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Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems

Natesan Settiagounder[a,*]

[a]*Advinus Therapeutics Limited, 21 & 22, Phase 2, Peenya Industrial Area, Bengaluru, India 560058*

Abstract

Histopathology evaluation of animal tissues from a nonclinical toxicological study by a study pathologist contributes substantially to the endpoint(s) of a GLP compliant study. Often, selected tissue slides, existing and new, evaluated by a study pathologist, are peer reviewed by an expert pathologist, to assure and improve quality of observations and interpretation. The peer review process, having scope to change certain components of a pathology report, can lead to changes in observations, interpretation and potential outcome/conclusions of a study. The GLP regulations of several countries provide quality system approaches, which are though similar have differences in their statutes and expectations. The heart of the matter of GLP quality systems is raw data to ensure their true reflection in final report and help reconstruction. In 1987, the U. S. FDA specially interpreted "*raw data*" applicable for histopathology evaluation. However, there is no conclusive change by other Agencies, except the OECD (2014) guidance. Inconsistencies and controversies prevailed during the last three decades on different perspectives of raw data applicable for histopathology evaluation and peer review of different types. This paper goes critically between the lines of GLP definitions, expectations and diverse practices, seeking harmonized interpretation by all stakeholders for complying with multiple regulations.

Keywords: raw data, quality system, good laboratory practice, histopathology, pathology peer review, nonclinical study

1. Introduction

Data generation by conducting nonclinical safety testing of a number of products in laboratory, greenhouse and/or field conditions for regulatory submission, for the purpose of obtaining clinical trial approval or appropriate marketing authorization, mandates adoption of Good Laboratory Practice (GLP) quality systems globally. Although the requirements covered in various regulations [27, 25, 2, 6, 8, 7] and the Council decision of the Organisation for Economic Co-operation and Development (OECD) [15] are nearly the same, certain differences continue to exist among them in spite of the fact that GLP quality systems are being adopted for nearly four decades. The differences are in the nature of statutes spelt out in the regulations, as well as those explained in agencies' guidances. Additionally, there are contrasting variations in the nature of interpretations published in articles or expressed in conferences or meetings by a variety of stakeholders, viz., (a) regulatory authorities of various countries who review study reports prior to authorizing applications for intended purposes; (b) monitoring authorities (in some countries regulatory authorities) who inspect/audit testing facilities that perform studies in compliance with GLP, in order to assess their extent of compliance; (c) applicants/sponsors who conduct studies themselves in their own testing facilities or outsource studies to external testing facilities; (d) testing facilities that undertake regulatory studies for conducting them in compliance with GLP; (e) study directors who are the single point of contact from planning to reporting for their respective studies; (f) study pathologists/histopathologists who evaluate tissue slides from animal toxicology studies and provide pathology reports to study directors for inclusion in study reports; (g) peer review pathologists who verify/evaluate histopathologists' observations by independently evaluating a defined set of slides and providing their observations to the respective study pathologists, and also by issuing appropriate peer review statement or report; and (h) quality assurance personnel who function as custodians for assuring the quality of studies and as watchdogs for cautioning about non-compliance with regulatory requirements.

For a pivotal animal toxicology study, histopathology evaluation of slides by a trained study pathologist (SP) is a critical phase that substantially contributes to the outcome and conclusions toward judging a product for further development, authorization or licensing. As histopathology evaluation is a qualitative/subjective assessment based on the experience and exper-

*Corresponding author: Natesan Settiagounder, Phone: +91-9845218726, Fax: +91-80-28394015. Email: natesan.s@advinus.com

tise of the SP, it is often decided – although no regulations other than the recent OECD (2014) guidance – to subject a defined set of slides for pathology peer review (PPR) by an independent expert review pathologist (RP), also known as peer review pathologist [18]. The processes and conditions applicable for PPR are delineated in a subsequent article of this publication [20]. Considering the subjective nature of evaluation of histopathology slides both by the SP and RP, it is well-recognized that there is a likelihood that their notes/observations/data keep changing during SP's evaluation, RP's peer review and/or resolution of their differences. GLP regulations have laid down definitions for raw data, described the method, manner and timing of their recording (applicable for paper and electronic records), and also covered the method and manner of making changes to any already recorded data, if and when desired. However, there have been continued inconsistencies in application and interpretation of these common laid down expectations among regulators as well as amongst stakeholders, leading to confusion. Such inconsistencies, as published in several articles associated with histopathology evaluation and peer review of nonclinical studies, form the basis for this article.

All GLP regulations, in their definition of raw data, primarily attribute raw data to the original, direct, accurate, legible and prompt record of an individual or electronic system of an observation or activity [27, 25, 2, 6, 8, 7, 15]. The United States Food and Drug Administration (FDA), while retaining the original definition, also allowed that the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens [28]. However, such an exception has not been accorded by other GLP regulations [25, 2, 6, 8, 7] or OECD Council decision [15] until now. Since 1988, there have been several articles in the literature relating to the diversity of interpretations of what constitutes raw data for histopathological evaluation and peer review of slides for a pathology report [3, 4, 11, 1, 13, 12]. The OECD (2014) guidance provides certain clarity, more or less endorsing the 1987 FDA addition [18, 28]. In 2016, the FDA issued the Proposed Rule for *Good Laboratory Practice for Nonclinical Laboratory Studies*, describing a complete quality system framework referred to as GLP Quality System when safety and toxicity studies support or are intended to support applications or submissions for products regulated by the FDA [30]. The quality system approach of the FDA is also aligned with the definition of GLP as quality system in the 1998 *OECD Series on Principles of Good Laboratory Practice* [15].

