

- 1 Recommendations for Pathology Peer Review ¹
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14 Running Title: Peer Review Recommendations

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Key Words: audit trail, pathology, peer review, quality

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55 Abbreviations

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57 CRO = Contract research organization

58 GLP = Good Laboratory Practices

59 FDA = United States Food and Drug Administration

60 NOEL = No observed effect level

61 PWG = Pathology working group

62 STP = Society of Toxicologic Pathology

63

64

ABSTRACT

65

66 Pathology peer review verifies and improves the accuracy and quality of pathology diagnoses

67 and interpretations. Pathology peer review is recommended when important risk assessment or

68 business decisions are based on nonclinical studies. For pathology peer review conducted before

69 study completion, the peer review pathologist reviews sufficient slides and pathology data to

70 assist the study pathologist in refining pathology diagnoses and interpretations. Materials to be

71 reviewed are selected by the peer review pathologist. Consultations with additional experts or a

72 formal (documented) pathology working group may be used to resolve discrepancies. The study

73 pathologist is solely responsible for the content of the final pathology data and report, makes

74 changes resulting from peer review discussions, initiates the audit trail for microscopic

75 observations after all changes resulting from peer review have been made, and signs the final

76 pathologist's report. The peer review pathologist creates a signed peer review memo describing

77 the peer review process and confirming that the study pathologist's report accurately and

78 appropriately reflects the pathology data. The study pathologist also may sign a statement of

79 consensus. It is not necessary to archive working notes created during the peer review process.

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80 SUMMARY OF RECOMMENDATIONS FOR PATHOLOGY PEER REVIEW

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82 Pathology peer review is most commonly performed before a study is completed.
83 Recommendations for pathology peer review conducted before the final pathology report has
84 been signed are presented below and may be modified to achieve the peer review objectives for a
85 specific study.

- 86 • Pathology peer review is recommended prior to study completion when important risk
87 assessment or business decisions will be based on nonclinical studies. The decision to
88 peer review a study should be made on a case-by-case basis considering the importance
89 of decisions based upon these studies, the experience and skill of the study pathologist,
90 and regulatory requirements.
- 91 • The pathology peer review should be conducted by a pathologist with appropriate
92 training and experience. The peer review pathologist may work for a contract research
93 organization (CRO), the sponsor, or a third party. The sponsor's peer review pathologist
94 may bring extensive knowledge to the peer review process that can improve the quality of
95 the pathology data and interpretations.
- 96 • If pathology peer review will be performed before the completion of the study, the
97 protocol or a protocol amendment should state that a peer review will be conducted.
98 Detailed methods for the pathology peer review are not required in the study protocol.
- 99 • The peer review pathologist generally is responsible for reviewing the relevant
100 pathology-related data, often including but not limited to clinical pathology results, organ
101 weight data, macroscopic observations, microscopic findings, ancillary pathology

102 information (electron microscopy, immunohistochemistry, *in situ* hybridization, etc.),
103 data interpretations, and the draft narrative report prepared by the study pathologist.

104 • The peer review pathologist must have broad flexibility to select materials for review
105 within wide, general guidelines (standard operating procedures and the objectives of the
106 peer review), and must have latitude to examine additional organs and other study data
107 necessary to thoroughly evaluate all potential pathology findings. The peer review
108 pathologist may choose to consult with the study pathologist in selecting the materials to
109 be evaluated, but is not obligated to do so.

110 • Peer review of target organs varies with the study design:

111 ○ In rodent toxicity studies, target organs from affected sexes should be examined from
112 all animals in the control group, all animals in the highest dose group lacking the
113 finding, and sufficient animals (50% or more) in affected groups to characterize the
114 finding.

115 ○ In non-rodent toxicity studies, target organs from affected sexes should be reviewed
116 in all control animals, all animals in affected dose groups, and all animals in the
117 highest dose group that lacks the finding.

118 ○ In recovery groups in rodent and non-rodent toxicity studies, all target organs should
119 be examined in all control animals and all treated animals in the dose groups and
120 sexes in which the finding was found at the end of the treatment period.

121 • In rodent toxicity studies, the peer review pathologist generally should examine all
122 protocol organs in at least 30% of high-dose animals of each sex in the treatment phase.

123 • In non-rodent toxicity studies, the peer review pathologist should examine all protocol
124 organs in at least half of the high-dose animals in the treatment phase (minimum of 2/sex).

- 125 • Examination of all protocol organs from a subset of control animals in rodent or non-
126 rodent toxicity or carcinogenicity studies may be performed at the discretion of the peer
127 review pathologist.
- 128 • In rodent carcinogenicity studies, the peer review pathologist should examine:
- 129 ○ All organs in at least 10% of rodents per sex in the high-dose animals for 2-year or
130 lifetime rodent carcinogenicity studies.
- 131 ○ All organs from 5 high-dose animals per sex in 6-month alternative (genetically
132 engineered mouse) carcinogenicity studies.
- 133 ○ All neoplasms in all animals.
- 134 ○ All target organs in all animals in all dose groups in which neoplastic treatment-
135 related findings are observed or suspected in any dose group. Each sex should be
136 considered separately.
- 137 ○ Target organs with non-neoplastic, treatment-related findings in all control animals,
138 all animals of the highest dose group lacking the finding (to establish the NOEL for
139 the finding), and sufficient animals in affected groups and sexes to verify the finding.
140 At least 30% of animals in affected groups should be reviewed, and the review should
141 concentrate on animals with target organ findings noted by the study pathologist.
- 142 • Differences of opinion between the peer review pathologist and the study pathologist
143 regarding the overall study interpretation may be resolved through consultation with
144 other pathologists and/or subject matter experts, or by convening a formal (documented)
145 pathology working group.

