Journal of Regulatory Science

http://journalofregulatoryscience.org

Letter to the Editor

The Pathology Community's Interpretation of Settiagounder's Proposals on GLP Process as Applied to Pathology Peer Review

Bindu M. Bennet [a], Karen S. Regan [b], Annette Romeike [c], Kenneth A. Schafer [d], Michael S. Thibodeau [e], Heath C. Thomas [f], Karyn Colman [g], James D. Fikes [h], Sabine Francke [i], Frank J. Geoly [j], Natalie D. Keirstead [k], Frederic Schorsch [l], John L. Vahle [m]

[a] *Janssen Research & Development, LLC, Spring House, Pennsylvania, USA*
[b] *Regan Path/Tox Services Inc., Ashland, Ohio, USA*
[c] *Covance Laboratory Inc., France*
[d] *Vet Path Services, Inc., Mason, Ohio, USA*
[e] *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA*
[f] *Experimental Pathology Laboratories Inc., Collegeville, Pennsylvania, USA*
[g] *Novartis Pharmaceutical Corporation, East Hanover, New Jersey, USA*
[h] *Biogen, Cambridge, Massachusetts, USA*
[i] *U.S. Food and Drug Administration, College Park, Maryland, USA*
[j] *Pfizer Worldwide Research and Development, Groton, Connecticut, USA*
[k] *Merck & Co. Inc., West Point, Pennsylvania, USA*
[l] *Bayer CropScience, Sophia Antipolis, France*
[m] *Eli Lilly & Company, Indianapolis, Indiana, USA*

The Journal of Regulatory Science recently published two articles on the topic of histopathology peer review for nonclinical studies, "Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems" (Settiagounder, 2017a) and "Histopathology Peer Review for Nonclinical Studies – GLP Processes and Conditions" (Settiagounder, 2017b). The comments contained herein represent the opinions of the Society of Toxicologic Pathology (STP) Scientific and Regulatory Policy Committee's working group on pathology peer review and are intended to clarify the process of pathology peer review and offer perspective on related U.S. regulation (21 CFR part 58) and international guidance (OECD No. 16). The views expressed in this manuscript do not necessarily represent the policies, positions, or opinions of their respective employers.

The STP is an international association of pathologists and scientists who work in academic institutions, government, the pharmaceutical and chemical industry, contract research organizations, or as consultants, and who are dedicated to the integration of toxicologic pathology into hazard identification, risk assessment,

and risk communication regarding human and animal exposure to potentially toxic substances. A key aspect of their work is the microscopic evaluation of tissues from nonclinical studies to generate histopathology diagnoses and interpretations. Peer review is frequently used as a vital component in this process.

Settiagounder's publications offer many insights and opinions on the peer review process and the respective federal regulation and international guidance pertaining to pathology peer review. However, the basis of these two manuscripts rests on a misinterpretation of the definition of pathology raw data and the process of peer review, which leads the author to inaccurately interpret the pertinent published final regulations and guidances:

- *U.S. Food and Drug Administration. 1987 Good Laboratory Practice Regulations*;
- *Organisation for Economic Co-operation and Development, 2014 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);*
- *Organisation for Economic Co-operation and Development Good Laboratory Practice: Frequently asked questions (FAQ), posted 27 March, 2017;*

and proposed rule to the regulation (currently draft, not yet codified, but the author appears to consider it as enforceable in its current form):

- *U.S. Food and Drug Administration. (2016). Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule, 21 CFR § 16 & 58.*

For clarity, direct quotes from the regulations/guidances and Settiagounder's publications are indented, but only the quotes from the regulatory documents are italicized.

Histopathology Peer Review: Brief Introduction

Unlike numerical endpoints in nonclinical studies, histopathology is a diagnostic endpoint that relies on the experience and extensive specialized training of a pathologist. The subsequent interpretation of histopathologic diagnoses is an iterative process, where a pathologist considers not only the morphology, but also other relevant information (such as variations of normal morphology in the test species, concurrent controls, historical controls, artifacts from tissue collection or tissue processing, and relevant pharmacology and literature). These complex sets of information are integrated into meaningful interpretations, which are subject to refinement throughout this process. This process is collaborative and it is common for pathologists to have *ad hoc* consultation with pathology colleagues to review/comment on a diagnosis or interpretation. Nonclinical study pathology results used to support regulatory filings are often reviewed by a peer (peer review pathologist) to further increase the quality, accuracy and consistency of the pathology diagnoses and interpretations (Crissman *et al*, 2004, Mann and Hardisty, 2013; Morton *et al*, 2010, Fikes *et al*, 2015). This pathology peer review process involves review of a subset of microscopic specimens by the peer review pathologist and discussion between the study pathologist and peer review pathologist to arrive at a consensus based on available information.