The objective of this paper is to bring out the fundamental points about GLP compliance associated with transparency of recording and retaining directly, accurately, legibly and promptly raw data that are generated by an individual or electronic system for an observation or activity applicable to histopathology evaluation by SP and peer review by RP. Accordingly, this paper covers the finer aspects of (a) the regulations that are fundamental for compliance and data integrity when a study protocol claims such compliance; (b) applicability of the GLP quality system for histopathology evaluation and PPR; (c) components of the pathology report that have scope for change following PPR, leading to significant change to the study outcome and conclusions; (d) the definition of raw data for histopathology observations by SP and RP, considering the diversity of regulatory requirements and interpretations; and (e) the types and timing of peer review evaluation, which can contribute to data quality by way of confirming the SP's observation, improving the SP's finding by facilitating changes to his/her observations or resolving differences by other ways.

The italicized text in this article reflects extracts of information from the OECD, FDA and the United States Environmental Protection Agency (EPA) documents. In certain places, the title, part, section and paragraph numbers of the Code of Federal Regulations (CFR) are cited for reference. As the term "*study plan*" used by OECD [15] and "*study protocol*" used by FDA [27] and EPA [25] have the same meaning, only the term "*study protocol*" or "*protocol*" is used uniformly, except in italicized text in this paper.

2. Regulations that Need to be Complied with for Data Integrity

Nonclinical laboratory studies performed for the purpose of regulatory submission claim compliance with one or more of the following GLP regulations or principles in the study protocol and in the study report:

- FDA (1987) – Final Rule under 21 CFR Part 58, "*Good Laboratory Practice for Nonclinical Laboratory Studies*", which prescribes the practices for conducting studies that support or are intended to support applications for research or marketing permits for products regulated by FDA [27]
- OECD (1998) – Council decision on the "*OECD Principles on Good Laboratory Practice*" for generating data for nonclinical health and environmental safety studies relating to pharmaceutical products, pesticide products, cosmetic products, and veterinary drugs, as well as food additives, feed additives, and industrial chemicals [15]
- EPA (1989) – Final Rule under 40 CFR 160, "*Good Laboratory Practice Standards*" (Federal Insecticide, Fungicide and Rodenticide Act) for conducting studies that support or are intended to support applications for research or marketing permits for pesticide products regulated by EPA. Also, Final Rule under 40 CFR 792, "*Good Laboratory Practice Standards*" (Toxic Substances Control Act) for conducting studies relating to health effects, environmental effects, and chemical fate testing [25]
- Based on the OECD Council 1998 decisions, several countries, such as the United Kingdom and Japan established national regulations for GLP [15, 6, 8, 7]

All these regulations, although similar, have differences with respect to certain definitions (e.g. raw data), interpretations and expectations. The provision of mutual acceptance of data (MAD), as per the OECD Council decision, supports acceptance of data generated in any OECD member country

or Full Adherent non-member country by other OECD member countries, and Full and Provisional Adherent non-member countries [14]. Such a provision prevents duplication of studies and helps save animals in the case of toxicology studies. Despite MAD provisions, sponsors who wish to submit study reports to regulatory agencies in different countries frequently request testing facilities to claim GLP compliance with two or more regulations and the OECD Council decision in the study protocol and study report. For example, it is not uncommon to claim GLP compliance with FDA (1987) and OECD (1998) for a study on a drug product [27, 15], and with EPA (1989) and OECD (1998) for a study on a pesticide or chemical [25, 15]. Such needs require that testing facilities have standard operating procedures (SOP) aligned to accommodate the compliance requirements of different regulations. Additionally, when data relating to histopathology evaluation by SP and peer review by RP are captured electronically, the Final Rule of 21 CFR Part 11 of FDA (1997) and the OECD (2016) advisory document on "*Advisory Document of the Working Goup on Good Laboratory Practice, Application of GLP Principles to Computerised Systems*" are considered applicable to ensure data integrity [29, 19].

3. Applicability of the GLP Quality System for Histopathology Evaluation and Pathology Peer Review

For a regulatory toxicology study involving histopathological evaluation of animal tissues, the GLP quality system is applicable for the SP to comply with the requirements and provide a signed pathology report to the study director for inclusion in the final report of the study. In the case of PPR, although there is no such regulatory requirement currently, it is commonly adopted for most pivotal toxicology studies. Considering the importance of PPR, it should preferably be done in a manner that would meet GLP quality system requirements. The OECD (2014) states that PPR "*can lead to changes in the interpretation of the slides and the reported results, and potentially the outcome and conclusions of the study.*" It further states that the purpose "*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*"[18]. Accordingly, the study director in the final report needs to make a compliance statement concerning the extent to which the study, including PPR, complies with the GLP quality system. Even if PPR is performed in a non-GLP organization, the study director needs to be satisfied that the PPR process is sufficiently well managed, and that peer review data are of adequate quality.