- 146 • If the peer review is performed before the final study report is signed, the audit trail for
147 microscopic findings should not be initiated until all changes resulting from the peer
148 review process have been made to the pathology data set and interpretations.
- 149 • The pathology peer review memo should be prepared using these general guidelines:
- 150 ○ The peer review pathologist prepares, signs, and dates a peer review memo
151 documenting materials, methods, and conduct of the review process and the peer
152 review pathologist's general agreement with the study pathologist's pathology report.
- 153 ○ An optional signed statement by the study pathologist documenting consensus with
154 the reviewed pathology data and study interpretations may be included in the peer
155 review memo.
- 156 ○ The peer review memo may be signed before the quality assurance review of the
157 pathology data, after the quality assurance review, or after the study pathologist's
158 contributing scientist's report (or an integrated study report signed by the study
159 pathologist) has been signed because peer review is a voluntary and flexible process,
- 160 ○ The peer review memo should be archived and/or included in the study pathologist's
161 report or the final study report, but is not considered raw data.
- 162 • Preliminary diagnoses, interim notes and worksheets of the study pathologist and peer
163 review pathologist, and the draft versions of the study pathologist's reports are not raw
164 data. It is not necessary to retain or archive these documents after the final study report is
165 signed.
- 166 • The study pathologist is solely responsible for making any changes resulting from the
167 peer review process, initiating the audit trail for microscopic observations, and signing
168 the study pathologist's final report. As a result, the peer review pathologist is not

169 considered a principal investigator for multi-site studies and is not required to sign a
170 compliance statement.

171
172 Pathology peer reviews conducted after studies have been completed and the study
173 pathologist's report has been signed often are performed to address specific concerns. These peer
174 reviews should be designed and conducted to achieve a particular goal, and the materials
175 examined and documentation will vary based on the peer review objectives. All changes to the
176 study data and interpretations and all discrepancies with the original pathology data and study
177 pathologist's report should be documented. If the original data are modified, the changes and the
178 reasons for each change should be recorded in the audit trail. The peer review objective and
179 process should be documented and signed by the peer review pathologist. In some cases, a
180 second independent report issued by the peer review pathologist is appropriate. Changes to study
181 data or interpretations resulting from peer review conducted after a GLP study report has been
182 finalized are considered raw data and should be documented in a study report amendment.

183

184 INTRODUCTION

185

186 Pathology evaluations in nonclinical toxicology and carcinogenicity studies are composed of
187 two critical steps: 1) the accurate diagnosis and recording of all pathology findings, and 2) the
188 integrated interpretation of all pathology information within the context of the entire study to
189 identify and characterize treatment-related findings. Unlike body weights and organ weights,
190 food consumption, pharmacokinetics, and most clinical pathology data, gross and microscopic
191 pathology interpretations are subjective and qualitative. Microscopic interpretations in particular

192 are developed, refined, and harmonized throughout the entire microscopic assessment and
193 construction of the pathology report. Consultation commonly is used to further refine diagnostic
194 terminology and criteria. This reiterative evaluation and revision to define and explain the entire
195 spectrum of treatment-related microscopic findings justifies delay of audit trail initiation and data
196 locking for microscopic observations until the study pathologist's report is completed.

197
198 During pathology peer review conducted before a study is completed, the peer review
199 pathologist assists the study pathologist with the assessment and refinement of microscopic
200 observations, appropriate terminology, all relevant study data, and the draft pathology report,
201 using published literature, historical understanding of the test article and related compounds, and
202 knowledge of additional experts as needed. Ultimately these interactions verify and improve the
203 quality of the final recorded pathology observations as well as the interpretation and integration
204 of pathology findings within the study pathologist's final report. This paper primarily addresses
205 peer review before the study report has been finalized and signed, with limited discussion of
206 pathology peer review after a study has been finalized.

207
208 Technological advances in pathology assessment and communications together with evolving
209 expectations within regulatory agencies have stimulated recent global discussions of best
210 practices for pathology peer review (Barale-Thomas and Bradley, 2009; OECD, 2009; McKay et
211 al, 2010). The Society of Toxicologic Pathology (STP) and many individual toxicologic
212 pathologists have published recommendations and commentary on the topic of pathology peer
213 review over the past two decades (Eighmy, 1996; Frantz, 1997; Mann, 1996; McCullough et al.,
214 1997; Morton et al., 2006; Sahota, 1997; STP, 1991; STP, 1997; Tuomari et al., 2004; Ward et

215 al., 1995). Collectively, these publications outline the evolving perspectives regarding the
216 purpose of the pathology peer review, the role of the peer review pathologist, and the most
217 appropriate conduct and documentation of the peer review process. In the present document,
218 prior recommendations are consolidated and expanded to define current preferred pathology peer
219 review practices for nonclinical toxicity and carcinogenicity studies.

220

221 HISTORICAL PERSPECTIVES ON PATHOLOGY PEER REVIEW

222

223 An early objective of pathology peer review was "to assure the development of accurate
224 pathology data which clearly and cogently support the scientific conclusions" (STP, 1991). In
225 general, pathology peer reviews occur before finalization of the study report (Isaacs, 2007; Ward
226 et al., 1995) because the peer review process is integral to refining and improving the accuracy of
227 the final pathology diagnoses and interpretations. Completing the peer review *before* the study
228 pathologist locks the database not only reduces the documentation required to obtain a high-
229 quality final product (Crissman et al., 2004), but also promotes incorporation of changes that
230 more accurately reflect the findings in a study. The interim notes and worksheets of the study
231 pathologist and the peer review pathologist are not essential for the reconstruction and evaluation
232 of the pathology section of the final study report, and thus are not considered raw data. Therefore,
233 it is not necessary to retain these interim notes and worksheets once the consensus pathology
234 data are incorporated into a signed final report (STP, 1997; United States Federal Register, 1987;
235 Ward et al., 1995). The single overriding principle of the pathology peer review process is that it
236 should facilitate "direct interaction between the original and the reviewing pathologists" to

237 produce agreement regarding the nature and interpretation of the pathology data and the final
238 pathology report (STP, 1991).

239

240 CURRENT PERSPECTIVES ON PATHOLOGY PEER REVIEW

241

242 *The Purpose and Extent of Pathology Peer Review*

243

244 The primary objective of a complete pathology peer review performed before the study is
245 completed is to assist the study pathologist to refine, verify and improve the accuracy and quality
246 of the final pathology data and interpretations. In executing this function, the peer review
247 pathologist should:

248

249 1. Examine all microscopic slides from a sufficient number of high-dose animals to generate
250 confidence that all significant microscopic treatment-related findings have been identified.

