Peer Review in Histopathology Evaluations

Regulatory Affairs & Drug Development: Current Thinking and Challenges
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Reasons for Pathology Peer Review

- Ensure data meets requirements of regulatory agencies
- Increase accuracy of data
- Increase confidence in data
- Confirm target organs
- Confirm no effect level (NOEL)/ No adverse effect level (NOAEL)
Reasons for Pathology Peer Review

- Ensure consistency of diagnoses within the study
- Intraorganizational harmonization of nomenclature and diagnostic criteria
- Continuing education
Pathology Peer Review

• Performed by a second pathologist
• Routinely performed by many companies
• May also be done to address specific issues
• Involves a subset of tissues from initial evaluation
Things a Peer Review is NOT

• A re-read of a study
• Does not generate a second data-set
• A “blinded” re-examination
• A performance review of the Study Pathologist
Recent Recommendations for Peer Review
EPL – Peer Review SOPs

• Complete Review Animals – Control

  – Subchronic Rodent – 20%
  – Rodent Carcinogenicity Study – 10%
  – Short Term Bioassay (Tg) – 10%
  – Dog Study – 25%
  – Non-Human Primate Study – 25%
EPL – Peer Review SOPs

• Complete Review Animals – High Dose
  – Subchronic Rodent – 60%
  – Rodent Carcinogenicity Study – 10%
  – Short Term Bioassay (Tg) – 25%
  – Dog Study – 75%
  – Non-Human Primate Study – 100%
EPL – Peer Review SOPs

• Early Deaths
  – Review of selected tissues from all animals that die on test to verify the probable cause of death

• Target Tissues
  – In order to accurately confirm the NOEL/NOAEL, we review all target tissues in all groups for all studies
EPL – Peer Review SOPs

• Recovery Sacrifice
  – Possible delayed toxicity
  – Complete review of same percentage of animals
    • Rodent:
      – 20% of controls
      – 60% of high-dose
  – All targets
  – All proliferative changes
• Proliferative Lesions

  – Neoplasms: All diagnosed neoplasms in all dose groups
  – Non-neoplastic proliferative changes: All proliferative changes (hyperplasia, foci, etc) in all dose groups – this approach includes review of all borderline lesions
Is Formal Peer Review Required by Regulatory Agencies?

Sometimes Yes and Sometimes No
Peer Review and Regulatory Agencies

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 25 July 2002
CPMP/SWP/2877/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)

NOTE FOR GUIDANCE ON CARCINOGENIC POTENTIAL
6. REPORTING ON CARCINOGENICITY STUDIES

6.1 General principles

Pre-neoplastic and neoplastic lesions should be described in conventional histopathological terms according to commonly used classifications (e.g. ILSI, STP, IARC, RENI and other recent texts on rodent pathology). Deviations from standard diagnoses should be explained in the report.

Ideally, one pathologist should be responsible for the histological evaluation. If several pathologists are involved, slides from all treatment groups must be distributed evenly among them. Peer-review of slides is required for all identified target organs and for at least 10% of all tumours. A complete review of 10% of the animals in each group should also be performed. If more than one pathologist is involved more extensive peer review is needed to assure consistency. The peer review should be documented in raw data and in the study report. Board certification or equivalent should qualify pathologists.
OECD GUIDANCE DOCUMENT ON PEER REVIEW

ISSUED SEPTEMBER 26, 2014
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING
Number 16

Advisory Document of the Working Group on Good Laboratory Practice - Guidance on the GLP Requirements for Peer Review of Histopathology
1. Background

1.1. The histopathological assessment of tissue samples is one of the key endpoints of a toxicology study, and the results obtained will contribute substantially to the outcome and conclusions of the study.

1.2. Because the assessment of tissue specimens is based upon the expert opinion of the slide reading pathologist, it is common for test facilities to have implemented a peer review process whereby a number of slides are assessed by a second pathologist. The process is a means of assuring the quality and the accuracy of interpretation and maintaining best practices. Although there is no absolute requirement in the GLP principles to conduct peer review, most receiving authorities expect that some level of peer review will be performed. This document is concerned with the processes used to organise, perform and record the results of this review.

