Pathology Peer Review

Sponsored by IATP, IFSTP, STP and STP-I

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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

Morton, D., et al., Recommendations for Pathology Peer Review. *Toxicol Pathol*., 38, 1118, 2010.

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

- 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

Peer Review and Regulatory Agencies

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.

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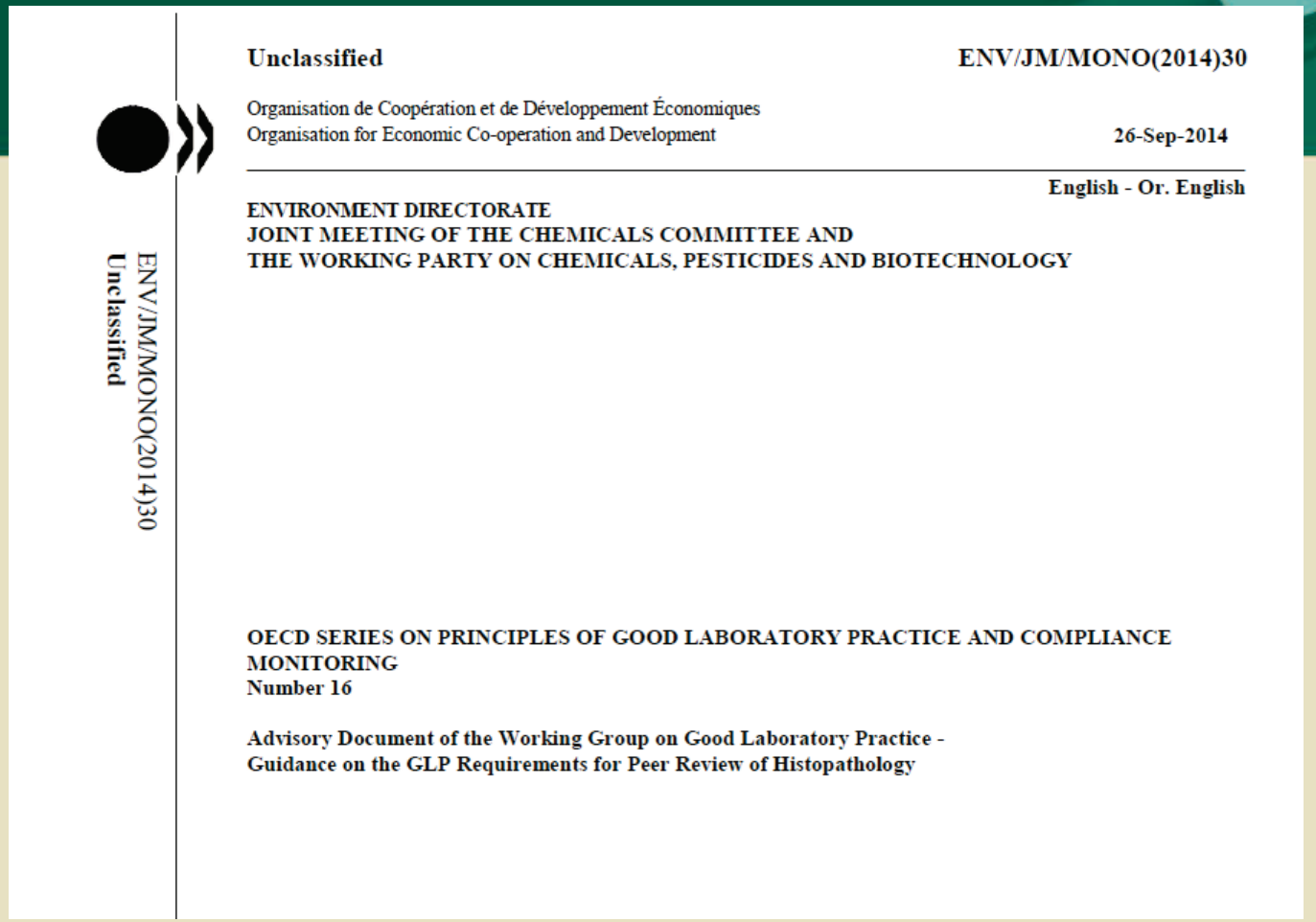
OECD GUIDANCE DOCUMENT ON PEER REVIEW

