Natesan Settiagounder

HISTOPATHOLOGY PEER REVIEW PROCESS

THE COMPLIANCE CONUNDRUM

Histopathology peer review or simply pathology peer review (PPR), though not a GLP requirement, has been in vogue for over three decades because of its value and acceptance by most regulatory agencies.

Yet interpretation of the term 'raw data' applicable for histopathology evaluation of histology slides by a study pathologist (SP) or peer review of a subset of such slides by a review pathologist (RP) varies among stakeholders, such as study directors who are primarily responsible for planning and conduct of studies in compliance with GLP, the SPs who support study directors with pathology reports, the RPs (wherever applicable as per requirement of study plans or their amendments) who collaborate with SPs by performing PPR, the QA personnel who inspect/audit such studies and review reports prior to providing QA statements for study reports, the sponsors who need such studies for regulatory submission, the GLP compliance monitoring authorities who inspect compliance of test facilities/sites by facility and study audits and the regulatory agencies who review study reports submitted for regulatory approvals.

INTRODUCTION

Considering the importance of histopathology evaluation, PPR and the need for a harmonised interpretation of the terms 'raw data' and 'PPR process', Settiagounder has recently published two articles[1, 2]. The first article covered the inconsistencies and controversies that have prevailed during the last three decades regarding the term 'raw data' as applied to histopathology evaluation and peer review and the second focused on practices and controversies around the 'peer review process', documentation and reporting. These articles[1, 2] brought out diverse requirements of the regulations, viz., the US FDA[3, 4] and US EPA[5] and the OECD Council decision[6], as well as the EPA's Pesticide Registration Notice (PRN)[7, 8] and the OECD advisory guidance[9]. Also, emphasis to the US FDA's recent Proposed Rule[10] was given, though this is not enforceable at present, with an intention to bring out the direction to which the FDA is thinking towards (a) its aim to align and be consistent with the OECD Principles of GLP and the EPA, (b) modification of the definition of 'raw data', (c) peer review as a regulatory requirement when a study protocol includes peer review of any phase of a study and (d) peer review scientist as a 'contributing scientist' or 'independent contributing scientist', who needs to provide an independent report. However, the latest clarifications provided by OECD for two frequently asked questions (FAQ)[11] relating to the OECD advisory document[9] were not discussed in the two articles[1, 2]. This article raises certain key questions that are pertinent to the diverse requirements, expectations and interpretations thereby enabling a better understanding of compliance requirements by professionals associated with GLP studies involving PPR.

The quoted text reflects information from regulations, advisory guidance and PRN. Where appropriate the title, part, section and paragraph numbers of the Code of Federal Regulations (CFR) and the OECD are cited. The OECD Council Decision[6] is treated like a regulation in this article.

HOW DO REGULATIONS AND ADVISORY DOCUMENTS DEFINE AND INTERPRET THE TERM 'RAW DATA' RELATING TO HISTOPATHOLOGICAL EVALUATION AND PPR?

AS PER REGULATIONS

Table 1 (see overleaf) raises explicit and implicit questions in order to decipher regulatory definitions, interpretations and expectations for 'raw data' as applicable for histopathological evaluation. None of these regulations, including those of the FDA[3] and the OECD have amended the definition of the term 'raw data' for findings of histopathological examination. The FDA regulation[3] only interpreted it to cover the signed and dated pathology report as 'raw data'.

AS PER ADVISORY GUIDANCE

There is no guidance document issued by the FDA to cover the definition/interpretation of 'raw data' and 'peer review process' relating to histopathological examination. The EPA had issued two PRN[7, 8] on these aspects. The OECD issued an advisory guidance[9]. Based on these, Table 2 (see overleaf) provides additional clarity in the form of response to several pertinent questions intended to clarify the matter related to 'raw data' as applicable for histopathological evaluation. It should be evident that neither the EPA nor the OECD has indicated that only the signed final pathology report is the histopathology 'raw data'. Hence, the common definition of 'raw data' as covered in Table 1 is applicable.