The FDA (2016) Proposed Rule requires compliance with GLP quality system when a study protocol includes the requirement of peer review of any phase [30]. Thus, for PPR, the GLP quality system will become a mandatory requirement when this rule becomes effective in the current form.

4. Components of Pathology Evaluation Generating Data for Pathology Report

It is pertinent to know the components of a pathology report for a nonclinical safety evaluation study, such as a 28-day or 90-day toxicology study, or a carcinogenicity study, which often goes for peer review at the request of the sponsor. The key components of a pathology report commonly available for peer review by an RP and the scope for change of the SP's observation/raw data following peer review are summarized in Table 1. Briefly, the key components that form a pathology report, whether draft or final, and which is shared along with selected tissue slides with an RP for the purpose of peer review are:

- Study design – treatment groups and period, species, strain, sex, number and age of animals, and target parameters and organs
- Quantitative parameters (non-subjective diagnostic measurements) – hematology, coagulation, clinical chemistry, urine analysis, terminal body weights, organ weights and ratios, etc.
- Qualitative parameters (descriptive/subjective diagnostic assessments) – gross pathology and histopathology observations, including extent/degree/intensity of toxic effect of the test item
- Interpretative analysis (narrative) – within study data, including statistical analysis and deviation to study protocol and its impact, if any; and comparison with historical control, published or known information; all of which lead to a derived conclusion
- Conclusion/outcome of the study – derived parameters, viz., no observed effect level (NOEL), no observed adverse effect level (NOAEL), target organ with toxic effect, etc.

Among the components that constitute the pathology report, the qualitative histopathologic assessment is a subjective judgment based on the knowledge and experience of the SP and the RP. Therefore, there is a probability of variation in diagnosis leading to diagnostic drift within each of them and between them. Additionally, subjective criteria associated with scoring the relative degree of severity of a particular lesion often lead to further drift in the diagnosis among pathologists. Thus, diagnostic drift may lead to change in interpretation and eventually change in NOEL and/or NOAEL in certain cases, as well as selection of target organ associated with effects of the test item. 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; (b) observations, including audit trail for changes, of the RP during his/her independent verification/evaluation of slides through the PPR process; and (c) documents and correspondence that lead to resolution of differences, if any, between the SP and the RP leading to changes to the original observation/raw data of

Key component	Possible role of RP [a] in a peer review process	Scope for change of observation, raw data and/or conclusion
Study design	No direct role	No
Quantitative parameters (numerical data)	Review of existing clinical pathology data, organ weights and ratios, etc., in the SP's [b] report (draft/final)	No
Qualitative parameters (non-numerical data)	• Review of existing gross pathology data in the SP's report (draft/final)	No
	• Review of existing microscopic data in the SP's report (draft/final)	Yes
	• Re-evaluation of existing microscopic slides of all or select target organs corresponding to chosen animals from identified treatment groups, and/or seeking preparation of new slides from paraffin blocks/tissues	Yes
Interpretative analysis (Narrative)	Review with the SP's observation, relate with dose, share views/findings with the SP for resolution of differences, if any	Yes
Conclusion / Outcome	Confirmation of the SP's finding and/or communicate/discuss for changing the NOEL [c], NOAEL [d] and/or target organ(s) with toxic effects	Yes

[a] RP = review pathologist
[b] SP = study pathologist
[c] NOEL = no observed effect level
[d] NOAEL = no observed adverse effect level

Table 1: Key components of a typical pathology report and scope for change of observation/raw data based on peer review.

the SP. This approach is considered appropriate, irrespective of whether the PPR is contemporaneous or retrospective [18].

5. Raw Data for Histopathology – Perspectives

5.1. Pathologists' Perspective

Among the communities of stakeholders who define, generate, use, analyze, interpret, inspect or audit and report raw data from GLP studies, it appears that only the pathologists feel a special need for treating raw data differently for their histopathological observations [13, 9, 21, 5]. The common justification for this is that changes to histopathological diagnosis are inevitable during the course of evaluation, and keeping track of such changes does not help the final report, despite the fact that GLP regulations do allow correction of raw data with no restriction on the number of times one wishes to correct them. The contention that the signed and dated pathology report alone is raw data, despite certain recognition by the FDA (1987), has neither stopped controversies during the last 30 years nor made regulatory authorities globally devoid of disconnectedness [28, 24, 15, 9, 10]. Reading critically between the lines of regulatory definitions and explanations in advisory documents, including the latest definition in FDA (2016), provides different perspectives and implications regarding whether raw data need to be treated differently for the histopathological observations of the SP or RP for the pathology report [30].