ISSUED SEPTEMBER 26, 2014



Unclassified ENV/JM/MONO(2014)30

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development 26-Sep-2014

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2014)30
Unclassified

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

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)30&doclanguage=en

Selected Sections of OECD Document

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 116[1], whose focus is on how histopathology peer review should be conducted.

Selected Sections of OECD Document

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).

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Selected Sections of OECD Document

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.

Selected Sections of OECD Document

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.

Selected Sections of OECD Document

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.

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Important Points to Consider (My Interpretations)

- Peer Review Procedures and Processes should be described in Study Protocols and SOPs
- Peer Review Notes DO NOT need to be retained in the Study File
- All correspondence between the SPONSOR, test site and the Peer Review Pathologist SHOULD be retained in the Study File
- If there are NO SIGNIFICANT differences, all that is needed is a simple Peer Review Statement

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Important Points to Consider (Continued)

- If there are SIGNIFICANT differences, a description of how the differences were handled, and changes to the original interpretation should be discussed in the final pathology report
- Question: What constitutes a “significant” difference of opinion. If the RP and the SP discuss the difference and arrive at a consensus, is this still considered “significant”?

Important Points to Consider (Continued)

- When should the PR be conducted? There is no mention of audit trails in the Guidance Document. In the US, the FDA has indicated that the Peer Review Statement should not be signed until after the final pathology report has been signed
- Our interpretation is that the PR can be conducted on draft findings, but that the PR Statement is not signed until after the final Pathology report has been signed

Sources of Disagreement in Pathology Reviews

- **Unfamiliarity with lesion.**
- Use of different criteria for tumor classification.
- Threshold for diagnosis of lesion (especially non-neoplastic aging lesions).
- Use of different terminology for same lesion.
- Diagnostic Drift.