TABLE 1. REGULATORY DEFINITION AND INTERPRETATION OF THE TERM 'RAW DATA' RELATING TO FINDINGS OF HISTOPATHOLOGICAL EXAMINATION OF SLIDES

SERIAL NO.	KEY QUESTION	US FDA GLP[3, 4]	US EPA GLP[5]	OECD GLP[6]
1	Which section of the regulation or OECD Council Decision defines 'raw data'?	21 CFR 58.3(k)	40 CFR 160.3 and 40 CFR 792.3	I.2.3.7
2	What is the definition of 'raw data' as per the regulation?	'Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study.'	'Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study.'	'Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study.'
3	Does the section in the regulation (referred in serial no. 1 above) 'amend the definition of raw data relative to the findings of histopathological examinations' (e.g. notes, interim notes and observations)?	No	No	No
4	Does the regulation cover any interpretation relating to 'notes taken by a pathologist during histopathological examination of slides'?	Yes[3]. The interpretation is, 'although the notes taken … are indeed the result of original observations, these notes are not necessary for the reconstruction and evaluation of the final report'.	No	No
5	Does the regulation interpret or direct that the 'notes taken by a pathologist during histopathological examination of slides' are to be disposed or not required to be retained in archives?	No[3]	No	No
6	Does the regulation interpret 'only the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens'?	Yes[3]	No	No
7	If 'signed and dated final report of the pathologist comprises raw data', does that mean no other data captured prior to signing the report is required to be retained in the study file?	No, the regulation is silent on this matter. See Note 1.	No, the regulation does not interpret that signed and dated final report of the pathologist comprises 'raw data'.	No, the OECD Council decision does not interpret that signed and dated final report of the pathologist comprises 'raw data'.
8	If 'signed and dated final report of the pathologist comprises raw data', how can QA review the final pathology report to assure that 'the reported results accurately reflect the raw data'?	QA requirement as per 21 CFR 58.35(b)6 is not feasible.	QA requirement as per 40 CFR 160.35(b)6 and 40 CFR 792.35(b)6 is not feasible.	QA statement requirement as per II.2.2.1.f. is not feasible.

Note 1: The regulation need not explicitly say every aspect of GLP requirements in multiple contexts. The general requirement of GLP is that all data generated that support the signed final report need to be retained in the study file.

TABLE 2. INTERPRETATION OF TERMS 'RAW DATA' AND 'PEER REVIEW PROCESS' RELATING TO HISTOPATHOLOGICAL EXAMINATION, BASED ON THE US EPA'S PRN AND OECD ADVISORY GUIDANCE

SERIAL NO.	KEY QUESTION	US EPA GLP PRN[7, 8]	OECD GLP ADVISORY GUIDANCE[9] AND FAQ[11]
1	Is there any guidance relating to 'raw data' and 'peer review process' relating to histopathological examination for non-clinical studies?	Yes[7, 8]	Yes[9, 11]
2	What is the definition of 'raw data' relating to histopathological examination?	No definition. However, there is interpretation[7] – 'pathologists interim notes are not essential for the reconstruction and evaluation of the pathology portion of the final report. 'Interim notes' are those interpretations made by the pathologist in the development of the first signed and dated version of the pathology report'. It is to be noted that the 'interim notes' are only interpretations and not 'records and documentation of readings' (refer to serial no. 4 below).	'For the purpose of reconstruction, raw data is defined as the documentation described in bullet 2.4 and 2.5' of the OECD[9]. This includes 'Correspondence ...and communications regarding the interpretation of any observations (preliminary or final) ...made during the review'.[11.] To interpret 'any observations (preliminary or final)', they need to be recorded by SP or RP somewhere (paper or electronic/computerised system) and they obviously become 'raw data'.
3	Does the PRN or advisory document require 'raw data', as defined/interpreted above, to be retained in the study file?	Yes. See also section 5.3 (p.50)[1].	Yes. See also section 5.4 (p.50)[1].
4	Does the PRN or advisory document define/interpret 'notes or interim notes' of a pathologist?	Yes[7]. Only defines 'interim notes' (refer to serial no. 2 above). Additionally, the statement 'it is recommended that all records and documentation of readings and interpretations be preserved...', implies that 'all records and documentation of readings' are the result of observations during evaluation of slides whereas 'interpretations' are those made by pathologist based on such observations.	No. The OECD advisory guidance[9] 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'. This statement clearly reflects generation of two types of data by the RP during histopathological examination of individual slides. One is the 'notes' of the RP that do not normally have to be retained in the study file and the other is the 'observations' that the RP needs to record using such 'notes'. Settiagounder[1] differentiates the 'notes' and 'observations' and emphasises the OECD's requirement of recording 'observations'. Further, from the OECD clarification to FAQ[11] – 'communications regarding the interpretation of any observations (preliminary or final)' – it is evident that unless the 'observations (preliminary or final)' are documented in the study file ('raw data'), the communications relating to peer review and interpretation of observations are not feasible.
5	Does the PRN or advisory document interpret that only the signed and dated final report of the pathologist comprises 'raw data' relating to histopathological evaluation of tissue specimens?	No	No
6	Does the PRN or advisory document expect independent report from RP?	Yes[7, 8]. Procedure for re-reads of submission to the Agency requires 'comprehensive peer review process' by RP. 'The pathology reports from both the study and peer review pathologist and the original slides are to be submitted to a Pathology Working Group (PWG)'.	Expectation is to provide a signed statement, 'in the absence of a signature' to pathology report or the final report. This implies that the RP can also sign the report and in such a situation, there is no need for a signed statement from the RP.