5.2. Definitions in GLP Regulations

In all the GLP regulations, the term "*raw data*" has been defined, and its meaning is similar, with some subtle differences. As per OECD (1998), "*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. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period*" [15]. As per FDA (1987), "*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 may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments*" [27]. The EPA (1989) definition is the same as that of the FDA, with the exception that the words "*nonclinical laboratory*" are

absent [25]. Thus, according to the FDA, to qualify any laboratory worksheets, records, memoranda, notes, or exact copies thereof as raw data, they should meet two criteria: (a) "*that are the result of original observations and activities of a nonclinical laboratory study*", and (b) "*are necessary for the reconstruction and evaluation of the report of the study*" [27]. These two criteria are separated by the word "*and*" in the definition, and therefore, both criteria need to be considered together and are not mutually exclusive. The criterion (a) is considered applicable not only for data generated based on the first original observation of an activity, but also subsequent changes after succeeding activities, if made to those original observations by adopting correction procedures specified in GLP regulations. If we focus only on the criterion (b) for reconstruction and evaluation of a report, then it implies that any other data generated for a study but not included in the study report need not be archived. It is possible that during the conduct of a study, several raw data may be collected or sample analysis may be repeated due to equipment or method failure, and it is probable that the study director may not include the results of every observation or activity in the report. In such a situation, the study director can take the option of not retaining such data in the study file, as such data are not reported and will not be required for reconstruction of the study report. In the OECD definition of raw data there is no explicit wording for criterion (b) above, although it is implied [15].

5.3. Special Provision by FDA

It is important to recognize the explanation of FDA (1987) in response to a specific comment urging the agency to amend the definition of raw data relating to the findings of histopathological examinations, which the FDA did not agree to: "*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. The final report is evaluated by an analysis of the pathology syndrome as described in the pathologist's report, which is required under 58.185(a)(12). 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. 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*" [28]. From this clarification, the following points emerge:

1. The FDA did not agree to amend 58.3(k), which includes "*notes*" as part of the definition of raw data.
2. The FDA recognized that the "*notes*" taken during histopathological examination of slides are indeed the result of original observations, but the "*notes*" are not necessary for the reconstruction and evaluation of the final report.
3. While the "*notes*" may not be necessary for the reconstruction and evaluation of the final report, the 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.
4. The FDA also recognized that the pathologist's "*interim notes*", which are subject to frequent changes as the pathologist refines the diagnosis, are not raw data, as they do not contribute to study reconstruction.
5. While "*interim notes*" are likely to undergo changes, the final notes (or simply "*notes*") of the pathologist form the basis for summarizing information as final diagnosis of histopathological evaluation in table, appendix or annex to a pathology report.
6. With regard to reconstruction, it is indicated that the final report can be reconstructed by verification of the pathology findings by a second pathologist (say peer review pathologist) or a team of pathologists by re-evaluation of the slides. Generally, reconstruction of a final report would involve comparison of the original diagnosis/data/final "*notes*" of the study personnel as documented in the study file or captured in a computerized system, with those presented in the signed report.
7. If reconstruction by verification means re-evaluation of all slides by other pathologist(s) and comparing their diagnosis/data/final "*notes*" against those reported in the signed final report, then there could be more challenges to the consistency of information than perceived.
8. 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.
9. If only the signed and dated final report of the pathologist comprises raw data of the histopathological evaluation of tissue specimens, then the quality assurance review of such portion in a final report, as per the requirements of section 58.35(b)6 of FDA (1987) and section II.2.2.1.d of OECD (1998), to confirm that the reported results accurately and completely reflect the raw data, cannot be done properly [27, 15].
10. The OECD requirement of a quality assurance statement that would serve to confirm that the final report reflects the raw data is, therefore, not justifiably applicable for the histopathology portion of the pathology report.

Thus, 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. Additionally, while the EPA (1987) intended to be consistent with the FDA for interpretation of raw data with respect to a histopathological

evaluation, the former clarified as, "*The pathologist's interim notes are not essential for the reconstruction and evaluation of the pathology portion of the final report. Although not essential, it is recommended that all records and documentation of readings and interpretations be preserved for possible future inspections by the facility's Quality Assurance Unit and/or the Agency*" [24]. Also, the EPA (1980 & 1993), under 40 CFR Part 169, requires retention of all "*underlying raw data*" and interpretations and evaluations thereof, whether in the possession of the producer or in the possession of the independent testing facility or laboratory (if any) which performed such tests, for as long as the registration is valid and the producer is in business [23].

5.4. OECD Advisory Document

It is also pertinent to recognize that the OECD (2014) advisory document relating to histopathology peer review defines raw data as, "*That which covers (a) details of documentation of how the peer review was conducted and retained within the study file, including information on the identity of the tissues that were reviewed, when the tissues were reviewed and by whom, and (b) 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, retained in the study file, including minutes of teleconferences between the sponsor and the test facility*" [18]. Additionally, it indicates that "*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 explanation 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*". Therefore, the implicit expectation is that such observations are to be recorded for individual slides during the examination and not later on, say, during discussion with the SP for any resolution of differences in diagnosis, nomenclature, etc.

The FDA Proposed Rule (2016) slightly modified the earlier definition and continues to retain "*notes*" as raw data. A part of the new definition is, "*Raw data includes any laboratory worksheets, correspondence, notes, and other documentation (regardless of capture medium) 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 also includes the signed and dated pathology report*" [30]. From a quality system perspective, this definition could be interpreted for histopathology examination of slides by either the SP or RP as: (a) "*notes*" of such examination are raw data and are the result of original observations and activities of a study as directed by the study protocol, and (b) the word "*also*" in "*Raw data also includes the signed and dated pathology report*" means that other elements are primarily raw data in addition to the signed and dated pathology report [30].

