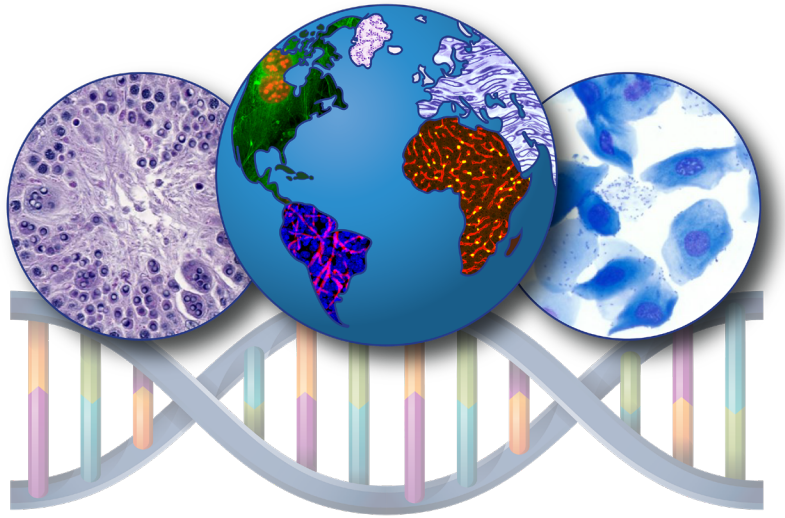
Peer Review in Toxicologic Pathology



Division of Translational Toxicology Global Toxicologic Pathology Training Program

National Institutes of Health • U.S. Department of Health and Human Services

Overview

- Definitions
- Reasons for Conducting a Peer Review
- Methodology of Conducting a Peer Review
- Digital Pathology and Peer Review
- Peer Review in the Division of Translational Toxicology at the National Institute of Environmental Health Sciences (NIEHS)

Definitions

- Peer review in the context of toxicologic pathology generally refers to a second pathologist reviewing some portion of a particular study.
- The purpose, scope, and documentation of the peer review depend on several factors that will be covered in this module.
- To start, this module will define the following types of peer reviews:
  - Contemporaneous vs Retrospective
  - Informal vs Formal
  - Internal vs External

Definitions

Contemporaneous vs Retrospective

- One of the most important aspects to understand about a peer review is the status of the data/study that is to be peer reviewed.
- The study/data can be broken down into two broad categories, depending on whether the study has been finalized.
  - Contemporaneous Peer Review is performed on draft data/study.
  - Retrospective Peer Review is performed on finalized data/study.

Definitions

Contemporaneous Peer Review

- **Contemporaneous Peer Review** involves performing a peer review on draft data that have not yet been finalized.
  - In this case, a Study Pathologist (SP) will finish reviewing all slides in the study and produce a draft report.
  - The Peer Review Pathologist (PRP) will then review a subset of the slides/data, and the two pathologists will come to a consensus.
  - The final report remains the responsibility of the Study Pathologist.
- As a result, the documentation of a contemporaneous peer review defines who conducted the review, when it was conducted, and what was reviewed.
  - The details of the peer review process and any discussions between pathologists are typically not documented.
- This is the most common type of peer review performed in industry.

Retrospective Peer Review

- **Retrospective Peer Review** involves performing a peer review on a finalized study/data set.
  - In this case, the SP does not have to necessarily be involved.
  - The PRP will review a subset of the slides/data, typically for the purposes of addressing a specific question or issue.
- The documentation process for a Retrospective Peer Review is much more extensive.
  - A revised report will be issued and the PRP must document what was changed from the original report and why.
- This is the most common type of peer review performed in the Division of Translational Toxicology (formerly the Division of the National Toxicology Program).

Informal vs Formal Peer Review

- Peer Reviews also fall into two broad categories known as Informal or Formal.
- Informal Peer Review – the pathologist seeks an opinion from a colleague on the diagnosis for one or, at most, a few slides.
  - This process is never documented.
- Formal Peer Review – a documented review of a portion of the study. Formal peer reviews are either contemporaneous or retrospective.
  - Documentation usually occurs in the protocol and lists who, where, and when the peer review is performed.
  - Methodology of the peer review is generally covered by an organization's Standard Operating Procedures (SOPs).
  - When complete, a peer review statement, signed by the PRP, will explain what portion of the study was reviewed.
  - This documentation is required for studies following Good Laboratory Practices (GLPs).