It is important to recognize that the study pathologist is ultimately responsible for the diagnoses, interpretation and conclusion of the pathology component of the study, and he/she finalizes the pathology

report based on his/her conclusions and input from peer-review and sometimes from other pathologist(s). For contemporaneous peer review, the peer review statement indicates whether the peer review pathologist agrees with the report based on their review. If the study pathologist and peer review pathologist cannot reach consensus, there are processes to be considered (e.g. convening a pathology working group which is a panel of experienced pathologists to provide diagnoses for disputed findings) to resolve differences, which represents an important part of the peer review process within the GLP framework (Fikes *et al*, 2015).

With few exceptions, there are often no regulatory mandates for pathology peer review (Morton *et al*, 2010). Therefore, peer review is generally a voluntary process, self-imposed by the pathology profession and study protocol to help ensure the accuracy of the diagnoses and interpretations.

Definition of Pathology Raw Data

Pathology raw data has been clearly defined in both the FDA's 1987 Final GLP Rule and the OECD's 2014 Advisory Document of the Working Group on Good Laboratory Practice - Guidance on the GLP Requirements for Peer Review of Histopathology (hereafter referred to as the 2014 OECD guidance) as only the signed and dated final report of the pathologist. In Settiagounder, 2017a (p.49) the author appropriately cites the FDA's 1987 Final Rule – Good Laboratory Practices:

> *"….Accordingly, <u>only</u> the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens"* [emphasis added]

However, the author then interprets pathology raw data to include all interim/working notes (pp. 47-48) by stating,

> "…it is considered critical to maintain …the original data and audit trail for data generated by the SP [study pathologist] during his/her independent histopathological evaluation…," [abbreviation expanded]

and, on p. 49,

> "… If the pathologist uses a computerized system for recording "interim notes" or "notes" of diagnosis, then the requirement as per section 58.130(e) for data entry or data change is applicable, thereby allowing continued availability of all notes, and consequently, diagnostic drift, if applicable, for any review or verification.".

Furthermore, on p.49, the author provides additional interpretation to the FDA's final rule GLP Regulations from 1987:

> "FDA did not direct that the notes taken as a result of the original observation of the evaluation of slides need to be discarded or not required to be archived".

These statements are in direct opposition to the FDA's 1987 Final Rule (see below), which clearly states that the histopathology interim notes are not raw data and thus are not necessary for reconstruction of the study:

> *"Although the notes taken by a pathologist during histopathological examination of slides are indeed the result of original observations, these notes are not necessary for the reconstruction and evaluation of the final report*",

and goes on to explain the reason by stating:

> "*Further, because 58.190(a) requires histopathological blocks, tissues, and slides to be retained as specimens, the final report can be reconstructed by verification of the pathology findings by, e.g., a second pathologist or by a team of pathologists*.",

and then reinforces that the notes are not raw data by stating:

> "*The pathologist's interim notes, therefore, which are subject to frequent changes as the pathologist refines the diagnosis, are not raw data because they do not contribute to study reconstruction. Accordingly, only the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens*". [emphasis added]

This position as stated in the FDA 1987 Final Rule is also supported by the global societies of toxicologic pathology (Fikes *et al*, 2015).

Peer Review Pathologists Do Not Generate Raw Data

The process of contemporaneous pathology peer review involves a second pathologist who reviews a subset of slides and the draft pathology diagnoses before finalizing the pathology report. The perspectives of the peer review pathologist are then discussed with the study pathologist, and their consensus diagnoses are reflected in the pathology diagnoses by the study pathologist in the final pathology report. In Settiagounder, 2017b (p. 61), the author indicates that the peer review pathologist is generating data when there is a disagreement with the study pathologist, stating:

> "Also, when any difference of interpretation results in a significant change leading to change in the Study Pathologist's original diagnosis, then the origin of such data is the Review Pathologist. Accordingly, it is appropriate to state that the Review Pathologist is indeed generating data while performing Pathology Peer Review for confirming the findings of the Study Pathologist and/or improving the quality of the pathology report."