5.5. Conundrum or Consternation

There is a need to relook at how the definition of raw data can be applied uniformly, including histopathological observations considering various points discussed in the previous paragraphs. A diagrammatic process flow of "*interim notes*" of the SP or RP transformed into final report is presented in Figure 1. A critical review reveals complexities of interpretations, inconsistency in applying the definition, diversity of expectations among regulations, and challenges of discarding notes of histopathological examination captured using computerized systems [29, 19] after recording observations from such notes [18]. Also, there is a negative implication of treating only the signed pathology report as raw data, when there is a necessity for the quality assurance unit to review such a report to make a statement to confirm the true reflection of raw data (which is nothing but the same signed report as per FDA [28]. It is therefore considered desirable to adopt the definition of raw data uniformly for all activities of GLP studies including histopathology evaluation and peer review.

6. Raw Data Generation During Pathology Peer Review

6.1. Report Review and Slide Review

Review may mean differently to different people and in different contexts. In most cases, a reviewer recognizes data as such and may sometimes get into the details of how the data were generated or derived, but generally does not get into the process of generating or verifying data independently. In the PPR process, while review by the RP of the written matter in the SP's report does happen, there is an additional component of review, a re-examination of the same slides or a subset of slides as an independent evaluation by the RP, with an intended implicit mandate (as directed by the study protocol) to provide findings that may confirm or disagree with the SP's observations. Figure 2 provides a diagrammatic sketch of the process applied for review by the peer reviewer, regulatory agency and/or the pathology working group, when there is a necessity. Such an evaluation of slides by an RP, although independent, is commonly not blinded. Thus, a PPR of the same slides by an independent RP does provide opportunities for a kind of quality control check, as indicated in many publications; assessing the differences in interpretation leading to possible resolution in favor of the SP's observations, RP's views or new diagnosis/terminology; reporting of both findings, in the event of non-resolution, if significant differences persist, with the conclusion of the SP; forming a pathology working group for further evaluation and conclusion. It is also recognized that for the peer review to be of scientific value, it has to be conducted by an RP having appropriate specialist experience and expertise, irrespective of whether working in a GLP test facility or not. Greater divergence of views may also reflect the complexities related to microscopic examination besides the expertise of individuals who function as SP or RP. Thus, the original data generated or observations made for the re-examination of slides by the selected RP, based on his/her expertise and experience, are important not only for improving the quality of diagnosis