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Rare or Unusual Findings

Moderate Mononuclear Inflammation- Myocardium - NHP

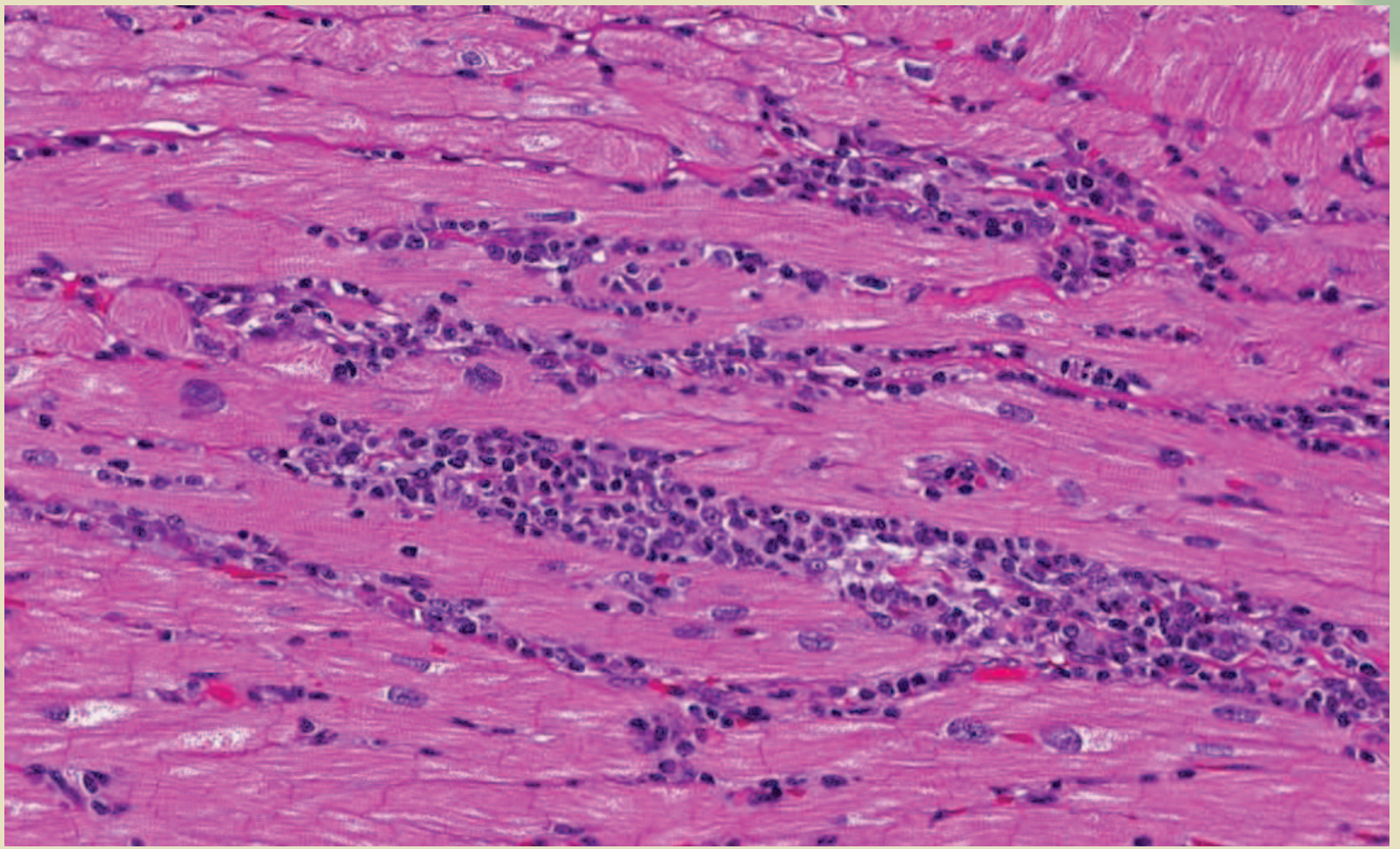

Image courtesy of Dr. Jim Rendel

Trypanosoma cruzi – Myocardial Inflammation and pseudocyst - NHP

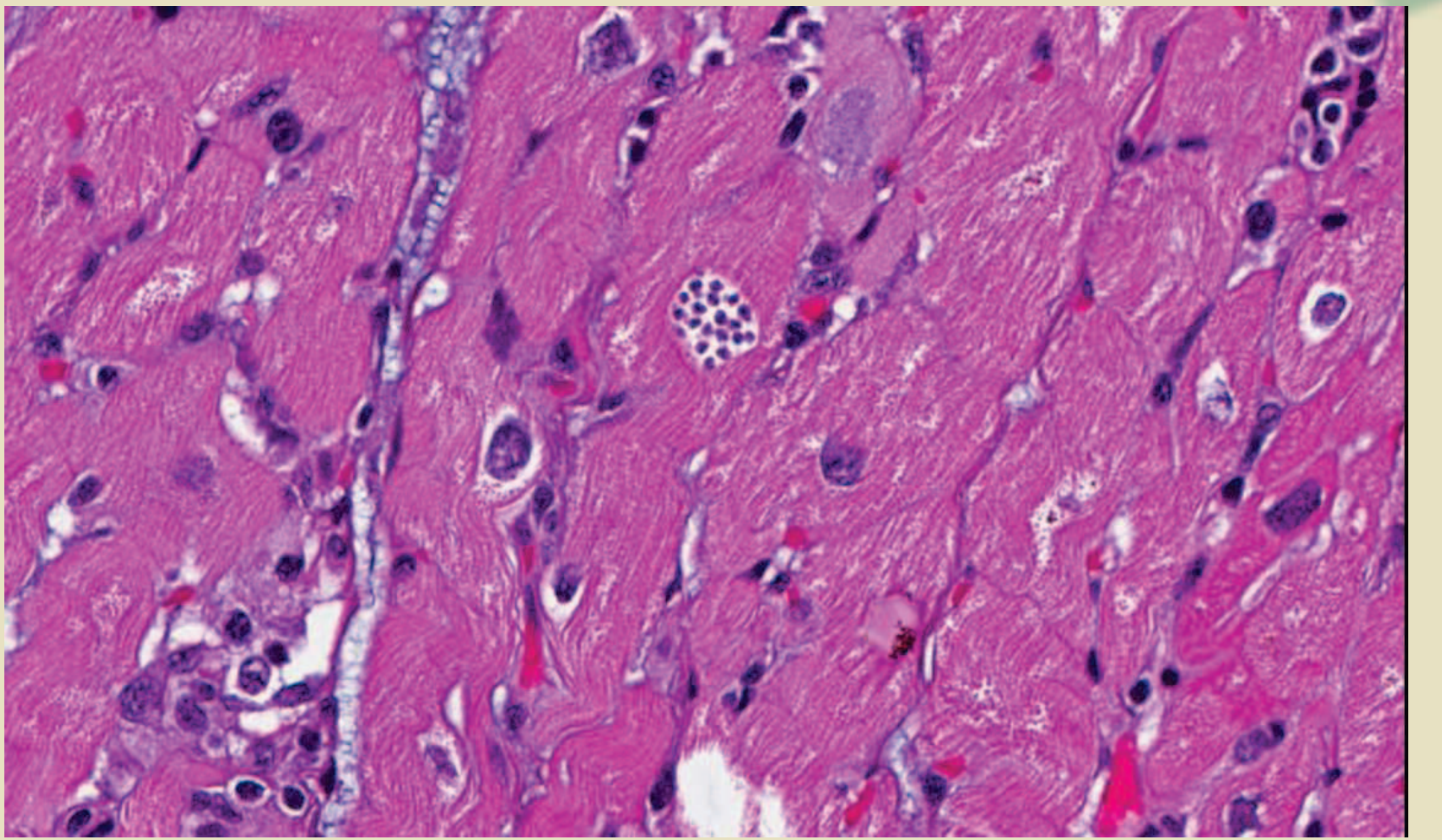

Image courtesy of Dr. Jim Rendel

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Malignant Lymphoma in B6C3F1 Mice Incidence Reported in Final Study Report

	Male Mice			Female Mice		
Group No.	1	2	5	1	2	5
No. of Animals Necropsied	50	50	50	50	50	50
Malignant Lymphoma	44	49	41	49	49	48

Comparison of Incidence of Malignant Lymphoma in B6C3F1 Mice

	Male Mice			Female Mice		
Group No.	1	2	5	1	2	5
Study Pathologist	88%	98%	82%	98%	98%	96%
Reviewing Pathologist	16%	18%	12%	36%	36%	18%
National Toxicology Program	Rate 8.3% Range 2-20% N = 1355			Rate 20.9% Range 6-42% N = 1353		