251 [Throughout this paper, treatment-related (or test article-related) findings are defined as
252 direct or indirect (secondary), adverse or non-adverse changes caused by the test article,
253 device, or other intentional manipulation studied in the animal model.]

254 2. Confirm that microscopic diagnoses are consistently recorded, terminology and grading
255 criteria are consistently and appropriately applied across the entire pathology data set,
256 microscopic findings are appropriately correlated to necropsy findings, and pathology
257 findings are appropriately correlated to causes of clinical signs, morbidity, or death.

258 3. Examine all target organs from all control animals and all treated animals down to and
259 including all target organs from all animals at the no-observed-effect-level (NOEL) for

260 each treatment-related microscopic finding. In rodent studies with high incidences of
261 treatment-related findings within specific organs, it may be sufficient for the peer review
262 pathologist to evaluate a subset of animals in affected groups to confirm the target organ
263 finding, nomenclature, and consistency of severity modifiers.

- 264 4. Ensure that the study pathologist's draft report accurately
- 265 • reflects and is supported by the individual animal data tables and summary tables,
 - 266 • identifies treatment-related microscopic observations and the dose groups in
267 which these findings occur, and
 - 268 • integrates these findings with treatment-related in-life findings, clinical pathology
269 results, organ weight findings, gross necropsy observations, and available
270 ancillary pathology findings (e.g. immunohistochemistry, EM) within the context
271 of the entire study.

272

273 *Selection of Studies for Pathology Peer Review*

274

275 Few regulatory agencies have issued guidelines mentioning pathology peer review. The only
276 clear regulatory requirement for pathology peer review of nonclinical studies supporting
277 pharmaceutical registration is found in the European Medicines Agency (EMA) guidance on the
278 conduct of carcinogenicity studies (EMA, 2002). Draft guidance under consideration by the
279 Organisation of Economic Co-operation and Development (OECD) emphasizes the role and
280 value of pathology peer review, but does not provide detailed recommendations on methodology
281 (OECD, 2009). The U.S. Environmental Protection Agency (EPA) requires peer review of
282 pathology data and confirmation of changes by a pathology working group for all submissions

283 requesting reconsideration of carcinogenicity decisions for chemicals based on changes in the
284 pathology diagnoses (EPA, 1994). Despite the paucity of mandated requirements for pathology
285 peer review, sponsors and regulatory agencies generally acknowledge that pathology peer review
286 can increase confidence in the pathology data and pathology interpretations.

287 In the absence of a clear requirement by regulatory agencies for pathology peer review, the
288 decision to peer review each study should be made by the sponsor on a case-by-case basis
289 considering the importance of decisions that will be based upon these studies, the experience and
290 skill of the study pathologist, and regulatory requirements. Pathology peer review is
291 recommended when important risk assessment or business decisions may be based on pathology
292 interpretations in nonclinical studies. Pathology peer review usually is appropriate for GLP
293 toxicity and carcinogenicity studies and biomarker qualification studies, and may add value for
294 mechanistic and investigative studies with pathology endpoints and exploratory (non-GLP)
295 toxicity studies that guide compound development decisions and dose selection.

296

297 *Who Should Perform the Peer Review?*

298

299 The individual(s) primarily responsible for performing pathology peer review must have the
300 training and experience to competently evaluate all pathology data within the context of the
301 entire study (Bolon, et al., in press). Peer review pathologists should be experienced with studies
302 using the same species and of similar duration and design as the study to be peer reviewed.
303 Experts engaged to consult on specific topics are not required to have the qualifications of a peer

304 review pathologist who evaluates the entire study, but their contributions should be limited to
305 their areas of expertise.

306

307 Pathology peer review may be performed by a pathologist within the same organization or
308 company, the sponsor's pathologist, or a third party. When appropriate, it may be of value to
309 have several individuals with specialized expertise (clinical pathology, special knowledge of a
310 given organ system, ultrastructure, etc.) participate in the peer review process. Regardless of
311 their affiliation(s), peer review pathologists assist the study pathologist to verify and refine the
312 diagnoses and interpretations to be included in the study pathologist's report.

313

314 *Peer Review of Studies at CROs by the Sponsor's Pathologist (Sponsor Peer Review)*

315

316 The sponsor's peer review pathologist frequently has access to information regarding target
317 biology, pharmacology and pharmacokinetic data, mechanisms of target-mediated and off-target
318 toxicity, previous findings with the same compound, supporting scientific literature, and class
319 effects with similar compounds that is not available to the CRO's study pathologist or an
320 independent peer review pathologist. This additional knowledge significantly improves the
321 quality of the pathology peer review process and the final pathology interpretations. Regulatory
322 agencies may have concerns that the sponsor's peer review pathologists and others within the
323 sponsor's organization may inappropriately influence the study pathologist's interpretations,
324 especially when the study pathologist is employed by a CRO (McKay et al., 2010). Sponsors and
325 their pathologists have little to gain and much to lose by misrepresenting pathology findings. The
326 sponsor's long-term interests are best served by ensuring that data interpretations in all studies

327 are of the highest possible quality and that the peer review process is rigorous and objective so
328 that the most advantageous business decisions can be made.

329

330 *Responsibilities of the Peer Review Pathologist and the Study Pathologist*

331

332 The peer review pathologist is responsible for the design and conduct of the peer review
333 within broad guidelines defined by standard operating procedures. “It is the responsibility of the
334 peer review pathologist to ensure that the method of review employed is sufficient to verify the
335 accuracy of the histopathologic findings” (STP, 1997). The peer review pathologist designs the
336 process, often in consultation with the study pathologist. The approach to the pathology peer
337 review and the materials selected for review may vary based on institutional procedures, the
338 objective of the peer review, the study design, and/or the study pathologist’s findings. The peer
339 review pathologist should examine sufficient data to ensure identification and interpretation of
340 treatment-related findings in each dose group. This applies to the interpretation of all pathology
341 data and is not simply limited to evaluation of the microscopic slides. The peer review
342 pathologist may benefit from discussions with the study pathologist prior to peer review and
343 should have access to the study protocol and protocol amendments, mortality information, in-life
344 observations and interpretations, clinical pathology and organ weight data (with means and
345 results of statistical analyses, if performed), all microscopic slides, the study pathologist’s
346 microscopic diagnoses for each animal, appropriate summary data tables, the draft pathology
347 report narrative, toxicokinetic data (if available), and other relevant data. For routine peer review
348 of all pathology findings, the peer review pathologist usually evaluates the individual and
349 summary data tables and interpretations for clinical pathology, organ weights, macroscopic

350 observations, microscopic findings, and ancillary pathology information (results of electron
351 microscopy, special histochemical and immunohistochemical stains, *in situ* hybridization or *in*
352 *situ* polymerase chain reaction information, etc.)

