

## Histopathology Peer Review for Nonclinical Studies – GLP Processes and Conditions

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### Abstract

Conduct of nonclinical studies in compliance with Good Laboratory Practice (GLP) for safety assessment of products is mandated and monitored by multiple regulatory agencies globally. Histopathology examination of slides from any pivotal toxicology study is a critical phase performed by a study pathologist, who contributes substantially to the outcome and conclusions toward judging a product for further development, authorization or licensing. Considering such examination is scientific yet subjective based on study pathologists experience and expertise, the practice/expectation has been to subject at least a subset of slides for peer review by another pathologist, despite absence of regulatory need. Diverse practices and controversies around the peer review process, documentation, and reporting have continued for over three decades. The Organisation for Economic Co-operation and Development (OECD) guidance on GLP requirements for peer review of histopathology (OECD, 2014) provided a concise account; nevertheless, dissension persists [20]. The United States Food and Drug Administration's (FDA) Proposed Rule 2016 (21 CFR Part 58) brings GLP quality system framework, consistency with the OECD and the United States Environmental Protection Agency (EPA) requirements, and inclusion in the study protocol of procedures to be followed when a study includes peer review of any phase [34]. This paper goes critically between the lines of GLP definitions, expectations, processes and conditions focusing purely on GLP compliance to peer review process across stakeholders globally.

**Keywords:** regulatory affairs, nonclinical/preclinical safety assessment, toxicologic pathology, good laboratory practice/GLP, histopathology, pathology peer review, quality assurance

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### 1. Introduction

Good laboratory practice (GLP) is a quality system covered in regulations globally to ensure adoption of processes and conditions for carrying out nonclinical studies meant for regulatory submissions for clinical trial approval or marketing authorization, as appropriate, for pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, industrial chemicals, etc. The GLP approach, as proposed by the FDA Commissioner in 1976, was “*process-oriented rather than product- or person-oriented*” [28]. In the Final Rule, when published by the FDA in 1978, it was concluded that the GLP regulations are both “*process-oriented and product-oriented*” [29]. In spite of this emphasis on “*process-oriented*” approach in GLP by the FDA nearly four decades ago, continued inconsistencies (inclination towards “*person-oriented*” approach) prevail when interpreting compliance requirements of peer review pathologist in histopathology peer review. The EPA GLP regulation [24], the

OECD Council decision [17] and the European Union legislations [5] define GLP as a quality standard/system concerned with the organizational process and the conditions under which studies are planned, performed, monitored, recorded, archived and reported. None of these regulations neither state nor imply that GLP is a quality system that is also person-oriented. Thus, the GLP processes are applicable to all personnel involved in planning, performing, monitoring, recording, archiving and reporting of study data in reports which finally reach regulatory authorities for review prior to approval of, seeking additional data for or rejection of a report or application. In the case of histopathology peer review, the peer review pathologist performs the role as directed by the study protocol.

The core of all the regulations therefore seeks test facilities and all personnel involved (obviously including peer review pathologist) to ensure adherence to processes, transparency of documentation of raw data, resolution of issues, retention of records and unbiased reporting with opportunity for reconstruction and independent evaluation of the report any time subsequently. In safety assessment of test article (the term defined by the FDA), test substance (the term defined by the EPA) or

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test item (the term defined by the OECD) by animal toxicology studies, evaluation of histology slides by trained study pathologists is a critical component of the GLP studies, in order to assess and derive study outcomes that support study conclusions by study directors while finalizing the reports, and also by the regulators while reviewing the final study reports. Considering that the microscopic evaluation by a trained study pathologist (SP) is a subjective methodology critical for safety evaluation of drugs, chemicals and biologics, it is often deemed useful to perform a reassessment of the slides, which includes having them re-viewed by an independent peer review pathologist (RP) to improve quality and accuracy of diagnosis and interpretation. Thus, sponsors do seek peer review, test facilities do accede to such requests, and regulatory agencies do accept/expect such study reports for regulatory review prior to considering issue of marketing license or approval of clinical trials for a specific chemical or biological entity.

