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Letter to the Editor

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

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1. Introduction

The comments of Bennet et al. (2018), representing the opinions of the Society of Toxicologic Pathology (STP) Scientific and Regulatory Policy Committee's Working Group on pathology peer review, focused solely on the U.S. FDA position on "*raw data*", to the exclusion of the U.S. EPA and the OECD positions, and wrongly interpreted the OECD position on "*raw data*" and "*peer review process*" [1]. They ignored the EPA requirements [9, 11].

My articles, comprehensive reviews of key regulatory positions (FDA, EPA, OECD), were written to encourage discussion around harmonization of regulatory requirements globally [6, 7]. The FDA's (2016) Proposed Rule was included to bring out the direction to which the FDA is thinking (e.g. "*raw data*"; inclusion of "*peer review*", which has been absent in regulation; independent peer review (PR) report similar to EPA's current requirement) and to alert the GLP testing community to prepare for appropriate processes if it becomes the Final Rule in the current form [14]. No claim was made that the Proposed Rule is enforceable at present. The statements, "Proposed Rule requires compliance … when this rule becomes effective in the current form" [6], and "Proposed Rule will be applicable for compliance when it is finalized in the current form and becomes effective" [7], were ignored by Bennet et al. (2018).

Only quotes from regulations and guidance are italicized. The OECD (1998) Council Decision is treated like a regulation [3].

2. Basis of the Settiagounder's Two Articles: Do they rest on misinterpretation?

Bennet et al. (2018) state, "the basis of these two manuscripts rests on a misinterpretation of the definition of pathology raw data and the process of peer review" and cite FDA (1987b, 2016) and OECD (2014, 2017) [1]. However, the EPA (1987, 1989 and 1994) requirements were conspicuously absent in

their comments [9-11]. Regarding "*raw data*" relating to histopathological evaluation, EPA requirements are not in alignment with FDA's. Neither OECD nor EPA have defined/interpreted that the signed and dated pathology report is "*raw data*". On "*peer review process*", FDA has no regulation/guidance, unlike EPA and OECD [4, 9, 11]. In the Proposed Rule, FDA addresses the PR [14]. I recognize that OECD (2017) FAQ, posted on 27th March 2017, missed inclusion in my articles as it appeared about 10 days before submission of manuscripts to the journal [5]. Key clarifications from this are:

(a) For section 2.5 of OECD (2014):

- "*Correspondence ... should include communications regarding* the *interpretation of any observations* (*preliminary or final)*". This is part of "*raw data*" (section 2.6 of OECD). To interpret/communicate "*any observations (preliminary or final)*", they must be recorded by the study pathologist (SP) or peer review pathologist (RP) on paper/computerized system and constitute "*raw data*".

(b) For section 2.8 of OECD (2014):

- For retrospective PR, describe and discuss in the final report how differences of interpretation were handled and changes made to the SP's original interpretation.

- "*For a contemporaneous peer review, ... all correspondence ... relating to differences in the interpretation (preliminary or final) of slides between the original pathologist and the peer reviewing pathologist ... are to be retained in the study file*." These become "*raw data*". No need to describe and discuss differences in interpretation in the final report. Accordingly, the information in Settiagounder (2017b) should be interpreted for contemporaneous PR [7].

The above clarifications reveal generation of "*raw data*", independent of final report. The interpretation, "*only the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens"* is unique to FDA [12].

Thus, there was no misinterpretation of the definition of "*raw data*" and the "*peer review process*" as erroneously stated by Bennet et al. (2018).

3. Definition of "*Raw Data*" Relating to Histopathological Evaluation

3.1. As Per Regulations

None of the regulations (FDA, EPA, OECD) amended the general definition of "*raw data*", especially for histopathological evaluation. Only the FDA interpreted it to cover the signed and dated pathology report, as I described (Settiagounder, 2017a), who also stated, "From the point of view of multiple GLP quality systems prevailing globally and data integrity, it is considered critical to maintain (a) the original data and audit trail for data generated by the SP during his/her independent histopathological evaluation …" [6]. However, Bennet et al. (2018) quoted it after truncating the underlined portion.

Recording "*raw data*", including changes, on paper and automated data collection systems, is covered in 58.130(e) of FDA. When computerized system is used to record "*interim notes*/*notes*" of diagnosis,

compliance with this requirement is needed, as FDA has not made exemptions when interpreting the signed and dated pathology report as "*raw data*". Furthermore, the statement, "FDA did not direct that the "*notes"* taken … be discarded …" is correct when one reads complete details in section 5 of the article [6].