Definitions

Informal Peer Review

- An informal peer review is the process of a pathologist seeking a second opinion.
  - This generally happens when reviewing histopathology slides but can occur with any data from a study.
  - It can be as simple as walking down the hall and asking for another pathologist's thoughts on the morphologic changes seen on a slide.
  - With digital pathology, that informal consultation can be worldwide.
- The pathologist is not bound to the opinion of the second pathologist, and the final diagnoses, interpretation, and conclusions remain the responsibility of the first pathologist.
- As a result, informal peer reviews are never documented.

Formal Peer Review

- A formal peer review, which could be contemporaneous or retrospective, is a process that is documented in a protocol (or an amendment).
  - The documentation designates who will perform the peer review and the documentation is required to follow good laboratory practices (GLPs).
- The procedures for conducting the peer review are generally covered by institutional SOPs.
  - This process is most often covered by the SOPs of the PRP's institution.
- As with informal peer reviews, the SP is not bound to the diagnoses, interpretations, or conclusions of the PRP during a contemporaneous peer review.
  - The final report remains the sole responsibility of the SP.
- Documentation that a formal peer review occurred is required, but documentation of discussions and interactions between the pathologists is not.

Internal vs Exernal Peer Review

- Peer Reviews can also be considered Internal or External
- An **Internal Peer Review** occurs when the SP and the PRP are from the same organization.
  - Advantages to this approach are the pathologists use similar processes and nomenclature.
  - The disadvantages are there may be a perceived bias and there is a potential for group think.
- An **External Peer Review** occurs when the PRP is from an organization different from the SP.
  - The advantages to this approach are that there may be less perceived bias, and the potential trap of group think is reduced.
  - The disadvantages are the PRP is likely less familiar with any previous work/data on the compound and processes and nomenclature must be aligned.

Reasons for Conducting a Peer Review

Reasons for Peer Reviews

- To improve the accuracy and quality of the pathology data and the interpretation of that data.
- To increase the confidence in the data for sponsors conducting the studies and regulatory agencies interpreting them.
- Ensuring harmonization of nomenclature across studies of a compound(s).
- Confirming the target organs identified by the SP.
- Identifying any target organs missed.
  - Target organs are those organs identified to have changes related to the test article.
- Sponsoring companies often peer review all studies where important risk assessment or business decisions will be made.

Reasons for Conducting a Peer Review

Additional Reasons

- Preventing diagnostic drift
  - Diagnostic drift occurs when a SP changes diagnostic criteria within a study.
  - This drift can most often happen in larger studies where the SP is reviewing the same study over long periods of time.
  - The PRP reviews the data over a shorter time frame and can notice when diagnostic criteria drift within a study.
- Confirming the No Observed Adverse Effect Level (NOAEL).
  - The NOAEL is dose level at which no adverse effects are seen in the study.
  - It is an important parameter used in regulatory and risk assessment decision making.

Methodology of a Peer Review

How to conduct a Peer Review

- There is not a universally agreed methodology for performing a peer review. However, guidance on the proper conduct of a peer review is available and includes:
  - Society of Toxicologic Pathology has produced multiple manuscripts describing best practices in peer review
    - Recommendations for Pathology Peer Review, Morton et al., Toxicologic Pathology 2010 https://doi.org/10.1177/0192623310383991
    - Scientific and Regulatory Policy Review: Review of the Organisation for Economic Co-operation and Development (OECD) Guidance on the GLP Requirements for Peer Review of Histopathology. Fikes et al., Toxicologic Pathology, 2015 https://doi.org/10.1177/0192623315596382
    - Scientific and Regulatory Policy Committee Points to Consider: Review of the United States Food and Drug Administration (FDA) Guidance on Pathology Peer Review in Nonclinical Toxicology Studies. McDorman et al., Toxicologic Pathology, 2024 https://doi.org/10.1177/01926233241248654