A recommendation by the EPA in 1987 for use of independent pathology peer review (PPR) explained that providing independent reports from SP and RP along with a consensus report that resolved any differences would greatly enhance the Agency's confidence in the pathology report of the study report [25]. Dua and Jackson (1988) described the FDA's regulatory review processes, viz., "initial review of data as reported" and "follow up review" [2]; the latter includes microscopic examination of slides that were already evaluated by the SP and request for new slides prepared from paraffin blocks and/or tissues, if desired. Since 1988, there have been several articles in the literature relating to the PPR including coverage on diversity of practices/processes [3, 13, 1, 16, 14]. Concerns regarding the diversity of processes and practices relating to the method and manner of performing PPR are often expressed in discussions, debates and publications. Overall, it is believed to reveal certain issues of compliance of the PPR processes in spite of genuineness and complexities associated with the nature of pathological examination of microscopic slides. In light of the nature of histopathology microscopic evaluation, the observations may be subjective to some extent, associated with the individual pathologist's education, training and experience, not to mention the complexity of animal species and strain, tissues, action of test item, etc. Thus, some differences in diagnosis of histopathology slides as well as nomenclature could be possible to a certain degree when (a) the same SP evaluates the same set of slides in blinded and un-blinded methodology or at two different timepoints; (b) one or more peer review pathologists re-evaluate the same set of slides in blinded and un-blinded methodology or at two different timepoints; and (c) a peer review working group comprising multiple pathologists evaluates the same slides or new slides prepared from paraffin blocks already archived or freshly prepared from retained tissues. While such differences are fully recognized in the field of toxicologic pathology, there are diverse points of view relating to the PPR processes, definition of raw data, documentation, data locking, reconstruction of a report, method of reporting the RP's observations, and resolution of differences in interpretation between the SP and the RP, and retention of records. Each of these is considered valid in isolation and in the con-

text of discussion in conferences, articles, meetings, etc. The prior article on "*Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems*" provides a detailed account of diversity of interpretations of raw data when applied to histopathology observations by SP and also by RP in PPR, thereby revealing a strong need for a harmonized interpretation and expectation across regulatory agencies [22].

Although GLP regulations of the FDA, EPA and OECD have been in force for nearly four decades [29, 24, 17, 30, 26] and PPR has been in vogue for about three decades [25, 2, 3, 13, 1, 16, 14], there was no guidance or guideline from any regulatory agency or GLP monitoring authority until the OECD (2014) guidance advisory document was published in 2014 [20]. Following this, Fikes *et al.* (2015) published a review article providing their consensus views and interpretations of the guidance on peer review [6]. The FDA document of 2016 is the only guidance for industry that covers briefly the PPR and pathology working group (PWG) [33]. Very recently in 2016, the FDA issued the Proposed Rule for "*Good Laboratory Practice for Nonclinical Laboratory Studies*", revealing 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 [34]. Additionally, the Proposed Rule seeks inclusion in the study protocol of "*the methods for the control of bias in the conduct of the study, analysis and reporting of study test results and procedures to be followed when a study includes a peer review of any phase*", thereby bringing regulatory requirements under the FDA's GLP quality system approach whenever any peer review, including PPR, is performed. The quality system approach of the FDA is also aligned to the definition of GLP as quality system in the OECD Principles of GLP [17]. It is therefore imperative that peer review, if performed, needs to comply fully with the regulations or principles of GLP. The interpretations of the OECD guidance [20] and the Proposed Rule of the FDA [34] go beyond what is conceived by Fikes *et al* [6].

The objective of this paper is to bring out the fundamental points that focus on GLP compliance associated with transparency of processes applicable for PPR. This article, therefore, discusses explicitly the basic requirements of regulations for a GLP study and applying the same to the PPR process when a GLP study protocol directs such an activity for the pathology phase of a study. Accordingly, this paper covers the finer aspects of (a) the regulations that are fundamental for compliance when a study protocol claims such compliance, (b) the GLP quality system processes and conditions that are applicable even for PPR, and (c) a detailed process approach for PPR from planning to reporting. It is likely that this article may open up more questions and interpretations which may help in continually evolving standard operating procedures (SOPs) for an improved and robust GLP-compliant PPR process.