353

354 The peer review pathologist should review the pathology terminology used and the draft
355 pathology narrative report. In-life observations and toxicokinetic data may be reviewed if
356 appropriate. When the peer review of clinical pathology data is conducted by an individual other
357 than the pathologist responsible for the peer review of gross and microscopic findings, the peer
358 review pathologist(s) should review enough clinical pathology data to ensure that clinical
359 pathology findings are appropriately integrated with other study data in the narrative of the study
360 pathologist's report. Correlation of pathology findings with in-life data and causes of deaths
361 should be reviewed. If a focused or targeted pathology peer review has been requested to address
362 a specific concern or issue, sufficient data must be reviewed to fully evaluate the concern or
363 issue.

364

365 The peer review pathologist and study pathologist should discuss all aspects of the data and
366 its interpretation and then come to general agreement that the target organs have been
367 appropriately identified; nomenclature for treatment-related findings is clear, well-defined, and
368 consistently applied; the affected dose groups for each treatment-related finding are clearly
369 specified; and related findings have been appropriately integrated in the study pathologist's
370 narrative. Ultimately, the study pathologist is responsible for all pathology data and
371 interpretations in the final pathologist's report. Any changes to study data and the pathologist's
372 narrative report based on the peer review consultation are made only by the study pathologist.

373 After all changes to the pathology data and draft pathology report resulting from pathology peer
374 review have been made, the study pathologist initiates the audit trail (“locks” the data) and signs
375 the separate final pathologist’s report or an integrated study report containing pathology findings.
376 In Japan, it is common for the pathology data and the pathology narrative to be incorporated
377 within the study report without a separate pathologist’s report, and the study pathologist may not
378 sign the study report. In this situation the study pathologist should retain responsibility for the
379 pathology data and interpretations and should initiate the audit trail of the microscopic data after
380 changes resulting from peer review have been made. In the past, Japanese regulators have
381 expected the audit trail to be initiated before the peer review process began. Japanese authorities
382 are considering revisions to expectations for the pathology peer review process.

383

384 The study pathologist is not obligated to agree with all suggestions of the peer review
385 pathologist. It is also not necessary to agree on every diagnosis or every severity classification if
386 these discrepancies do not significantly alter the overall interpretation of the pathology data.
387 Discrepancies in terminology or classification for microscopic findings that are unrelated to
388 treatment and minor differences in incidence and severity grading of treatment-related findings
389 are to be expected, and are acceptable.

390

391 *Review of All Organs in a Subset of High-Dose Animals in Rodent Toxicity Studies*

392

393 In rodent toxicity studies, all organs from at least 30% of high-dose animals per sex from the
394 treatment phase should be reviewed in order to verify treatment-related findings and to generate
395 confidence that no treatment-related findings have been overlooked. Thus, in rodent studies with

396 10 animals per sex per group necropsied at the end of treatment, all organs should be examined
397 in at least 3 animals per sex from the high-dose group. In chronic rodent studies with 15 animals
398 per sex in the treatment phase, examination of all organs in 5 high-dose animals per sex is
399 recommended. In complicated studies with multiple routes of delivery or administration of
400 combinations of multiple compounds, there may be more than one “high-dose” group. Review of
401 all organs in a subset of recovery animals should not be required and is not routinely performed.

402
403 Some companies recommend that the peer review pathologist evaluate at least a certain
404 percentage of the total number of animals from the treatment phase of the study (e.g. 10%). In
405 this case, the number of animals reviewed in the high-dose group is not specified. This strategy is
406 acceptable only if the peer review pathologist evaluates sufficient high-dose animals to provide
407 reasonable assurance that all target organs have been identified. If this approach is utilized, the
408 peer review pathologist often will need to examine all organs in at least 30% of high-dose
409 animals to confirm all treatment-related findings with reasonable confidence. In some cases, 3
410 animals per sex are insufficient to confidently identify all target organs. Ultimately, the peer
411 review pathologist should examine all organs in enough animals to be confident that all target
412 organs have been identified.

413
414 *Review of All Protocol Organs in a Subset of High-Dose Animals in Non-Rodent Toxicity Studies*

415
416 Non-rodent toxicity studies often utilize only 3 or 4 animals per sex in each dose group, so
417 peer review examination of all organs in at least 50% of animals (at least 2 per sex) of the high-
418 dose group in the treatment phase is recommended for adequate peer review. It is common in

419 non-rodent studies to review all organs from all high-dose animals sacrificed before or at the end
420 of the treatment period.

421

422 *Should All Protocol Organs Be Examined in a Subset of Control Rodents or Non-Rodents?*

423

424 The decision to examine all protocol organs from a subset of control animals and the number
425 of animals to be examined should be determined by the peer review pathologist based on review
426 of the pathology data tables, microscopic findings in treated groups, the potential value of this
427 examination, and applicable standard operating procedures. Review of all organs from a subset
428 of control animals should not be required for all studies.

429

430 *Confirming No-Effect Levels by Review of Target Organs*

431

432 In both rodent and non-rodent toxicity studies, the peer review pathologist should examine
433 each target organ in the affected sexes from all control animals and from all animals in the
434 highest dose group lacking the treatment-related finding in order to confirm the NOEL for each
435 finding. In addition, the peer review pathologist usually examines all target organs in all animals
436 of the affected sexes in all affected dose groups. In some rodent studies, examination of target
437 organs in a subset of animals (50% or more) in affected groups may be sufficient to adequately
438 confirm the findings. If target organs are reviewed in a subset of rodents in affected groups, the
439 review should concentrate on animals with treatment-related findings noted by the study
440 pathologist. If only a few animals are affected, all affected animals identified by the study
441 pathologist should be reviewed.