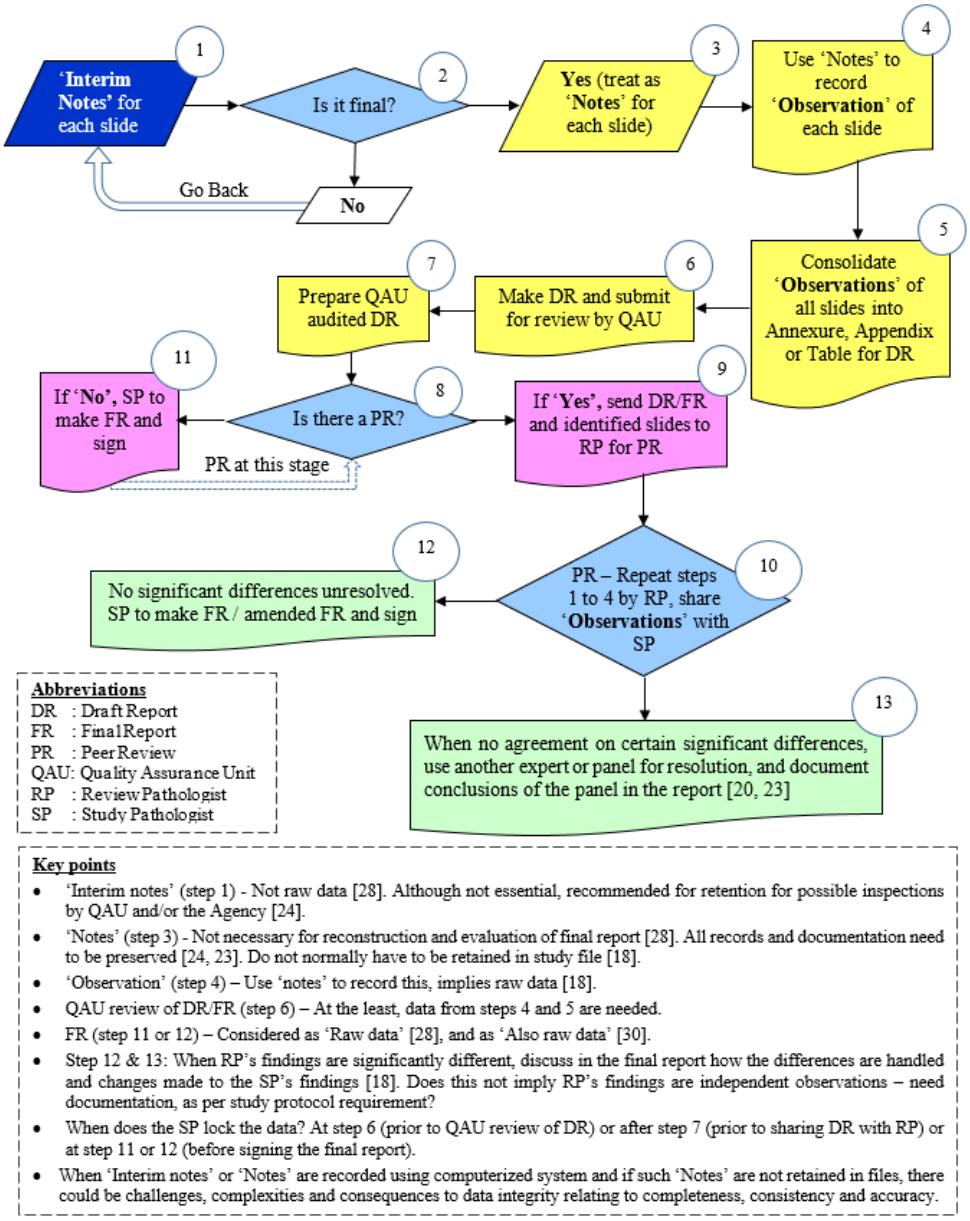

Figure 1: Metamorphosis of data/notes of histopathology examination and peer review of slides into raw data.

through the PPR process but also for reconstruction of the report.

6.2. *Types and Timing of Peer Review*

Figure 3 depicts different ways by which the PPR is being performed, all of which may or may not generate documentation of raw data. While a formal peer review is driven by a study protocol requiring documentation of raw data, the informal peer review does not have such scope for documenting raw data. It may not be uncommon for an SP to informally discuss with or show the slides to other pathologist(s) in the same facility for their views on diagnosis [4, 11, 31]. Such informal consultation may happen routinely among pathologists in large facilities to build confidence, get feedback for improving the quality of diagnosis prior to finalization of a pathology report, and train people. However, such informal review is neither considered as typical PPR mandated by the study protocol nor are the views of such RPs on diagnosis documented and discussed in the study report.

In the case of a formal PPR process, it is necessary to include the intent in the study protocol or study protocol amendment, and identify the RP, who could be either an internal expert pathologist within the facility or an external expert working in a GLP-compliant test facility or non-GLP organization, or an independent consultant pathologist. The external RP could also be from the sponsor organization. It is also possible that a test facility conducting a GLP toxicology study in consultation with the sponsor may engage an external test facility for the pathol-

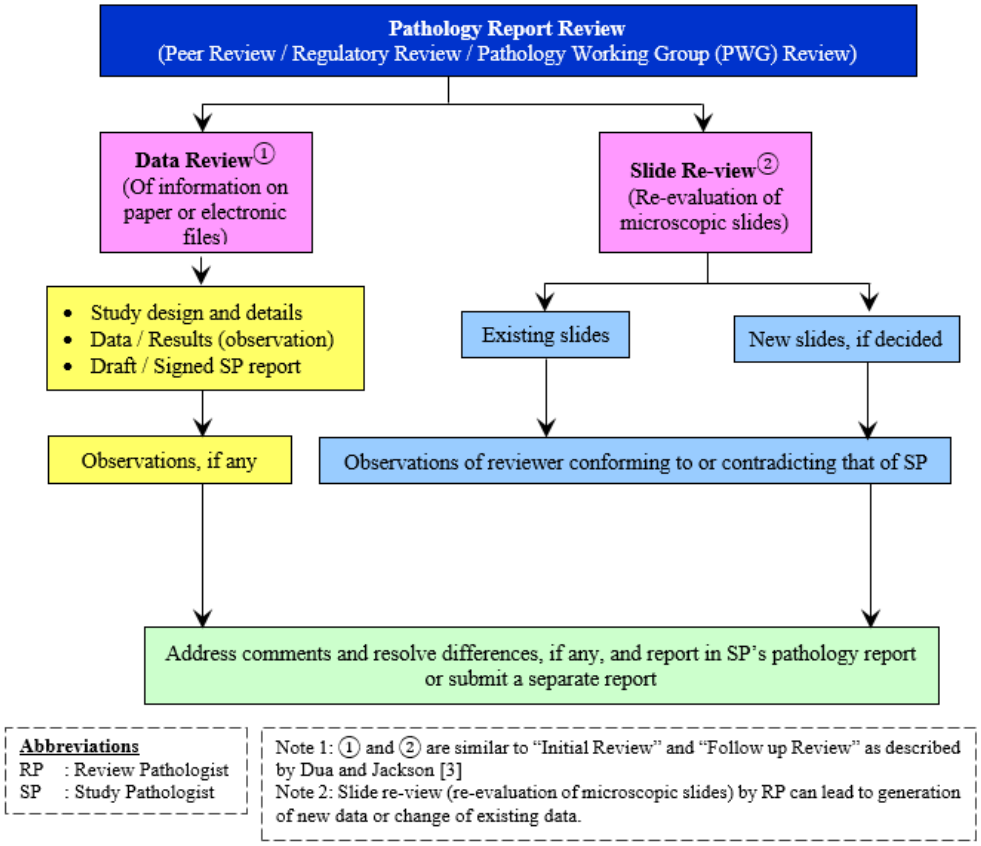

Figure 2: Pathology data review and microscopic slide re-view during peer review.

ogy phase work covering the entire pathology report. In such a situation, the study will be treated as a multi-site study, with the involvement of the external test facility as test site and the SP as principal investigator for the pathology phase [30, 16]. When a PPR is considered for any study, irrespective of whether it is a multi-site study or not, the RP is not considered as principal investigator but recognized as "*contributing scientist*" [18, 30].