How to conduct a Peer Review

- In addition, regulatory guidance covering peer review has been issued:
  - US FDA
    - Pathology Peer Review in Nonclinical Toxicology Studies: Questions and Answers, December 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pathology-peer-review-nonclinical-toxicology-studies-questions-and-answers
  - OECD
    - Guidance on the GLP Requirements for Peer Review of Histopathology, January 2015 https://doi.org/10.1787/9789264228306-en

How to conduct a Peer Review

- The conduct of a peer review can cover many aspects, but this module will focus on the following:
  - Materials available to the PRP
  - What should be reviewed
  - In-person or remote
  - Resolving differences
  - Documentation of the peer review

Methodology of a Peer Review

What should be reviewed

- Which tissues and how many should be reviewed depend on several factors, such as species, size of the study, and diagnoses made. Some general guidance follows:
  - Target organs – generally all target organs declared by the SP should be reviewed.
  - Early death animals – animals that died on study should have all tissues peer reviewed and the cause of death agreed upon.
  - Neoplasia – generally all diagnoses of neoplasms (benign and malignant tumors) should be peer reviewed.
  - Additional animals – a certain percentage of control and dosed animals should be randomly selected for review to ensure test article-related lesions were not overlooked. The number of animals depends on many factors but should be scientifically justified.

Methodology of a Peer Review

Materials available to the PRP

- To perform a proper and comprehensive peer review, the PRP should have all relevant data that was available to the SP, to include:
  - Access to all slides of the study, not just the slides designated in the peer review plan
  - Other relevant data from the study to include body weights, organ weights, clinical pathology data, and toxicokinetic data
  - Prior findings in the same compound or similar class
  - Mechanism of action or target biology, if known

In-person vs Remote Peer Review

- A contemporaneous peer review can be performed in person, where the pathologists meet face to face, or remotely where slides are reviewed in different locations. There are advantages to either method:
  - In-person peer review
    - Advantages - slides do not require shipping, pathologists can resolve differences via direct discussion, the duration of the peer review can be shorter as reconciliation is achieved while the PRP is on-site.
  - Remote peer review
    - Advantages: no travel required, easier to resolve scheduling conflicts
  - Note: The use of digital pathology, where slides can be scanned as whole-slide images and reviewed online, has increased the use of remote peer reviews.

Resolving differences

- The PRP will highlight areas of disagreement.
- Disagreements can be in several forms, such as:
  - Diagnoses missed by the SP
  - Incorrect diagnoses or inappropriate terminology used by the SP
  - Suggestions on grouping diagnoses or other techniques to improve the quality of the data
  - Suggestions on the narrative report, including formatting, to improve the interpretation of the data
- If the peer review is contemporaneous, the SP will then review the differences and decide whether to make changes to the data or report.

Resolving differences

- The peer review process should produce a general agreement on the key aspects of the study, when applicable, which include:
  - General agreement on nomenclature/diagnoses
    - Not every diagnosis must be agreed upon by the SP and PRP
  - Determination of target organs
  - Diagnoses for treatment-related findings
  - Dose groups with treatment-related findings
- If the SP and PRP cannot agree on a critical aspect of the study, a Pathology Working Group (PWG), composed of a panel of expert pathologists, to include the SP and PRP, will examine the disagreement and issue a final determination.

Documentation of the Peer Review

- Based on recent FDA guidance (2021), the documentation of the peer review should include:
  - Who performed the PPR and when
  - Type of peer review: contemporaneous or retrospective
  - Applicable regulatory compliance (GLP)
  - Format: Glass slides or whole slide images (digital)
  - What data and documents were available to the PRP
  - What was examined
    - Animal identification, dose/treatment group, tissues, etc.
  - Whether the terminology, diagnoses, and interpretations used in the pathology report were agreed upon by the SP and PRP
  - Signed and dated by the PRP

Digital Pathology

- The use of whole slide images (WSIs), which are digital representations of the histopathology slide, have altered the way peer reviews are performed.
- The use of WSIs and corresponding image management systems to conduct peer reviews were greatly increased during the COVID-19 pandemic, when travel was restricted.
- Since then, many of the barriers to the use of WSIs were overcome and there remains widespread use of digital pathology to perform peer reviews.
- The next few slides will discuss the advantages and disadvantages to using digital pathology for peer review.