442

443 If the study includes recovery groups, target organs should be reviewed in all recovery
444 animals of the affected sexes in the control group and in groups with treatment-related
445 microscopic findings identified in the treatment phase. Review of target organs in recovery
446 groups receiving the test article that did not have treatment-related microscopic findings at the
447 end of the treatment phase should not be required.

448

449 *Review of All Organs in Additional Animals When Mortality Is High*

450

451 When more than 50% of the animals in the high-dose group die or are terminated prior to the
452 end of the treatment period, the highest surviving dose group with at least 50% survival usually
453 is reviewed as described above for the high-dose group. The peer review strategy for the group(s)
454 with high mortality should be determined by the peer review pathologist, study pathologist, study
455 director, and sponsor with consideration of the duration of survival, the length of the study, and
456 other study-specific factors; however, within the broad objectives of the peer review, the ultimate
457 responsibility for selection of the materials to be reviewed rests with the peer review pathologist.
458 Peer review of additional organs in dead or moribund animals in any dose group may be helpful
459 in confirming the cause(s) of death or moribundity and evaluating treatment-related findings at
460 lethal doses.

461

462 *Pathology Peer Review in Rodent Carcinogenicity Studies*

463

464 Peer review requirements outlined in European guidance for 2-year rodent carcinogenicity
465 studies involving pharmaceuticals include examination of slides for all target organs, review of
466 all organs in 10% of animals in all treated and control groups, and review of 10% of all
467 neoplasms (EMA, 2002). These requirements do not address peer review for alternative 6-
468 month carcinogenicity models using genetically modified mice.

469

470 This paper recommends a different strategy for pathology peer review of rodent 2-year or
471 lifetime carcinogenicity studies and 6-month studies designed to assess carcinogenic potential in
472 genetically modified mice. The rationale for this recommendation is to ensure that an adequate
473 amount of material has been examined to verify treatment effects and affected dose groups.

474

- 475 • *Examine all protocol organs in at least 10% of high-dose animals in each sex in 2-year*
476 *studies and at least 5 high-dose animals/sex in 6-month alternative mouse model studies.*

477 Peer review of all organs from a subset of animals in carcinogenicity studies does not
478 contribute meaningfully to the evaluation of carcinogenic potential, but may assist in the
479 identification of non-neoplastic, treatment-related findings. Review of all organs in some
480 control animals may be performed at the discretion of the peer review pathologist to
481 accurately distinguish non-neoplastic, treatment-related findings from incidental
482 background observations and to comply with regulatory expectations. Routine review of
483 all organs in selected animals in the low- and intermediate-dose groups is not
484 recommended.

- 485 • *Examine all neoplasms identified by the study pathologist.* Some neoplasms may be
486 difficult to classify, and multiple possible diagnoses may exist for similar lesions. For all
487 neoplastic findings, standardized terminology must be used correctly and consistently,
488 and “Fatal” and “Nonfatal” designations must be assigned (taking into account all
489 findings in each animal). Misclassification or reclassification of one or a few neoplasms
490 in a study may change the pathology interpretation by altering the statistical and
491 qualitative identification of treatment-related neoplastic findings or affected dose groups.
492 *Therefore, peer review evaluation of every neoplasm in every animal in all groups is*
493 *considered best practice.*
- 494 • *Examine all target organs in all animals of all dose groups of affected sexes with*
495 *observed or suspected treatment-related neoplastic findings in any dose group.*
- 496 • *Examine target organs with non-neoplastic, treatment-related findings in all control*
497 *animals, all animals of the highest dose group lacking the finding (to establish the NOEL*
498 *for the finding), and sufficient animals in affected groups and sexes to verify the finding.*
499 If target organs are reviewed only in a subset of animals, at least 30% of animals in the
500 affected groups should be reviewed. The review should concentrate on animals with
501 target organ findings noted by the study pathologist. If only a few animals have a specific
502 treatment-related microscopic finding, all affected animals with this finding identified by
503 the study pathologist should be reviewed.
- 504 • *Examination of apparently incidental, non-neoplastic proliferative findings should be*
505 *made at the discretion of the peer review pathologist based on knowledge of the test*
506 *article’s toxicity profile and mechanism of action, review of pathology data tables, and*
507 *consultation with the study pathologist.* It may be appropriate to examine non-neoplastic

508 proliferative lesions considered precursors of neoplasia (e.g. atypical hyperplasia, some
509 forms of focal hyperplasia, and foci of cellular alteration) that appear to be unrelated to
510 treatment to confirm that these lesions are not neoplasms. However, examination of very
511 common proliferative lesions without evidence of a treatment effect (e.g., adrenal gland
512 spindle cell hyperplasia and endometrial hyperplasia in mice, pituitary gland
513 adenohypophyseal hyperplasia and adrenal gland medullary hyperplasia in rats) adds
514 little value to the peer review process.

- 515 • *In 6-month mouse carcinogenicity studies with positive control groups, review at a*
516 *minimum all neoplasms in expected target organs in the positive control group.*

517

518 *Resolving Differences of Opinion*

519

520 In most studies that include a pathology peer review, the study pathologist and peer review
521 pathologist should reach consensus on target organs, terminology for treatment-related findings,
522 dose groups with treatment-related findings, and other major conclusions within the study
523 pathologist's report. When differences of opinion regarding pathology findings or interpretations
524 exist that could affect risk assessment, informal consultations and/or formal (documented)
525 consultations with additional experienced pathologists and/or subject matter experts often lead to
526 resolution of discrepancies. If consultation results in agreement by the study pathologist and peer
527 review pathologist on the major pathology findings and dose groups affected, documentation of
528 the informal consultations with other experts should not be required because consensus has been
529 reached and is documented in the peer review memo.