TABLE 2. INTERPRETATION OF TERMS 'RAW DATA' AND 'PEER REVIEW PROCESS' RELATING TO HISTOPATHOLOGICAL EXAMINATION, BASED ON THE US EPA'S PRN AND OECD ADVISORY GUIDANCE

SERIAL NO.	KEY QUESTION	US EPA GLP PRN[7, 8]	OECD GLP ADVISORY GUIDANCE[9] AND FAQ[11]
7	Does the 'peer review process' needs to be compliant with GLP requirements?	Considered to be a requirement although not stated explicitly. When a study protocol includes peer review, then one needs to comply with GLP, unless stated otherwise.	Yes[9]. OECD states, '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' and 'if the peer review has been conducted in a non-GLP facility then this should be documented within the study director's statement'.
8	Is there any criteria defined to differentiate contemporaneous and retrospective peer review?	No. However, retrospective peer review is applicable if peer review is performed by RP after completion of pathology report by SP.	No. However, retrospective peer review is applicable if peer review is performed by RP after completion of pathology report by SP.
9	Does the PRN or advisory document indicate the timing for issue of RP's statement or report for contemporaneous peer review? Before or after signing the pathology report by SP?	No. EPA requires independent report from RP.	No. OECD[9] states, 'there is no requirement for the peer reviewing pathologist to sign the pathology report or the final report. However, in the absence of a signature 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'. Since PPR is a subset of pathology report, this implies that the RP's statement needs to be issued before SP signs the pathology report (contemporaneous peer review) or amended pathology report (retrospective peer review).

AS PER OECD FAQ

In the first FAQ[11], the OECD clarifies 'correspondence' (which forms a part of 'raw data') and emphasises that it 'should include communications regarding the interpretation of any observations (preliminary or final)'. This clarification strengthens the earlier interpretation[1] that there is a need to record the observations and only then communication regarding interpretation of any observations is possible between SP and RP. In the second FAQ[11], the OECD clarifies that section 2.8 of the OECD[9] requirement to describe significant differences of interpretation in the final report 'relates specifically to retrospective peer review'. It further emphasises that 'for a contemporaneous peer review, there is an expectation that all correspondence… 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 (…) are to be retained in the study file'. For retrospective peer review, not only should all the documents/correspondence be retained in the study file, but significant differences also need to be discussed in the final report.

Taking the two clarifications together, it should be recognised that the term 'correspondence' includes 'interpretation of any observations (preliminary or final)' as well as 'differences in the interpretation (preliminary or final) of slides'; all of which are to be treated as 'raw data'.

DO PEER REVIEW PATHOLOGISTS NOT GENERATE 'RAW DATA'?