Digital Pathology – Advantages for Peer Review

- No travel or shipping required – the PRP does not need to travel to the location of the glass slides and slides do not need to be shipped to the PRP.
- More expert opinions are accessible – WSIs can be sent almost anywhere in the world, resulting in greater access to expert pathologists.
- Resolving differences with SP – WSIs can be shared in real time and the SP and PRP can more easily resolve any differences by “looking at the same thing at the same time”.

Digital Pathology – Disadvantages for Peer Review

- Cost – the cost of a digital scanner, image management system (IMS), and IT infrastructure can be prohibitive for some.
- Pathologist hesitation – some pathologists, especially those with many years of experience looking at glass slides, may be reluctant to review digital slides.

Peer Review at the National Institute of Environmental Health Sciences (NIEHS)

- There are some notable differences between the peer review process described herein and the Quality Assessment (QA) process used at NIEHS by the Division of Translational Toxicology (DTT).
- The DTT, formerly the Division of the National Toxicology Program (DNTP), has developed a process (QA) over the past 40+ years for reviewing contracted animal toxicology studies for quality.
- This process involves much more than a simple peer review with a second pathologist reviewing some of the work of the study pathologist.
  - For more information on the peer review process used at the DTT, see Sills et al. National Toxicology Program position statement on informed (“nonblinded”) analysis in toxicologic pathology evaluation. Toxicologic Pathology, 47(7), 887–890. https://doi.org/10.1177/0192623319873974

Peer Review at NIEHS

- There are several additional steps taken in the QA process to include:
  - Pathology Data Review (PDR) – review of all pathology data (not including the actual slides) to create a road map for what will be reviewed and to align terminology with specifications.
  - Audit of Pathology Specimens (APS) – review of 10% of wet tissues/slides/blocks to ensure tissue collection and processing procedures meet specifications.
  - Pathology Quality Assessment (PQA) – This step is typically a retrospective peer review and involves a second pathologist reviewing some portion of the study.
  - Pathology Working Group (PWG) – almost all toxicity studies have a PWG where a panel of pathologists reviews and agrees on the treatment-related findings, confirms the diagnoses of neoplasms, and resolves remaining diagnostic discrepancies.

Peer Review at NIEHS

- Additional differences:
  - Reconciliation of differences – Differences the QA Pathologist (QAP) has with the SP are typically resolved in consultation with a DTT pathologist. Generally, the SP is not involved.
  - Proprietary computer software is used to produce an audit trail of the QAP and PWG process.
    - All original diagnoses made by the SP that were changed by either the QAP or the PWG are trackable.
  - A full QA report is issued by the QAP as opposed to a simple peer review statement.