530

531 If the study pathologist and peer review pathologist cannot reach agreement through informal
532 discussion and consultation during a peer review conducted before a study is completed, a formal
533 (documented) pathology working group (PWG) consisting of the study pathologist, the peer
534 review pathologist, and at least one other pathologist may be created to resolve differences of
535 opinion (Ward et al., 1995). A PWG may also be convened to review the overall pathology
536 interpretations within a study or if the study pathologist and peer review pathologist seek
537 additional expertise to resolve and document a complicated issue. Additional pathologists and/or
538 subject matter experts may be included in a PWG. If the study has been conducted at a CRO and
539 the peer review pathologist is employed by the sponsor, membership of the PWG should be
540 balanced, and at least one PWG member (in addition to the study pathologist) should be a neutral
541 party not employed directly by the sponsor. It is appropriate for the sponsor's pathologists to
542 participate in the PWG because the sponsor's representatives often possess the most complete
543 knowledge of the history, pharmacology, and toxicity of the test article. The method the PWG
544 will use to resolve differences of opinion should be determined in advance, and documentation
545 of the conclusions should be archived with the study data. The PWG reviews the pertinent data
546 and specimens to resolve interpretations of pathology findings. If consensus agreement cannot be
547 reached within the PWG, discrepancies may be resolved by majority vote.

548

549 *When Should the Audit Trail of Microscopic Findings Begin When Peer Review Is Conducted*
550 *Before A Study Is Completed?*

551

552 It is recommended that the audit trail be initiated (i.e., microscopic findings “locked”) *after*
553 changes resulting from pathology peer review have been completed, but *before* the quality

554 assurance review of the pathology data and draft pathology report. Regulatory agencies and
555 quality assurance units often expect that quality assurance review of the microscopic findings
556 and study pathologist's draft narrative should occur after the audit trail for microscopic findings
557 has been initiated. Initiating the audit trail just prior to beginning the quality assurance review
558 will clearly demonstrate any changes to the microscopic observations made during or after the
559 quality assurance review while facilitating implementation of changes identified during the
560 pathology peer review process.

561

562 The definition of "raw data" for microscopic findings varies in different regulatory
563 jurisdictions. The U.S. Food and Drug Administration (FDA) has declared that only the study
564 pathologist's signed final report constitutes raw data for microscopic observations.

565

566 "The pathologist's interim notes, therefore, which are subject to frequent changes as the
567 pathologist refines the diagnosis, are not raw data because they do not contribute to study
568 reconstruction. Accordingly, only the signed and dated report of the pathologist
569 comprises the raw data respecting the histopathological evaluation of tissue specimens."

570 (United States Federal Register, 1987).

571

572 In practice, the computerized individual animal microscopic findings are considered raw data in
573 Japan, the U.S. and Europe once the electronic audit trail has been initiated or paper copies have
574 been signed by the study pathologist. Based on these regulatory considerations, retention and
575 archiving of working notes from the pathology peer review process should not be required, nor
576 should changes to the diagnoses made before the draft pathology report is submitted for quality

577 assurance review be recorded in an audit trail. This recommendation is supported by the concept
578 that the pathology peer review process assists the study pathologist to verify and refine draft
579 pathology diagnoses and interpretations. Therefore, for peer review conducted before a study is
580 completed, the audit trail for the microscopic pathology data should not be initiated (i.e. the data
581 should not be locked or fixed) until *after* any changes to the original microscopic observations
582 and interpretations resulting from pathology peer review have been made (Tuomari et al., 2004).
583 Initiating the audit trail for the microscopic findings after all changes resulting from the peer
584 review process have been completed is considered best practice regardless of the affiliations of
585 the study pathologist and peer review pathologist, including when a sponsor's pathologist
586 performs a pathology peer review for a study conducted at a CRO. This view is consistent with
587 the positions of the Japanese Society of Toxicologic Pathology (JSTP, 2009) and the
588 International Federation of Societies of Toxicologic Pathologists (McKay et al., 2010) and is
589 widely held within the global toxicologic pathology community (Barale-Thomas and Bradley,
590 2009).

591

592 *Recommended Documentation When the Pathology Peer Review Occurs Before the Study*

593 *Completion*

594

595 If pathology peer review is planned prior to completion of a study, the pathology peer review
596 should be mentioned in the study protocol or acknowledged in a protocol amendment. It is
597 sufficient to state that a pathology peer review will be performed. Detailed protocol methods
598 describing the pathology peer review process are not recommended as these should be

599 determined by the peer review pathologist within broad limits defined by the peer review
600 objectives and standard operating procedures.

601

602 The peer review pathologist should create and sign a peer review memo (peer review
603 statement). The peer review memo should identify the study, specimens, and data reviewed and
604 include a clear declaration that the peer review pathologist(s) agrees with the overall
605 interpretation of the pathology data for the study. If a standard operating procedure clearly
606 describes the specimens and data to be examined, it may not be necessary to reiterate the
607 materials examined in the peer review memo. If more than one formal pathology peer review is
608 conducted, peer review memos should be created for each peer review process. If a formal PWG
609 is utilized, a memo documenting the issue or issues addressed, the members of the PWG, the
610 specimens and data examined, and the conclusions of the PWG (signed by all members of the
611 PWG) should be created. An optional signed statement by the study pathologist confirming
612 agreement regarding the study interpretations may be added to a peer review memo to strengthen
613 the documentation of consensus. The peer review memo should be archived with other pathology
614 and study records. A copy of the peer review memo may be included in the study pathologist's
615 report or the study report, but this should not be required because documentation of data
616 verification and review processes generally are not included in study reports. If the peer review
617 and the study pathology assessment are not performed at the same site, appropriate chain-of-
618 custody records documenting the transfer and inventory of specimens (slides) shipped between
619 sites should be maintained and archived.

620

621 The peer review memo should be signed after all changes resulting from the peer review
622 process have been made to the microscopic findings and draft pathology report . The exact
623 timing of the signature on the peer review memo should be selected by the sponsor because peer
624 review is an optional, unregulated process (with the exception of two-year rodent carcinogenicity
625 studies in Europe) and the timing of the signature does not impact the value of the interactions
626 between the peer review pathologist and the study pathologist. It is acceptable to sign the peer
627 review memo:

- 628 1) At the conclusion of the peer review process *prior* to initiation of the audit trail for the
629 microscopic findings and quality assurance review (Isaacs, 2007),
- 630 2) After quality assurance review of the pathology data and draft report are completed, or
- 631 3) After the pathology report or an integrated study report containing the pathology findings
632 is finalized and signed. This timing documents the peer review pathologist's agreement
633 with the study pathologist's *final* report.