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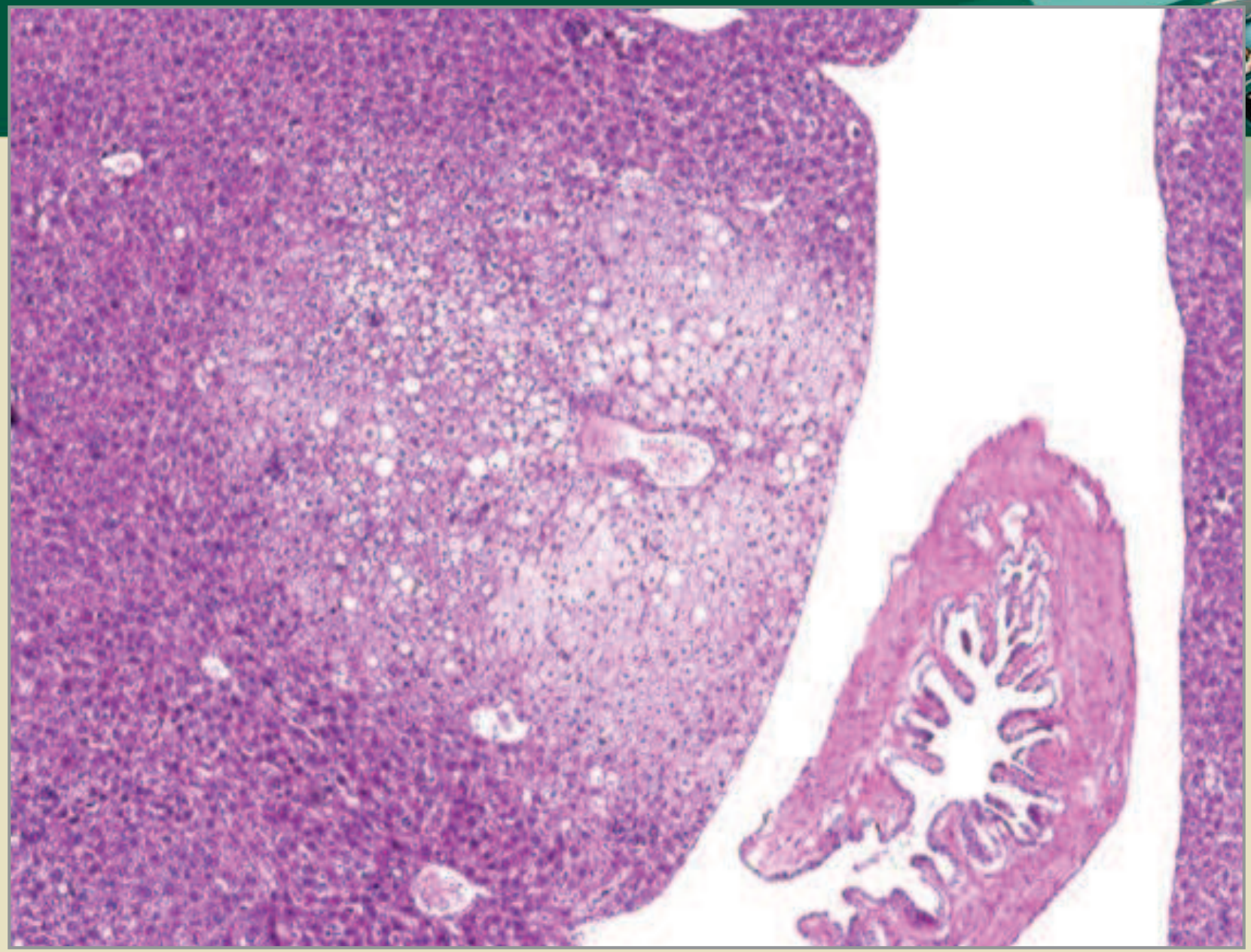

Mouse Liver – Tension Lipoidosis

Sources of Disagreement in Pathology Reviews

- Unfamiliarity with lesion.
- Use of different criteria for tumor classification.
- Threshold for diagnosis of lesion (especially nonneoplastic aging lesions).
- **Use of different terminology for same lesion.**
- Diagnostic drift.
- Computer pathology reporting system data input and reporting problems.