1.3. The peer review process can lead to changes in the interpretation of the slides and the reported results, and potentially the outcome and conclusions of the study. The purpose of this document is to provide guidance to pathologists, test facility management, study directors and quality assurance personnel on how the peer review of histopathology should be planned, managed, documented and reported in order to meet GLP expectations and requirements. This document is a complement to the guidance provided in section 3.6.3.7 of OECD Guidance Document 116¹, whose focus is on how histopathology peer review should be conducted.
2. GLP Requirements

2.1. Any requirements for peer review performed at the test facility or by external consultants, should be clearly described in the study plan or subsequent study plan amendments. This should include information on how the pathology peer review will be planned, managed, documented and reported. It should also be stated whether the review will be performed contemporaneously or retrospectively. If some or all of the above information is documented in an SOP a reference to the current version of the SOP would be acceptable.

2.2. The study plan or subsequent amendments should provide an appropriate level of information to allow reconstruction of how tissues will be selected for peer review whilst allowing sufficient flexibility to react to unexpected pathology findings.

2.3. If the pathologist that is appointed to perform the peer review is located at a site geographically remote from the site where the study was performed there is no requirement for them to be formally appointed as a principle investigator. Because the reviewing pathologist is interpreting data and not generating data it would be appropriate for them to be considered as a contributing scientist. The study director maintains ultimate responsibility for ensuring that the peer review process is conducted in accordance with the principles of GLP (see bullets 3.1-3.3).
2.4. Details of how the peer review was conducted should be documented and retained within the study file. These activities will include information on the identity of the tissues that were reviewed, when the tissues were reviewed and by whom. Notes made by the peer review pathologist which are used to record observations during the histopathological examination of individual slides do not normally have to be retained in the study file.

2.5. All correspondence regarding the histopathological evaluation of the slides used for peer review between the sponsor and representatives of the test facility and the peer review pathologist should be retained in the study file, including minutes of teleconferences between the sponsor and the test facility.

2.6. For the purpose of reconstruction, raw data is defined as the documentation described in bullet 2.4 and 2.5. The original histology slides that are assessed by the reviewing pathologist are derived from the test system and meet the definition of specimens. However, the slides and corresponding blocks are needed for the reconstruction of the histopathology portion of the study and consequently must be archived for the same duration as the raw data.
2.7. If the peer reviewing pathologist does not concur with all or some of the conclusions drawn by the original pathologist a clear, transparent and unbiased process should be implemented to resolve their differences. This process should be documented within the facility’s SOPs or procedures.

2.8. Where the peer reviewing pathologist’s findings were significantly different from the original interpretation of the study pathologist, a description of how differences of interpretation were handled and changes made to the study pathologist’s original interpretation should be discussed in the final report.

2.9. If, despite following procedures designed to resolve any differences of opinion, agreement cannot be reached then an independent expert or panel of experts may be used to resolve the issue. The conclusions of the panel should be clearly documented in the final report.

2.10. In most cases where there are no significant differences of opinion it will not be necessary to report in detail the outcome of the peer review in the pathology report or the final report. A simple statement that it was conducted and that the pathology report presents the agreed findings would usually suffice.
4. Summary of Expectations

4.1. Peer review of histopathology is an important part of the process which ensures the quality of the interpretation of study results and can have a significant impact on the study outcome. It is therefore essential that peer review procedures are planned, conducted, documented and reported such that the integrity of the regulatory study is not compromised and activities can be fully reconstructed and verified.

4.1.1. Histopathology peer review activities should be described within the study plan or subsequent amendments.

4.1.2. Documentation of the peer review should describe the tissues and documents examined by the peer review pathologist. Reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and of the opinions expressed.