However, these statements are an inaccurate reflection of the purpose and the process of a pathology peer review. Changes to diagnoses recommended by the peer review pathologist only become raw data if the study pathologist agrees to include the change within the final report. Thus, the study pathologist is the only one issuing and signing the pathology report (which constitutes the raw data), and therefore the only one generating raw data, not the peer review pathologist. Thus, during a contemporaneous pathology peer review, notes by both pathologists (study pathologist and peer review pathologist) are not raw data, and as such, in accordance with the FDA's 1987 Final Rule, do not need to be retained in the study file. This is further substantiated by Section 2.4 of the 2014 OECD guidance, which states:

> *"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*." [emphasis added]

and in Section 2.3 of the same document:

> *"…the reviewing pathologist is interpreting data and not generating data.."* [emphasis added]

It should be pointed out that section 2.5 of the 2014 OECD guidance states:

> *"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."*

The OECD FAQs posted in March of 2017 further clarify Section 2.5 as follows:

> *"Correspondence refers to any communication that is needed to reconstruct how slides were selected and reviewed. This should include communications regarding the interpretation of any observations (preliminary or final) on adverse or non-adverse effects made during the review."* (Posted on 27 March 2017)

Since the peer review pathologist is making *interpretations* (Section 2.5), the study file is to contain records of the slides (i.e., animal identification and tissue specimen) that the peer review pathologist reviewed and upon which he/she based interpretation and/or difference in interpretation for adverse or non-adverse study-related effects. However, since the peer review pathologist is not generating data, his/her observation notes *per se* do not need to be retained in the study file as per Section 2.4 of the OECD guidance.

Pathology Data is Not Required to Be Locked Prior to Contemporaneous Peer Review

Before arriving at draft diagnoses prior to the peer review, the study pathologists often refines their diagnoses (including considering additional information, alternate terminology, severity grades, etc.). As new information becomes available during the peer review phase, the study pathologists may continue to refine or change their diagnoses and/or interpretation. Feedback from the peer review pathologist may contribute additional information for the study pathologist to consider. Thus, the pathology diagnoses are draft, interim notes until the study pathologist determines that the diagnoses are final, at which time the diagnoses are locked. Locking the pathology diagnoses begins an audit trail that captures all subsequent changes to the diagnoses; however, with draft histopathology diagnoses, an audit trail is not required since these are not raw data (which is only the signed pathology report, per FDA's 1987 GLP rule). The flexibility in rethinking and refining of the pathology notes is a key component of the quality and accuracy of the histopathology data, and is supported by the FDA's 1987 GLP rule, which states that interim notes are subject to frequent changes and do not contribute to study reconstruction.

In Settiagounder, 2017b (p. 63-64), the author states the following regarding contemporaneous peer review, although there is no evidence that 2014 OECD guidance or the PMDA currently require locking of pathology diagnoses prior to peer review:

> "Certainly, such data locking is expected before sending the draft report for PPR [Pathology Peer Review] considering the OECD (2014) requirement for describing how differences of interpretation were resolved and changes made to the SP's original interpretation in the final report…" [abbreviation expanded]
>
> "The Japanese regulatory authorities expect data locking prior to sending the draft report – or worksheet signed and dated by SP [study pathologist] (raw data) – to the external/sponsor PPR [Pathology Peer Review]". [abbreviations expanded]

This line of reasoning is in direct opposition to the published U.S. regulations (21 CFR part 58) and international guidance (OECD No.16), which state that only the signed final pathology report is the histopathology raw data.