6.3. Prospective and Retrospective Peer Review

From the point of view of timing of a formal pathology peer review, there is no clarity and consistency of approach. It has been generally classified as prospective pathology peer review and retrospective pathology peer review. In prospective pathology peer review, it is expected that the peer review process is described in the study protocol, and pathology data are not considered final until the peer review is completed [31, 22, 17]. Therefore, it implies that the RP reviews the draft pathology report of the SP by re-examining the selected slides, and provides the review findings to the SP; then, both discuss them to resolve any differences, the RP completes the peer review statement/memo/report, provides it to the SP, and the latter finally incorporates the statement/memo/report into the pathology report and finalizes it by signing and dating it. With regard to the timing of signing of the RP's statement/memo/report, there are differences in practice [13, 5]. Based on certain FDA expectations that the PPR should not be completed until the pathology report is signed by the SP, the practice adopted by many RPs is to conduct the PPR using the draft pathology report of the SP but issue the signed statement/memo/report only after the SP signs the pathology report [12]. It is not clear whether this is indeed the expectation. When a study protocol calls for prospective peer review, then it is expected that not only should the PPR findings be discussed and resolved in the pathology report, but also that the RP's signed statement/memo/report be completed before the pathology report is signed and dated by the SP. It is therefore not obvious whether the expectation of the agency is to obtain a kind of declaration in the form of statement/memo from the RP reflecting that the findings were discussed and resolved in the signed pathology report, and that he/she is in agreement or disagreement with the conclusions drawn by the SP. The OECD (2014) guidance document indicates, "*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*" [18]. Such a statement needs to be retained in the study file and there is no need for the RP to sign the pathology report or study director's final report. This also implies that such a statement/memo/report signed by the RP be completed after the pathology report is signed by the SP. Another view is that since the peer review is a part of a study protocol require-

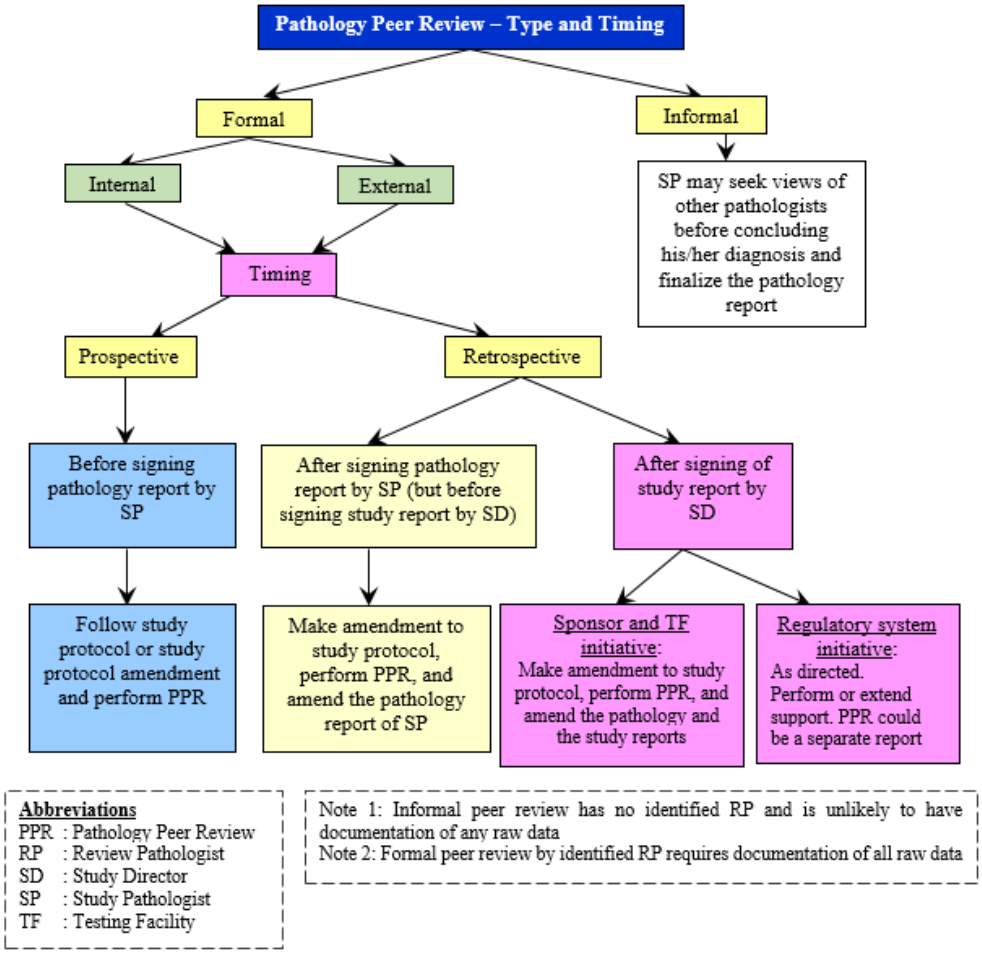

Figure 3: Type and timing of pathology peer review process.

ment for the pathology phase of a study, and the RP functions as a contributing scientist to the SP (who is responsible for the pathology report/phase), there is also a logical expectation that the RP's statement/memo/report should be completed prior to signing of the pathology report by the SP. This process is akin to completion of independently signed phase reports of principal investigators or contributing scientists, as applicable, prior to signing of a study report by the study director.