Often it is expressed that RPs do not generate 'raw data' because the SP is the only one who signs the pathology report, which constitutes the 'raw data'. However, the details provided in the previous section and Tables 1 and 2 clearly reveal that (a) with respect to histopathological evaluation, though the FDA[3] interpreted that the signed pathology report alone is 'raw data', it has no interpretation or guidance relating to data generation by an RP during PPR process, (b) EPA[7, 8] requires retention of 'all records and documentation of readings and interpretations', which form 'raw data', for inspections by QA and/or agencies and also needs independent report of RP and (c) OECD[9, 11] defines 'raw data', which includes correspondence between SP and RP, covering 'interpretation of any observations (preliminary or final)'. The OECD[9] also indicates 'this [advisory] document is concerned with the processes used to organise, perform and record the results of this [peer] review', which clearly reveals that the person (RP) who performs peer review needs to record the results, which obviously means generation of 'raw data'. Despite the OECD[9] statement, '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 'raw data' defined in OECD[9] and clarifications to the FAQ[11] support generation of 'raw data' by RPs.

Further key points to consider are:

- When the signed and dated pathology report is 'raw data' as per the FDA[3], then should we not consider the signed and dated statement of RP (expectation of FDA and OECD[9]) equally as part of 'raw data'?
- EPA[7, 8] expects 'both the report of the original pathologist as well as that of the reviewing pathologist(s) along with a consensus pathology report which resolved any differences of professional opinion between the original pathologist and the independent reviewing pathologist(s)'. Thus, an independent report by RP is feasible only when certain 'raw data' are generated by the RP or when such an independent report itself is treated as 'raw data'.
- EMA[12] states, 'the peer review should be documented in the raw data and in the study report', which directs documentation of 'raw data' by RP.

The foregoing points support that RPs do generate 'raw data' (which may be diagnosis, interpretation, correspondence, peer review statement and/or independent report).

IS THERE ANY REGULATORY PROVISION FOR LOCKING DATA OF HISTOPATHOLOGICAL EVALUATION AT SOME LATER STAGE RATHER THAN COMPLETE AUDIT TRAIL FROM BEGINNING?

None of the regulations and advisory documents provide any direct information relating to locking of pathology data and when to lock them. Thus, the 21 CFR 58.130(e) of the US FDA[4], 40 CFR 160.130(e) and 792.130(e) of the US EPA[5] and section II.8.3.3-5 of the OECD[6] are applicable relating to capturing of any data and change of any data thus captured in compliance with GLP.

WHAT COULD BE THE KEY CRITERION FOR DIFFERENTIATING CONTEMPORANEOUS AND RETROSPECTIVE PEER REVIEW?

As described in Settiagounder's previous article[1], the OECD advisory guidance[9] has not provided any explicit reference points (criteria) for classifying the pathology 'peer review process', viz., contemporaneous and retrospective peer review for a study. Thus, the single logical reference point (criterion) for their classification is date of completion of peer review by RP by way of issue of peer review statement/ report with respect to that of pathology report by SP. That is, whether the peer review is performed (means completed) by RP prior to (contemporaneous) or after (retrospective) signing the pathology report by the SP. However, there are interpretations that a contemporaneous peer review may begin before issue of the signed pathology report, but should not end until after review of the SP's final report. This means such a peer review starts contemporaneously but ends retrospectively. In this scenario, what happens if any significant difference with regard to diagnosis and/or interpretation between the two pathologists emerges through RP's peer review statement at that stage? How is it possible for a SP to handle the situation of incorporation of appropriate information in the pathology report (which is already signed)? The option then is to either amend the pathology report to incorporate additional information, if there is consensus, or amend the study protocol for another peer review by 'an independent expert or panel of experts – to resolve the issue'[9], if there is no consensus.

In a GLP toxicology study, the pathology report signed by an SP is a subset of the complete study report signed by a study director. Similarly, when peer review is performed by an RP to evaluate a subset of slides that are previously evaluated by an SP, then the peer review is a sub-process of histopathological evaluation and the peer review outcome (statement or report by RP) is a subset of the pathology report. Hence, peer review evaluation results in a subset of data, diagnosis and/or interpretation, for the purpose of improving accuracy and quality of pathology report by the SP. Accordingly, in a contemporaneous PPR, this subset of final outcome from the RP needs to be known to the SP before he/she signs the pathology report.