4.1.3. There should be documented procedures that describe how any differences of opinion will be resolved.

4.1.4. Any differences of interpretation that result in a significant change of the study pathologist’s original interpretation should be discussed in the final report.

4.1.5. The identity and affiliation of the peer reviewing pathologist should be clearly stated in the final report.
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 26 September 2014

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE
MONITORING
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3. GLP Compliance of Peer Review

3.1. The peer review process can lead to changes in the interpretation of histopathology findings that in turn may influence the outcome and conclusion of the study. Consequently, there is an expectation that the peer review should be conducted in compliance with GLP. However, it is recognised that for the peer review to be of scientific value it has to be conducted by a person with the appropriate specialist experience and expertise; consequently that may necessitate the use of acknowledged experts in particular fields who do not work within a GLP test facility. When a decision is made to perform pathology peer review in a non GLP facility it should be justified and recorded within the study plan and final report. Alternatively consideration should be given to whether it would be more appropriate for the pathologist who conducts the peer review to perform their review at the test facility that conducted the study. This would remove the need to transfer histopathology slides from one site to another and would also allow the peer reviewing pathologist to perform their work under the umbrella of an established GLP quality system. In such circumstances there is an expectation that the peer reviewing pathologist would receive an appropriate level of training in the relevant facility procedures.

3.2. The study director will be making a statement concerning the extent to which their study complies with GLP. If electing to utilise a non-GLP organisation for peer review the study director needs to be satisfied that the peer review process is sufficiently well managed, and that peer review data is of adequate quality. Key elements to consider include, but are not necessarily limited to:
Pathology Peer Review
Slide Review Worksheet

• Lists study pathologist’s findings to be reviewed
• Documents the reviewing pathologist’s opinion
• Documents the resolution of differences of opinion
• Records the final diagnosis and the action taken to finalize the study data
# SLIDE REVIEW WORKSHEET

**Chemical Name**

**Compound Name Appears Here**

**Chemical Number**

**Laboratory**

**Laboratory Name**

**CASE Project ID**

**2020-01-01**

**Sacrifice**

**Terminal**

**Group Id**

**I**

**Dose**

**0**

**Sex & Species**

**Female Rats**

<table>
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<th>Animal (id)</th>
<th>Histology Number</th>
<th>No. of Slides</th>
<th>Study Pathologist’s Diagnosis</th>
<th>Reviewing Pathologist’s Comments</th>
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<td>3</td>
<td>LIVER - BASOPHILIC FOCUS</td>
<td>ASSESS LIVER - DIGITOPHILIC FOCUS (a)</td>
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<td>AP45</td>
<td>2</td>
<td>LIVER - BASOPHILIC FOCUS, focal</td>
<td>ASSESS LIVER - BASOPHILIC FOCUS (1,2)</td>
<td>[OTHER ANIMALS ARE NOT QUALIFIED AS TOTAL]</td>
<td>ASSESS WITH REVIEWING PATHOLOGIST</td>
<td>DATA BASE CHANGE CHANGE STUDY PATHOLOGIST’S DIAGNOSIS TO REVIEWING PATHOLOGIST’S DIAGNOSIS</td>
</tr>
<tr>
<td>AN46</td>
<td>5</td>
<td>GALL BLADDER - REGENERATION</td>
<td>ASSESS LIVER - NECROSIS, CRUDE LYMPHOCYTIC (1,2)</td>
<td>ASSESS WITH REVIEWING PATHOLOGIST</td>
<td>DATA BASE CHANGE CHANGE STUDY PATHOLOGIST’S DIAGNOSIS TO REVIEWING PATHOLOGIST’S DIAGNOSIS</td>
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<td>ASSESS LIVER - DIGITOPHILIC FOCUS (a)</td>
<td>ASSESS WITH REVIEWING PATHOLOGIST</td>
<td>DATA BASE CHANGE CHANGE STUDY PATHOLOGIST’S DIAGNOSIS TO REVIEWING PATHOLOGIST’S DIAGNOSIS</td>
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[More data...]