634

635 Completing the pathology peer review and signing the peer review memo prior to quality
636 assurance review (option #1) is consistent with the execution of data verification procedures
637 before data sets and draft reports are submitted for quality assurance review, and enables the
638 quality assurance unit to verify that the peer review process was conducted as described in the
639 study protocol and standard operating procedures. This timing complies with all current
640 published regulatory guidance. In this scenario, the peer review memo documents the peer
641 review pathologist's agreement with the study pathologist's diagnoses and *draft* report at the
642 time the peer review memo is signed. The study pathologist would finalize the microscopic
643 observations and initiate the audit trail for microscopic data soon after the peer review memo is

644 signed, and before the initiation of the quality assurance review. The study pathologist is
645 responsible for ensuring that the peer review pathologist is consulted regarding proposed changes
646 before the final pathologist's report is signed. If major changes are proposed after the original
647 peer review memo is signed, the peer review pathologist must be given the opportunity to
648 consider their validity, and if necessary to reevaluate the pathology data and slides. Consensus
649 following this reappraisal should be documented by the peer review pathologist via an annotation
650 on the original peer review memo or by preparing a second peer review memo.

651

652 As stated previously, the peer review memo is a record of data verification and is not raw
653 data. The notes and worksheets created or annotated by the peer review pathologist or study
654 pathologist as well as records of changes made to the microscopic findings and study report as a
655 result of peer review are also not raw data and do not need to be retained after the study report is
656 signed (STP, 1997; McKay, 2010).

657

658 The peer review pathologist should not be considered a principal investigator, and should not
659 be required to sign (and should not sign) the final study pathologist's report. In addition, the peer
660 review pathologist should not be expected to sign a compliance statement because the study
661 pathologist assumes the responsibility for evaluation of pathology data and interpretations in
662 compliance with regulatory guidance (OECD, 2002).

663

664 *Documentation When the Peer Review Occurs After Study Completion*

665

666 If the peer review process is conducted after the study pathologist's report and the final study
667 report are finalized and signed, it is preferable to include the original study pathologist in this
668 review process, but this is not always possible. In some cases the peer review pathologist must
669 perform a complete independent review of all pathology data and prepare a separate signed
670 pathology report. If changes to pathology data or the study pathologist's narrative are required in
671 a GLP-compliant study after the final study report has been signed, a formal study report
672 amendment is required that documents all changes to the findings and interpretations described
673 in the original study pathologist's report. A peer review memo, a PWG memo, or a pathology
674 report documenting the purpose and scope of the peer review, the materials and information
675 examined, and any modifications or disagreements with the original pathology data and report
676 should be signed by all reviewers. If the original microscopic data files are changed, the audit
677 trail should document each change.

678

679 *Remote Peer Review and Peer Review Using Digital Images*

680

681 Direct and detailed communication between the study pathologist and the peer review
682 pathologist is essential to successful peer review. While face-to-face interaction over a multi-
683 headed microscope is ideal, pathology peer review often can be performed successfully at a site
684 remote from the study pathologist. Discussion and reconciliation of findings and wording in the
685 draft report usually can be managed by telephone, email, and/or sharing of written
686 communications and images. When findings are unusually complicated, face-to-face discussion

687 and concurrent review of selected glass slides should be considered to resolve details of the
688 pathology findings.

689

690 Direct light microscopic examination of tissue sections on glass slides is the “gold standard”
691 for histopathologic assessment. Recent advances in the quality of digital imaging technology
692 permit entire microscopic sections to be scanned and reviewed from any location with an internet
693 connection. “Sections” may be examined at high resolution over the full range of magnifications
694 typically available to an anatomic pathologist using a light microscope. In principle, therefore,
695 pathology peer review could be conducted using digital images if the peer review pathologist can
696 effectively evaluate tissue changes using images of each entire specimen represented on the glass
697 slides. The study pathologist and peer review pathologist(s) at distant locations then might
698 discuss and interpret individual microscopic findings from the same image, often working by
699 teleconference in "real time". If the digital image cannot be suitably interpreted, the glass slide(s)
700 should be used to resolve any concerns (Tuomari et al., 2007). Microscopic examination of
701 histologic sections using digital images should become more common over time as appropriate
702 processes are defined and accepted.

703

704 CONCLUSION

705

706 Pathology peer review has evolved over several decades of collective experience by
707 thousands of toxicologic pathologists. Despite multiple publications about the peer review
708 process, many details of pathology peer review have not been widely described or universally

709 accepted. This paper presents current views on pathology peer review in an attempt to further
710 harmonize and communicate effective pathology peer review strategies and practices.

711
712 It is anticipated that pathology peer review expectations within companies, research
713 institutions, and regulatory agencies worldwide will continue to evolve, and that the
714 recommendations proposed in this paper will be further refined in the future. However, the key
715 features of pathology peer review conducted prior to study completion, i.e. flexibility to meet
716 changing needs and unique study requirements, the ability of the peer review pathologist to fully
717 explore all possible evidence of toxicity within nonclinical toxicity and carcinogenicity studies,
718 direct interaction of two or more pathologists to ensure the quality and consistency of pathology
719 data and reports, and increased confidence in the data and interpretations, should not change over
720 time. Any future changes in the process should facilitate and enable these current strengths.

721
722 Footnote

723
724 ¹ This paper has been endorsed by the Society of Toxicologic Pathology, the European
725 Society of Toxicologic Pathology, the Japanese Society of Toxicologic Pathology, the British
726 Society of Toxicologic Pathologists, the French Society of Toxicologic Pathology, the Italian
727 Society of Toxicologic and Experimental Pathology, the Society of Toxicologic Pathology—
728 India, the Korean Society of Toxicologic Pathology, the Latin American Society of Toxicologic
729 Pathology, and the American College of Veterinary Pathologists.