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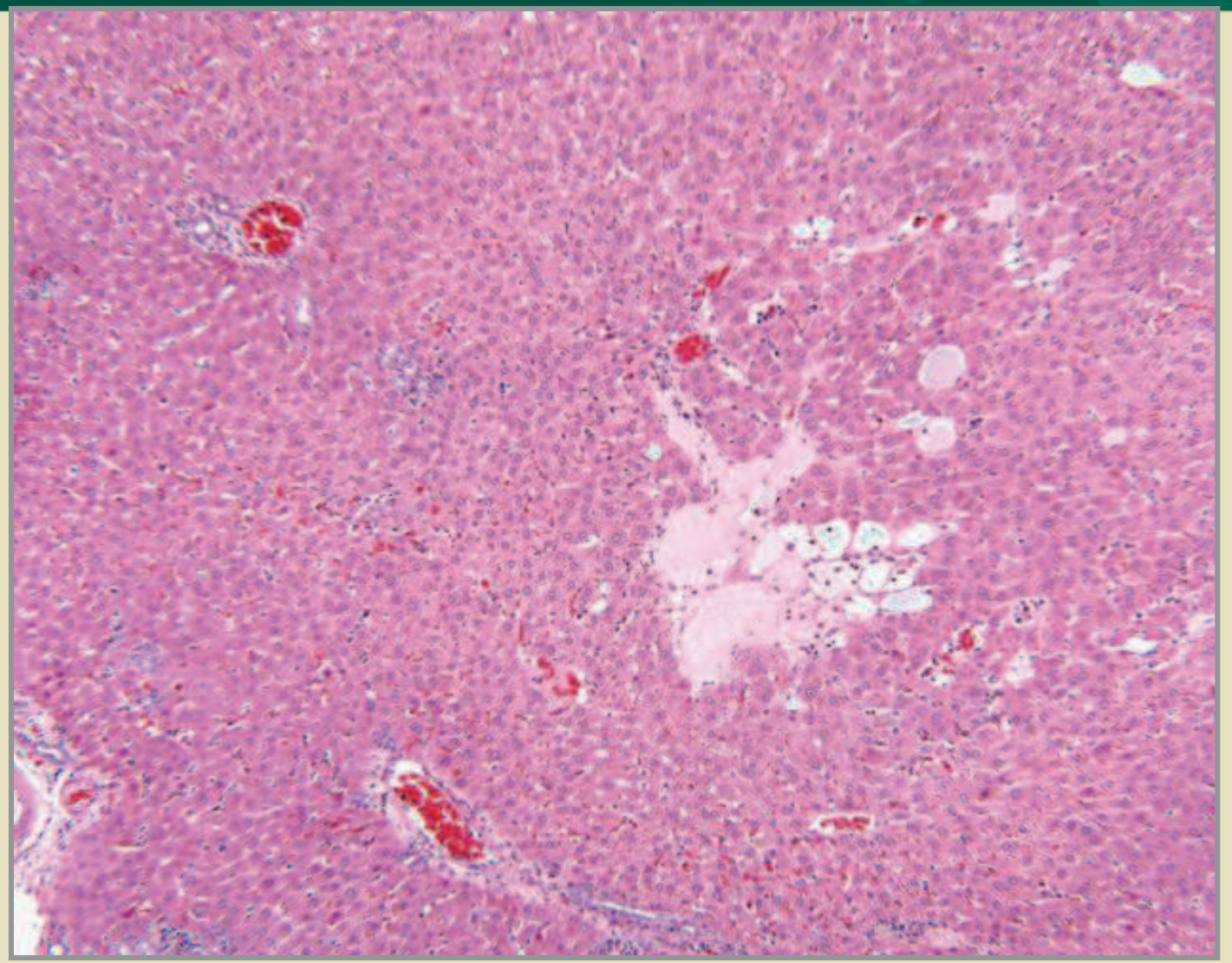
Spongiosis Hepatis vs Cystic Degeneration



Sources of Disagreement in Pathology Reviews

- Unfamiliarity with lesion.
- Use of different criteria for tumor classification.
- Threshold for diagnosis of lesion (especially nonneoplastic aging lesions).
- Use of different terminology for same lesion.
- **Diagnostic drift.**

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Incidence of Cataract Lesions in Female Rats