When a study protocol or its amendment does not require any PPR, the SP makes the signed final pathology report and submits it to the study director for inclusion in the study report. Subsequently, if for any reason a sponsor asks for a PPR, irrespective of whether the final study report is signed by study director or not, then such a PPR should be considered as retrospective PPR. Also, if a regulatory agency requests a PPR after reviewing the final study report submitted to it by the sponsor, this would obviously be interpreted as retrospective peer review [1, 31, 17]. A retrospective peer review could be performed by amending the study protocol describing the PPR process, and discussing the findings of the RP in the amended pathology report of the SP and in the amended final study report of the study director. When a pathology working group, as directed by an agency, is constituted for review, then the agency expects independent signed reports by the SP and the RP and the original slides [26]. This situation warrants a necessity for retention of all raw data generated by the SP and RP for their respective activities, as directed by the study protocol.

The OECD (2014) states: "*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*" [18]. The term contemporaneous peer review is considered equivalent to the earlier term prospective peer review. Additionally, although the OECD does not explicitly provide any reference points (criteria) for classifying a PPR as "contemporaneous" or "retrospective", it is inferred that the only logical criterion could be whether it is completed prior to (contemporaneous) or after signing the pathology report by the SP (retrospective). This poses another problem because if the RP's statement/memo/report on the PPR is signed after the pathology report is signed by the SP, then it means that it gets completed

only after the pathology report is signed, and therefore, it is a kind of retrospective peer review. It is also debatable whether signing the final study report by the study director should be the criterion for such classification, since the study gets completed only when the study director signs the final report. If the final study report is still not signed by the study director, but the pathology report is already signed by the SP, there is an opportunity to amend the study protocol and carry out a PPR possibly as contemporaneous peer review.

The points described above are of great significance, not only from the viewpoint of the scientific outcome of the pathology findings and/or any improvements achieved through the PPR process, but also from the GLP quality system point of view for organizational SOPs and documenting all raw data/correspondence in order to comply with multiple regulations. It is also to be recognized that the OECD (2014) treats both contemporaneous and retrospective peer review uniformly for the purpose of (a) describing the PPR process either in the study protocol or in its amendment; (b) recording observation by the RP (from "*notes*") during the histopathological examination of individual slides; (c) defining raw data as the documentation of how the PPR was conducted and all correspondence, including minutes of teleconferences, in the study file, and observations recorded from "*notes*"; (d) describing how differences of interpretation were handled and changes made to the SP's original interpretation in the study report; (e) retaining the RP's signed statement in the study file in the absence of his/her signature in the pathology report or final report; and (f) reflecting the identity and affiliation of the RP in the final report [18]. It is also evident that the OECD (2014) does not differentiate the method, manner and extent of documentation of raw data between contemporaneous and retrospective peer review [18].

7. Conclusion

This paper brings out the mandatory requirement of compliance to GLP quality systems covered in key regulations such as those of the U.S. FDA and U.S. EPA, and the OECD Council decision, including the provision of MAD applicable for OECD member countries as well as Full Adherent and Provisional Adherent non-member countries, for conduct of nonclinical studies by testing facilities for regulatory submission to agencies for approval or authorization of products. The applicability of GLP quality systems for data generated by histopathology evaluation of tissues obtained from a toxicology study by a study pathologist, and pathology peer review, when a study protocol includes such a requirement, of a set of existing or new slides by an expert peer review pathologist has been emphasized. Considering that certain components of a pathology report can possibly undergo changes during or following peer review through changes to observations and interpretation, leading to potential changes/amendments to the outcome or conclusions of a study, the emphasis of this article is the meticulous adoption of the principles of the GLP quality system not only for data recording (or capturing in electronic system) but also for subsequent correction of any such data. The definition of raw data stipulated in different quality systems and its applicability to histopathology observations, including certain contrasting perspectives of different stakeholders, reveals varying interpretations, inconsistent expectations and diversity of practices. The article also brings out that raw data generated under different types of peer review processes do require compliance to GLP quality systems. Overall, the multiple issues relating to definition of raw data applied to histopathology observations of study pathologist and peer review pathologist reveal a need for a harmonized interpretation and expectation across regulatory agencies. This would further help consistent interpretation and adoption by various stakeholders, including testing facilities that conduct studies; study pathologists who are responsible for pathology reports; peer review pathologists who function as contributing scientists for study pathologists; study directors who are the single point of study control and responsible for the final report, including the GLP compliance statement; the quality assurance personnel who monitor/audit studies and provide quality assurance statement to each study report; and others, as they all need to perform their respective functions in compliance with GLP quality systems.

8. Declaration of Conflicting Interest

The author declares that there is no conflict of interest.

9. Disclaimer

The interpretations and views expressed in this review article are those of the author and not necessarily the official position of the author's employer. The author is also the President of the Indian Chapter of the Society of Quality Assurance.

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