730

730 REFERENCES

731

732 Barale-Thomas, E., Bradley, A. (2009). Results of the “Peer review survey”: the report is open
733 for comments. Poster presented at the annual general meeting of the European Society of
734 Toxicologic Pathology, held September 15-18, 2009, The Hague, The Netherlands.

735

736 Bolon, B., Barale-Thomas, E., Bradley, A., Ettlin, R. A., Franchi, C. A. S., George, C.,
737 Giusti, A. M., Hall, R., Jacobsen, M., Konishi, Y., Ledieu, D., Morton, D., Park, J-H.,
738 Scudamore, C., Vijayasarithi, S. K., Wijnands M. V. W. International
739 recommendations for training future toxicologic pathologists participating in
740 regulatory-type, nonclinical toxicity studies. *Toxicol Pathol*, in press.

741

742 Crissman, J. W., Goodman, D. G., Hildebrandt, P. K., Maronpot, R. R., Prater, D. A., Riley, J. H.,
743 Seaman, W. J., Thake, D. C. (2004). Best practices guideline: toxicologic histopathology.
744 *Toxicol Pathol* **32**, 126-131.

745

746 Eighmy, J. J. (1996). Study pathologist perspective of pathology peer review. *Toxicol Pathol* **24**,
747 647-649.

748

749 European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP).
750 (2002). *Note for guidance on carcinogenic potential*.
751 <http://www.ema.europa.eu/pdfs/human/swp/287700en.pdf>. (Accessed January 16, 2010).

752

- 753 U.S. Environmental Protection Agency (EPA) (1994). Pesticide registration (PR) notice 94-5:
754 *Requests for re-considerations of carcinogenicity peer review decisions based on*
755 *changes in pathology diagnoses.* http://www.epa.gov/PR_Notices/pr94-5.html. (Accessed
756 06 February 2010).
- 757
- 758 Frantz, J. D. (1997). Letter to the editor [on pathology peer review]. *Toxicol Pathol* **25**, 335-337.
- 759
- 760 Isaacs, K. (2007). Issues of quality in pathology. In *Good Clinical, Laboratory, and*
761 *Manufacturing Practices*, pp. 317-34. Royal Society of Chemistry, Cambridge, UK.
- 762
- 763 Japanese Society of Toxicologic Pathology (2009). Panel discussion: Regulatory perspective for
764 pathology data. *J Toxicol Pathol* **22**, 209-227.
- 765
- 766 Mann, P. C. (1996). Pathology peer review from the perspective of an external peer review
767 pathologist. *Toxicol Pathol* **24**, 650-653.
- 768
- 769 McCullough, B. M., Valerio, G., Miller, G., Pino, M., Mirsky, M. (1997). Letter to the editor [on
770 pathology peer review]. *Toxicol Pathol* **25**, 337-338.
- 771
- 772 McKay, J. S., Barale-Thomas, E., Bolon, B., George, C., Hardisty, J., Manabe, S., Schorsch, F.,
773 Teranishi, M., Weber, K. (2010). A commentary on the process of peer review and
774 pathology data locking. *Toxicol Pathol* **38**, 508-510.
- 775

- 776 Morton, D., Kemp, R. K., Francke-Carroll, S., Jensen, K., McCartney, J., Monticello, T. M.,
777 Perry, R., Pulido, O., Roome, N., Schafer, K., Sellers, R., Snyder, P.W. (2006). Best
778 practices for reporting pathology interpretations within GLP toxicology studies. *Toxicol*
779 *Pathol* **34**, 806-809.
- 780
- 781 Organisation for Economic Co-operation and Development (OECD) Working Group on Good
782 Laboratory Practice (2002). *The application of the OECD principles of GLP to the*
783 *organization and management of multi-site studies.*
784 [http://www.oelis.oecd.org/olis/2002doc.nsf/LinkTo/NT00000B8A/\\$FILE/JT00128856.PD](http://www.oelis.oecd.org/olis/2002doc.nsf/LinkTo/NT00000B8A/$FILE/JT00128856.PD)
785 F. (Accessed February 20, 2010).
- 786
- 787 Organisation for Economic Co-operation and Development (OECD) Committee on the
788 Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. (2009).
789 *OECD guidance document for the performance of chronic toxicity and carcinogenicity*
790 *studies.* Chapter 3.6 Investigations (including histopathological guidance). Annex 1 to
791 CC/09/09.
792 <http://iacoc.org.uk/papers/documents/CC0909OECDGuidanceUKChapter.pdf>.) Accessed
793 January 16, 2010).
- 794 Sahota, P.S. (1997). Letter to the editor [on pathology peer review]. *Toxicol Pathol* **25**, 337.
- 795
- 796 Society of Toxicologic Pathologists (STP) (1991). Peer review in toxicologic pathology: some
797 recommendations. *Toxicol Pathol* **19**, 290-292.

798 Society of Toxicologic Pathologists (STP) (1997). Position of the Society of Toxicologic
799 Pathologists: documentation of pathology peer review. *Toxicol Pathol* **25**, 655.
800

801 Tuomari, D.L., Elliott, G., Kulwich, B., Yarrington, J., Foillet, X., Geoly, F., Long, P. (2004).
802 Society of Toxicologic Pathology position on histopathology data collection and audit
803 trail: compliance with 21 CFR parts 58 and 11. *Toxicol Pathol* **32**, 122-123.
804

805 Tuomari, D.L., Kemp, R.K., Sellers, R., Yarrington, J.T., Geoly, F., Fouillet, X.L.M., Dybdal, N.,
806 Perry, R., Long, P. (2007) Society of Toxicologic Pathology position paper on pathology
807 image data: compliance with 21 CFR Parts 58 and 11. *Toxicol Pathol* **35**, 450-455.
808

809 United States Federal Register (1987). *Preamble to the good laboratory practice regulations*. **52**
810 (172), September 1, 33768-33782.
811

812 Ward, J. M., Hardisty, J. F., Hailey, J. R., Streett, C. S. (1995). Peer review in toxicologic
813 pathology. *Toxicol Pathol* **23**, 226-234.
814

814