To comply with the 58.35(b)(6) requirement, "*The quality assurance unit* [QAU] *shall: Review the final study report to assure ... the reported results accurately reflect the raw data*", the QAU needs two independent documents, viz., "*raw data*" and "*final report*" [13]. If the SP's signed final report alone is "*raw data*", then QAU cannot comply with this requirement. The FDA has not exempted the pathology report from this requirement.

Similar requirements of data recording and QAU review are covered in EPA (40 CFR 160.130(e), 792.130(e), 160.35(b)(6) & 792.35(b)(6)) and OECD (II.8.3.3-5 and II.2.2.1.f) [3, 10], as I delineated (Settiagounder, 2017a), also stating, "there are inherent challenges and imminent conflicts of interpretations not only within the FDA regulations but also among those of the OECD and other regulations" [6]. Bringing out these points in no way means that "These statements are in direct opposition to the FDA's 1987 Final Rule", as construed by Bennet et al. (2018).

3.2. As Per Guidance

The FDA has no guidance to cover "*raw data*" and "*peer review process*" relating to histopathological examination. The EPA's Pesticide Registration Notices and the OECD guidance do not define/interpret a signed pathology report as raw data [4, 9, 11]. Hence, Bennet et al.'s (2018) assertion, "Pathology raw data has been clearly defined in both the FDA's 1987 Final GLP Rule and the OECD's 2014 Advisory … as only the signed and dated final report of the pathologist", is inaccurate with respect to OECD [1].

Tomlinson & Leininger (2014) have separately opined "histopathology raw data should be defined as the observations made by the study pathologist (printed and/or electronic formats) rather than … the pathology report as is the current position of some regulatory agencies" [8].

4. "Peer Review Pathologists Do Not Generate Raw Data" (Bennet et al., 2018): Is this position correct?

Bennet et al. (2018) believe, quote and interpret that RPs do not generate raw data. Their contention is, "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." However, EPA and OECD do not consider that the signed pathologist report is "*raw data*". Additional points are:

(1) When the SP's signed report is "*raw data*", then should not the RP's signed statement be part of "*raw data*"?

(2) EPA recommends:

(a) Retention of "*all records and documentation of readings and interpretations*" for possible inspections by QAU and/or Agency; and submission of "*both the report of the original pathologist as well as that of the reviewing pathologist(s)*" [9]

(b) "*The pathology reports from both the study and peer review pathologist ... are to be submitted*" [11].

Unless the RP generates "*raw data*", independent report is impossible.

(3) As per OECD (2014, 2017), "*correspondence*" between SP and RP, covering "*interpretation of any observations (preliminary or final)*" is "*raw data*" [4, 5].

(a) Is it possible to perform PR without "*correspondence*" from the RP?

(b) The contention of Bennet et al. (2018), "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", is flawed and inaccurate, because the RP's "*correspondence*" becomes "*raw data*", as per OECD, whether the SP agrees to it or not.

(4) Section 2.11 of OECD (2014): "*there is an expectation that the peer reviewing pathologist will* sign *the statement described in section 2.10. This statement should be retained in the study file*." [4]. Such statement in the study file qualifies as "*raw data*".

(5) Bennet et al.'s (2018) quote from OECD (2014), "*Notes made by the peer review pathologist which are used to record observations … do not normally have to be retained in the study file*" reveals their failure to distinguish "*notes*" (not required to be retained) and "*observations*" (required to be retained).

(6) From OECD (2014, 2017):

(a) Section 2.3: "*Because the reviewing pathologist is interpreting data and not generating data …* "

(b) Section 2.5: "*All correspondence … retained in the study file*"

(c) FAQ: Refer to 2(a) above

(d) Section 2.6: Defines "*raw data*"

(e) Section 4.1.2: "*Reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and of the opinions expressed*" requires sufficient detailing for reconstruction of both process and opinions expressed by the RP.

These interconnected sections require generation and retention of "*raw data*".

(7) The European Medicines Agency (2002) mandates, "*The peer review should be documented in raw data and in the study report*", which requires generation of "*raw data*" during PR, and necessitates "*raw data*" and report as independent documents [2].

From the foregoing, it should be evident that RPs do generate "*raw data*" (diagnosis, interpretation, correspondence, PR statement and/or independent report).

5. "Pathology Data is not Required to be Locked Prior to Contemporaneous Peer Review" (Bennet et al., 2018): Currently No Regulatory Provisions

No regulation/guidance covers this aspect for histopathology raw data or PR until now, although explanations like that of Bennet et al. (2018) are abundant in the literature. Therefore, the common compliance requirements of FDA (58.130(e)), EPA (160.130(e) and 792.130(e)), and OECD (II.8.3.3-5) apply to data capture and their change [3, 10, 13]. Thus, my interpretations are logical and well-grounded [7]. Bennet et al.'s (2018) repeated assertion, "… international guidance (OECD No. 16), which state that only the signed final pathology report is the histopathology raw data", is baseless.