Contemporaneous vs. Retrospective Peer Reviews

Pathology peer reviews may be conducted contemporaneously (i.e., beginning with interim pathology notes before generation of raw data by issuance of a signed final report) or retrospectively (i.e., review of raw data in the final report). For contemporaneous peer reviews, the histopathology diagnoses are not final and are subject to refinement by the study pathologist. In a retrospective pathology peer review, the pathology data have been finalized (i.e., became raw data by publication in a signed final pathology report) and all changes to the data must be recorded in compliance with GLP's. Although the author describes differences in the timing of the conduct of the peer review, in Settiagounder, 2017a (p. 53-54), the author's comments demonstrate a misunderstanding regarding the distinction between contemporaneous vs. retrospective peer review when stating:

> "…if the RP's [reviewing pathologist's] statement/memo/report on the PPR [pathology peer review] is signed after the pathology report is signed by the SP [study pathologist], then it means that it gets completed only after the pathology report is signed, and therefore, it is a kind of retrospective peer review." [abbreviations expanded]

This statement is incorrect. Though a contemporaneous peer review begins before issue of the final report, this type of peer review should not end until after review of the study pathologist's final report/narrative and/or locked data (i.e., raw data). Furthermore, the author's line of thinking contributes to his conclusion that all changes during a contemporaneous peer review be documented and retained. Notably, Section 2.8 of the OECD guidance states:

> *"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."*

However, the OECD issued a clarification to this, stating:

> *"Section 2.8 relates specifically to a retrospective peer review. For a contemporaneous peer review, there is an expectation that all correspondence (letters, e-mail etc.) relating to differences in the interpretation (preliminary or final) of slides between the original pathologist and the peer reviewing pathologist which may impact on the conclusions of the study (e.g. NOEL/NOAEL) are to be retained in the study file". (Posted on 27 March 2017)*

Thus, it is not the expectation or requirement of the guidance to track each change to the interim pathology diagnoses during a contemporaneous peer review.

Concluding Comments

Although the two recent publications on histopathology peer review in nonclinical studies highlight the overall complexity of the pathology peer review process, the conclusions are inaccurate and/or confusing regarding the interpretation of relevant guidances. Both publications contain statements that are personal opinions of the author and are misleading regarding the essence of the pathology peer review and what constitutes raw data. The author's arguments are furthermore confounded by citing the FDA's 2016 proposed amendment to the GLP regulations (currently in draft) as if already adopted for enforcement. Given the importance of histopathology data in the assessment of human risk, the STP wishes to underscore the pivotal importance of the peer review process in arriving at reliable quality data and

interpretation of nonclinical studies and the need for flexibility in this process that the U.S. regulations and international guidance clearly provide.

References

Crissman, J. W., Goodman, D. G., Hildebrandt, P. K., Maronpot, R. R., Prater, D. A., Riley, J. H., Seaman, W. J., and Thake, D. C. (2004). Best practices guideline: Toxicologic histopathology. *Toxicol Pathol* 32, 126–31

Fikes, J. D., Patrick, D. J., Francke, S., Frazier, K. S., Reindel, J. F., Romeike, A., Spaet, R. H., Tomlinson, L., and 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. *Toxicol Pathol*, 43, 907-914

Mann, P. C., and Hardisty, J. F. (2013). Peer review and pathology working groups. In Handbook of Toxicologic Pathology (W. M. Haschek, C. G. Rousseaux, M. A. Wallig, B. Bolon, R. Ochoa, and B. W. Mahler, eds.), 3rd ed., pp. 551–64. Elsevier, New York

Morton, D., Sellers, R., Barale-Thomas, E., Bolon, B., George, C., Hardisty, J., Irizarry, A., McKay, J. S., Odin, M., and Teranishi, M. (2010). Recommendations for pathology peer review. *Toxicol Pathol* 38, 1118–27

Organisation for Economic Co-operation and Development. (2014) 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, ENV/JM/MONO (2014)30, 1-11. Retrieved from http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)30&doclanguage=en

Organisation for Economic Co-operation and Development Good Laboratory Practice: Frequently asked questions (FAQ), posted 27 March, 2017. Retrieved from http://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm

Settiagounder, N. Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems. *Journal of Regulatory Science* 5(2) (2017a) 45–55

Settiagounder, N: Histopathology Peer Review for Nonclinical Studies – GLP Processes and Conditions. *Journal of Regulatory Science* 5(2) (2017b) 56–66

U.S. Food and Drug Administration. (1987). Good Laboratory Practice Regulations; Final Rule, Federal Register 52, 33768–82. Retrieved from https://www.fda.gov/ICECI/Inspections/NonclinicalLaboratoriesInspectedunderGoodLaboratoryPractices/ucm072706.htm

U.S. Food and Drug Administration. (2016). Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule, 21 CFR § 16 & 58. Retrieved from https://www.gpo.gov/fdsys/pkg/FR-2016-08-24/pdf/2016-19875.pdf