References

- Morton, D., Kemp, R. K., Francke-Carroll, S., Jensen, K., McCartney, J., Monticello, T. M., Perry, R., Pulido, O., Roome, N., Schafer, K., Sellers, R., & Snyder, P. W. (2006). Best practices for reporting pathology interpretations within GLP toxicology studies. Toxicologic Pathology, 34(6), 806–809. https://doi.org/10.1080/01926230601034624
- Morton, D., Sellers, R. S., Barale-Thomas, E., Bolon, B., George, C., Hardisty, J. F., Irizarry, A., McKay, J. S., Odin, M., & Teranishi, M. (2010). Recommendations for pathology peer review. Toxicologic Pathology, 38(7), 1118–1127. https://doi.org/10.1177/0192623310383991
- Sills, R. C., Cesta, M. F., Willson, C. J., Brix, A. E., & Berridge, B. R. (2019). National Toxicology Program position statement on informed (“nonblinded”) analysis in toxicologic pathology evaluation. Toxicologic Pathology, 47(7), 887–890. https://doi.org/10.1177/0192623319873974-analysis-in-toxicologic.pdf)
- Fikes, J. D., Patrick, D. J., Francke, S., Frazier, K. S., Reindel, J. F., Romeike, A., Spaet, R. H., Tomlinson, L., & Schafer, K. A. (2015). Scientific and Regulatory Policy Committee review: Review of the Organisation for Economic Co-operation and Development (OECD) guidance on the GLP requirements for peer review of histopathology. Toxicologic Pathology, 43(7), 907–914. https://doi.org/10.1177/0192623315596382
- McDorman, K. S., Bennet, B. M., Colman, K., Fikes, J. D., Keirstead, N. D., Lanning, L., Munch, B., Romeike, A., Schafer, K. A., Schorsch, F., Thibodeau, M. S., Thomas, H. C., Troth, S., Vahle, J. L., & Geoly, F. J. (2024). Scientific and Regulatory Policy Committee Points to Consider: Review of the United States Food and Drug Administration (FDA) Guidance on Pathology Peer Review in Nonclinical Toxicology Studies. Toxicologic Pathology, 52(2–3), 138–148. https://doi.org/10.1177/01926233241248654
- U.S. Food and Drug Administration. (2021, December). Pathology peer review in nonclinical toxicology studies: Questions and answers (Guidance for industry). U.S. Department of Health and Human Services. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pathology-peer-review-nonclinical-toxicology-studies-questions-and-answers

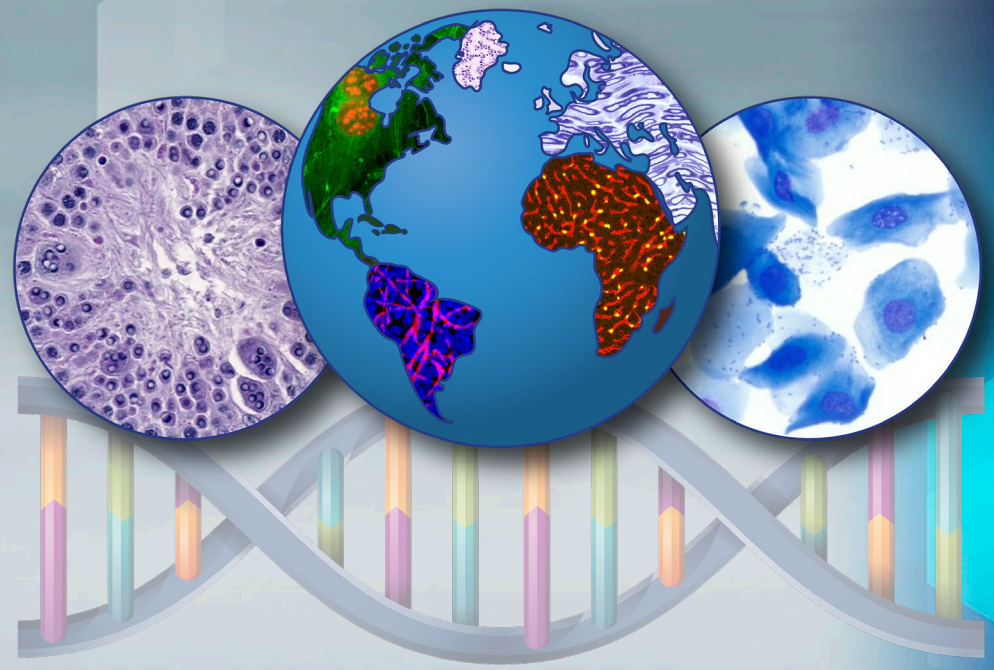
National Institute of Environmental Health Sciences
Division of Translational Toxicology

Authors

- Tom Steinbach, DVM, DACVP, DABT – EPL, Inc.

Reviewers

- Beth Lubeck, PhD, MBA – Division of Translational Toxicology, NIEHS
- Cynthia J. Spryng, MS, PhD, DVM, DACVP, DABT – Inotiv-RTP
- Mark F. Cesta, DVM, PhD, DACVP – Division of Translational Toxicology, NIEHS



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