Control		Low		High	
SP	RP	SP	RP	SP	RP
4	21	8	19	20	29

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

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EPL Slide Review Worksheet

SLIDE REVIEW WORKSHEET

Chemical Name COMPOUND NAME APPEARS HERE Chemical Number _____

Laboratory LABORATORY NAME Client Project Id. 2000-01-01 Sacrifice TERMINAL

Group Id I Dose 0 Sex & Species FEMALE MICE

Animal Id.	Histology Number	No. of Slides	Study Pathologist's Diagnosis	Reviewing Pathologist's Comments	Comments	Action To Be Taken
AF01		3	LIVER - BASOPHILIC FOCUS	AGREE		
				LIVER - EOSINOPHILIC FOCUS (2)	AGREE WITH REVIEWING PATHOLOGIST	DATA BASE CHANGE: ADD REVIEWING PATHOLOGIST'S DIAGNOSIS
			MAMMARY GLAND - ADENOCARCINOMA	AGREE		
AF02		2	LIVER - BASOPHILIC FOCUS, FOCAL	LIVER - BASOPHILIC FOCUS (1,2) [OTHER ANIMALS ARE NOT QUALIFIED AS FOCAL]	AGREE WITH REVIEWING PATHOLOGIST	DATA BASE CHANGE: CHANGE STUDY PATHOLOGIST'S DIAGNOSIS TO REVIEWING PATHOLOGIST'S DIAGNOSIS
			LIVER - EOSINOPHILIC FOCUS	AGREE		
AF03		5	ADRENAL GLAND - PHEOCHROMOCYTOMA	AGREE		
			LIVER - BASOPHILIC FOCUS	AGREE		
			LIVER - NEPHROPATHY	LIVER - NECROSIS, CENTRILOBULAR (1,2)	AGREE WITH REVIEWING PATHOLOGIST - DATA ENTRY ERROR	DATA BASE CHANGE: CHANGE STUDY PATHOLOGIST'S DIAGNOSIS TO REVIEWING PATHOLOGIST'S DIAGNOSIS
			LIVER - EOSINOPHILIC FOCUS	NOT PRESENT IN SECTION (1,2)	DISAGREE WITH REVIEWING PATHOLOGIST - PRESENT ON SLIDE 1R	NO CHANGE: AGREEMENT BY REVIEWING PATHOLOGIST
AF04 (C.B)		12	PITUITARY - ATROPHY	NO REMARKABLE LESION	AGREE WITH REVIEWING PATHOLOGIST BUT MAINTAIN FOR CONSISTENCY	NO CHANGE: AGREEMENT BY REVIEWING PATHOLOGIST
			BRAIN - WITHIN NORMAL LIMITS	AGREE		
			EYE(S) - WITHIN NORMAL LIMITS	AGREE		

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Sample Peer Review Statement

EPL® Experimental Pathology Laboratories, Inc.

ABC CORPORATION

STUDY NO. XO217
STUDY NO. XYZ-553
EPL PROJECT NO. 999-001

"A 10-DAY DAILY ORAL (GAVAGE)
TOXICITY STUDY OF COUMPOUND 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 CRO

DATE

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

DATE

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Recommended Reading

Boorman G.A., J.K. Haseman, M.D. Waters , et. Al., (2002). Quality review procedures necessary for rodent pathology databases and toxicogenomic studies: the National Toxicology Program experience. Toxicol Pathol. 30(1):88-92.

Boorman G.A., D.C. Wolf , S. Francke-Carroll and R.R. Maronpot. (2010). Pathology Peer Review. Toxicol Pathol. 2010;38(7):1009-10.

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Mann, P.C., J.F. Hardisty and M.D. Parker . (2002). Managing Pitfalls in Toxicologic Pathology. In Handbook of Toxicologic Pathology, 2nd edition. ed. W.M. Haschek, C.G. Rousseaux and M.A. Wallig, 187-206. San Diego: Academic Press.

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Recommended Reading

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