6. Contemporaneous vs. Retrospective Peer Reviews

The OECD (2014) guidance states, "*It* [PR] *should also be stated* [in study plan/protocol or its amendment] *whether the review will be performed contemporaneously or retrospectively*", but no criteria for classification are given. The logical criterion of whether PR is performed prior to (contemporaneous) or after (retrospective) signing the pathology report by the SP was applied. Bennet et al. (2018) similarly state, "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)", which applies only FDA's interpretation of "*raw data*" and ignores OECD's. Further, they state, "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)". This position opens up multiple options for the end of the PR process, the signed PR statement/report:

(a) Before signing the final pathology report, comparable to the QAU review of the final report and issue of the QAU statement (refer to section 3.1 above).

(b) After signing the final pathology report; although PR starts contemporaneously, it ends retrospectively.

(c) After PR of the final narrative (draft report).

(d) After PR of locked data; narrative may or may not have been finalized.

While flexibility is needed, clarity of process is essential. In a GLP study, the pathology report, a subset of study, is signed by the SP prior to the study director's signing of the study report. Similarly, the PR statement signed by the RP after reviewing a subset of slides as a collaborative process is a subset of the pathology report.

In contemporaneous PR, if any unresolved significant differences relating to diagnosis and/or interpretation between the two pathologists emerge through the PR statement, then the SP may consider the following courses of action:

- For option (a) above: Retain all correspondence and PR statement ("*raw data*") in the study file and ask the study director to amend the protocol for another PR by "*an independent expert or panel of experts … to resolve the issue*", prior to finalization of the pathology report [4, 5].

- For option (b) above: Follow as above (becomes retrospective PR) and amend the already signed pathology report.

To address other comments in this section, note that although the OECD guidance is silent about tracking changes, the reality is that it requires "*raw data*" even for contemporaneous PR (refer to 4.(6) above) [4, 5].

7. Conclusion

Like the two papers published earlier, this reply also goes critically between the lines of GLP definitions for "*raw data*", "*peer review process*", and regulatory expectations to address the comments of Bennet et al. (2018). It should be evident that there was no misinterpretation of information published in the earlier articles. It is unfortunate that Bennet et al. (2018), representing the opinions of the STP Scientific and Regulatory Policy Committee's Working Group on pathology peer review:

(1) Inaccurately stated that I had "confounded by citing the FDA's 2016 proposed amendment … as if already adopted for enforcement", when in fact they overlooked explicit statements made in the articles.
(2) Ignored the EPA requirements covered in the articles.
(3) Incorrectly asserted, "(OECD No. 16), which states that only the signed final pathology report is the histopathology raw data".
(4) Interpreted individual points in OECD (2014) in isolation, rather than their connecting and collective requirements.
(5) Did not recognize "*raw data*" requirements beyond the signed pathology report.
(6) Disregarded compliance requirements of FDA's 58.35(b)(6) and 58.130(e), and similar EPA and OECD requirements.
(7) Inaccurately stated, "Pathology Data is Not Required to Be Locked Prior to Contemporaneous Peer Review", when no regulation/guidance provides any such special provisions.
(8) Quoted truncated extract from Settiagounder (2017a), with potential for misinterpretations.
(9) Loosely claimed in the concluding sentence, "need for flexibility in this process that the U.S. regulations and international guidance clearly provide", without citing any U.S. regulation for "*peer review process*", and when none exists currently.
(10) Exhibited lack of comprehension of GLP compliance requirements of multiple regulations.

Overall, the comments in the letter lack accuracy, consistency and quality. Individual readers may make their own judgement regarding the extent to which they are valid, supported by various regulations/guidance.

When histopathology PR, contemporaneous or retrospective, is covered in a nonclinical study protocol or its amendment, compliance requirements should be as per GLP regulations and guidance, and not as per individual's or group's wishes. Complexities relating to histopathology "*raw data*" and "*peer review process*" are more than meet the eye. Any flexibility needs to be enabled through harmonization of regulations and/or guidance for uniform understanding and adoption by all stakeholders.

8. Disclaimer

The views expressed in this reply are of the author and not necessarily the position of his employer.

9. Acknowledgments

Thanks to Bennet et al. (2018) for providing an opportunity to clarify several points.

10. References

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