock the database of pathology findings before the start of the peer-review process to
208 ensure that changes to the pathology findings will be recorded in an audit trail.

209

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

213

⁵ Final rule, “Good Laboratory Practice Regulations,” September 4, 1987 (52 FR 33768).

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

216
217 A9: The study pathologist is the individual responsible for the overall analysis and interpretation
218 of the pathology data. If the peer-review pathologist does not concur with the study pathologist's
219 interpretations, then changes to the interpretations might be made by the study pathologist to
220 reflect consensus with the peer-review pathologist. The difference in interpretation should be
221 documented by the peer-review pathologist before engaging in a dialogue to resolve the
222 interpretative differences. If no resolution can be reached, the study pathologist and peer-review
223 pathologist should carefully follow a transparent and unbiased process that is clearly described
224 in the testing facility's SOPs for resolving interpretative differences during pathology peer
225 review.

226
227 Depending upon the directives of the SOPs, consensus may be achieved through consultation
228 with additional experienced pathologists. Records of communications pertinent to the process of
229 slide evaluation and records of meeting summaries (e.g., meeting minutes) relevant to the
230 pathology peer review should be retained in the study file.