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[www.epl-inc.com](http://www.epl-inc.com)
Sample Peer Review Statement

ABC CORPORATION

STUDY NO. X0217
STUDY NO. XYZ553
EPL PROJECT NO. 999-001

"A 10-DAY DAILY ORAL (Gavage)
TOXICITY STUDY OF COMPOUND X IN
MALE BEAGLE DOGS"

PEER REVIEW STATEMENT

A microscopic peer review was performed as follows for this study:

1. Reexamination of all tissues from one animal from the Group 1 (Control) and three animals from Group 4.
   - Group 1M: 6976
   - Group 4M: 6965, 6970, 6971

2. Reexamination of all tissues from one male in group 2 and three in group 3 that were sacrificed prior to scheduled necropsy to identify potential target tissues/lesions that may have contributed to the reason for sacrifice.
   - Group 2M: 6967
   - Group 3M: 6966, 6969, 6974

3. Reexamination of the following target organs: testes, pancreas, GI tract (including Peyer's patches), thymus, lung, spleen, and bone marrow from all dogs in all groups.

Following the review of the microscopic findings reported by the study pathologist, the results were discussed and appropriate terminology and diagnoses mutually agreed on. Differences of opinion between the study and reviewing pathologists were resolved with agreement on the diagnoses.

PATHOLOGIST A, D.V.M., Ph.D.
Diplomate, ACVP, ABT
Study Pathologist
International CASO

PATHOLOGIST B, D.V.M.
Diplomate, ACVP
Reviewing Pathologist
Experimental Pathology Laboratories, Inc.

DATE

DATE
Pathology Working Group (PWG)
What is a Pathology Working Group?

- Panel of expert pathologists assembled to review a specific question concerning study results
- Members selected from academia, private consultants, government, and industry
- PWG participants selected based on their experience in toxicologic pathology and expertise with the target organ
What is the purpose of a Pathology Working Group (PWG)?

- Independent assessment to address specific questions concerning the study results
- The PWG does not review the entire study
- Review limited to specific findings or toxicologic end points
- Pathology peer review and data audits are used to provide a detailed review
Is a PWG review of study data required by regulatory agencies?

- Generally not required for data submitted to regulatory agencies
- EPA Pesticide Regulation (PR) Notice 94-5 is the only regulatory requirement for a PWG review
- May be required on a study-by-study basis depending on the issues to be resolved by other regulatory agencies
When should a PWG review be considered?

- Studies with final reports
- Pivotal studies with controversial end points
- Address questions that are of concern by regulatory agencies
- Comparison of results of multiple studies that may have been conducted and evaluated by different laboratories and/or pathologists
Benicar Carcinogenicity Concerns Resolved By Pathology Working Group

FDA was able to resolve concerns of carcinogenicity and genotoxicity related to Sankyo’s antihypertensive Benicar (olmesartan medoxomil) through the formation of a “pathology working group” comprised of members chosen by both the sponsor and FDA, NDA review documents indicate.

Renal tumors seen in a two-year rat study initially concerned Office of Drug Evaluation I Director Robert Temple, MD, enough to recommend a “not approvable” action for the drug, which was ultimately approved April 25. Temple also was concerned by an increased incidence of hyperplasia in rat kidneys that was difficult to distinguish from adenomas and by olmesartan’s genotoxicity profile.

FDA’s concern over toxicity was heightened by its general sense that Benicar is unremarkable in the angiotensin II receptor blocker (ARB) class. “The potential for carcinogenicity has been considered by the [Cardio-Renal Division] to be an approvability issue for an antihypertensive drug that has no unique clinical advantages over currently marketed members of its class,” FDA said (see preceding story).

The decision to form a pathology working group came after reviews by the Carcinogenicity Assessment


Recommended Reading


Recommended Reading


Recommended Reading

United States Federal Register (1987). Preamble to the Good Laboratory Practice Regulations. 52 (172), September 1, 33768-82.