A comparison is that the timing of issue of peer review statement by an RP is akin to that of issue of QA statement by QA unit after review of [unsigned] final report to assure that 'the reported results accurately reflect the raw data', as per the requirements of the FDA[4] 21 CFR 58.35(b)(6&7), EPA[5] 40 CFR 160.35(b)(6&7) and 792.35(b)(6&7) and OECD[6] section II.2.2.1.f.

CONCLUSION

Histopathology peer review, though not mandatory, is often considered to improve accuracy, consistency and quality of diagnosis and interpretation. Diversity of interpretations, expectations and practices exist relating to definition of 'raw data', documentation of 'peer review process' and reporting the outcome of peer review results. Thus, there are more complexities than meets the eye. A harmonised interpretation across the regulations and/or advisory/ guidance documents would bring in a uniform understanding and adoption by all stakeholders.

DISCLAIMER

The interpretations and views expressed in this article are those of the author and not necessarily the position of the author's employer.

REFERENCES

1. Settiagounder, N. (2017a). Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems. Journal of Regulatory Science, 5(2), 45-55. https://journals.tdl.org/regsci/index.php/regsci/article/view/71
2. Settiagounder, N. (2017b). Histopathology Peer Review for Nonclinical Studies – GLP Processes and Conditions. Journal of Regulatory Science, 5(2), 56-66. https://journals.tdl.org/regsci/index.php/regsci/article/view/70
3. US Food and Drug Administration. (1987a). Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58. www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133730.pdf
4. US Food and Drug Administration. (1987b). Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58. www.ecfr.gov/cgi-bin/text-idx?SID=f2d99567d909a79da0e1bbfe2879e4ec&mc=true&node=pt21.1.58&rgn=div5
5. US Environmental Protection Agency. (1989). Good Laboratory Practice Standards, 40 CFR Parts 160 & 792. www.ecfr.gov/cgi-bin/text-idx?SID=e5f53f9ca071b342c182f09a9f961eda&mc=true&node=pt40.26.160&rgn=div5 and www.ecfr.gov/cgi-bin/text-idx?SID=e5f53f9ca071b342c182f09a9f961eda&mc=true&node=pt40.35.792&rgn=div5
6. Organisation for Economic Co-operation and Development. (1998). OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1. OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17, 1-41. www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en
7. US Environmental Protection Agency. (1987). Notice to Pesticide Applicants, Registrants and Petitioners (PR Notice 87-10)
8. US Environmental Protection Agency. (1994). Requests for Reconsiderations of Carcinogenicity Peer Review Decisions Based on Changes in Pathology Diagnoses (PR Notice 94-5). www.epa.gov/pesticide-registration/prn-94-5-requests-re-considerations-carcinogenicity-peer-review-decisions
9. 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. www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)30&doclanguage=en
10. US Food and Drug Administration. (2016). Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule, 21 CFR. Part 16 and 58. www.gpo.gov/fdsys/pkg/FR-2016-08-24/pdf/2016-19875.pdf
11. Organisation for Economic Co-operation and Development (2017). OECD Good Laboratory Practice: Frequently asked questions (FAQ), posted 27 March, 2017. www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm
12. European Medicines Agency. (2002). Note for Guidance on Carcinogenic Potential, CPMP/SWP/2877/00, 1-8. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003258.pdf

PROFILE

Natesan is Vice President, Business Excellence & Corporate QA at Eurofins Advinus Limited. He has a PhD, RQAP-GLP and is the President of the Indian Chapter of the Society of Quality Assurance. He has over 35 years of R&D experience, including over 25 years in GLP (OECD, FDA, EPA) and over 10 years in cGMP quality systems. His professional career includes study director, head of department, test facility management and corporate QA. He successfully facilitated several GLP inspections by Monitoring Authorities of Germany, Netherlands, India, the FDA and by several global clients. He has over 65 publications including chapters for books and a book. He has made presentations at several national and international conferences.