The italicized text in this article reflects extracts of information from the OECD, FDA and 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 [17] and "*study protocol*"

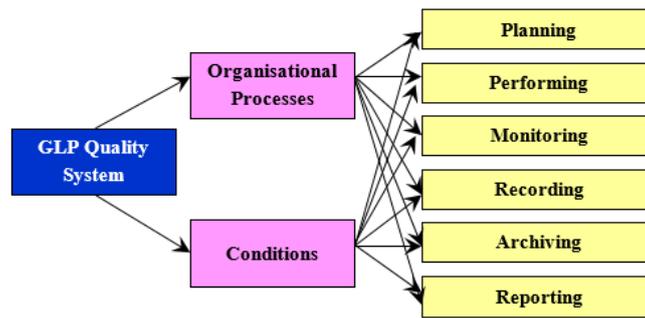


Figure 1: GLP Quality System – Generic processes and conditions.

used by FDA [30, 34] and EPA [26] 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 are performed for the purpose of regulatory submission to obtain necessary regulatory approvals from one or more countries. The sponsors of studies, as well as the test facilities that conduct such studies, claim compliance with one or more of the GLP regulations or principles in the study protocol and in the study report. Applicable key regulations are the FDA (1987) and the EPA (1989), and the OECD (1998) Council decision [30, 26, 17]. Based on the OECD Council decision, several countries, such as the United Kingdom and Japan established national regulations for GLP [9, 10, 11]. Key aspects of these are covered in another publication by the author [22]. The OECD (1998) also covers mutual acceptance of data (MAD) and adherence of non-member countries to Council Acts enabling acceptance of studies conducted in any member or full-adherent non-member country by other member or non-member (both full adherent and provisional adherent) countries for purposes of assessment and other uses relating to the protection of man and the environment [17]. The scope of application of the OECD (1998) Council decision for conducting nonclinical safety testing of test items is much wider, covering pharmaceutical products, pesticide products, cosmetic products, and veterinary drugs, as well as food additives, feed additives, and industrial chemicals [17].

Although the regulations are similar, subtle differences exist in the definition of certain terms, interpretations and expectations. The provision of MAD as per the OECD Council decision supports prevention of duplication of studies. This is all the more critical for toxicology studies conducted on animals. For carrying out nonclinical studies, sponsors frequently request testing facilities to claim GLP compliance with one or more regulations or Council decision in the study protocol and the study report, since they would like to submit the study reports to regulatory agencies in different countries. For drug substances and drug products, it is not uncommon to claim GLP compliance with both FDA (1987) and OECD (1998) [30, 17].

Similarly, for pesticides and chemicals, GLP compliance is frequently claimed to EPA (1989) and OECD (1998) [26, 17]. Such needs necessitate test facilities to have SOPs aligned to accommodate the compliance requirements of different regulations. Accordingly, processes applicable for PPR need to take into account the definitions, interpretations and expectations of the different regulatory/monitoring authorities. Additionally, when data are captured electronically, the Final Rule of 21 CFR Part 11 of the FDA (1997) [31] and the OECD (2016) advisory document on “*Application of GLP Principles to Computerised Systems*” are considered applicable [21]. It is also to be recognized that the FDA (2016) Proposed Rule will be applicable for compliance when it is finalized in the current form and becomes effective [34].

## 3. GLP Quality System – Applicable Processes and Conditions for Pathology Peer Review

The first line of the introduction section of the 1998 OECD Principles of GLP starts with a preface: “*Government and industry are concerned about the quality of nonclinical health and environmental safety studies upon which hazard assessments are based. As a consequence, OECD Member countries have established criteria for the performance of these studies*” [17]. Thus, the concern about the quality of data was addressed by way of establishing criteria for study performance. Accordingly, the OECD Council defines GLP as “*a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported*” [17]. Figure 1 depicts the interlinking of processes and conditions that are the applicable criteria for each GLP study, from planning to reporting. The 2014 OECD advisory document covering histopathology peer review is also concerned with the processes used to organize, perform and record the results of peer review [20]. Thus, for any facility conducting a GLP study involving PPR, the organizational process and the conditions become important for (a) planning such a study (through study protocol describing PPR process); (b) performing the study (by all study personnel including the RP as directed by the study protocol); (c) monitoring the study (by the quality assurance unit (QAU), as appropriate); (d) record-

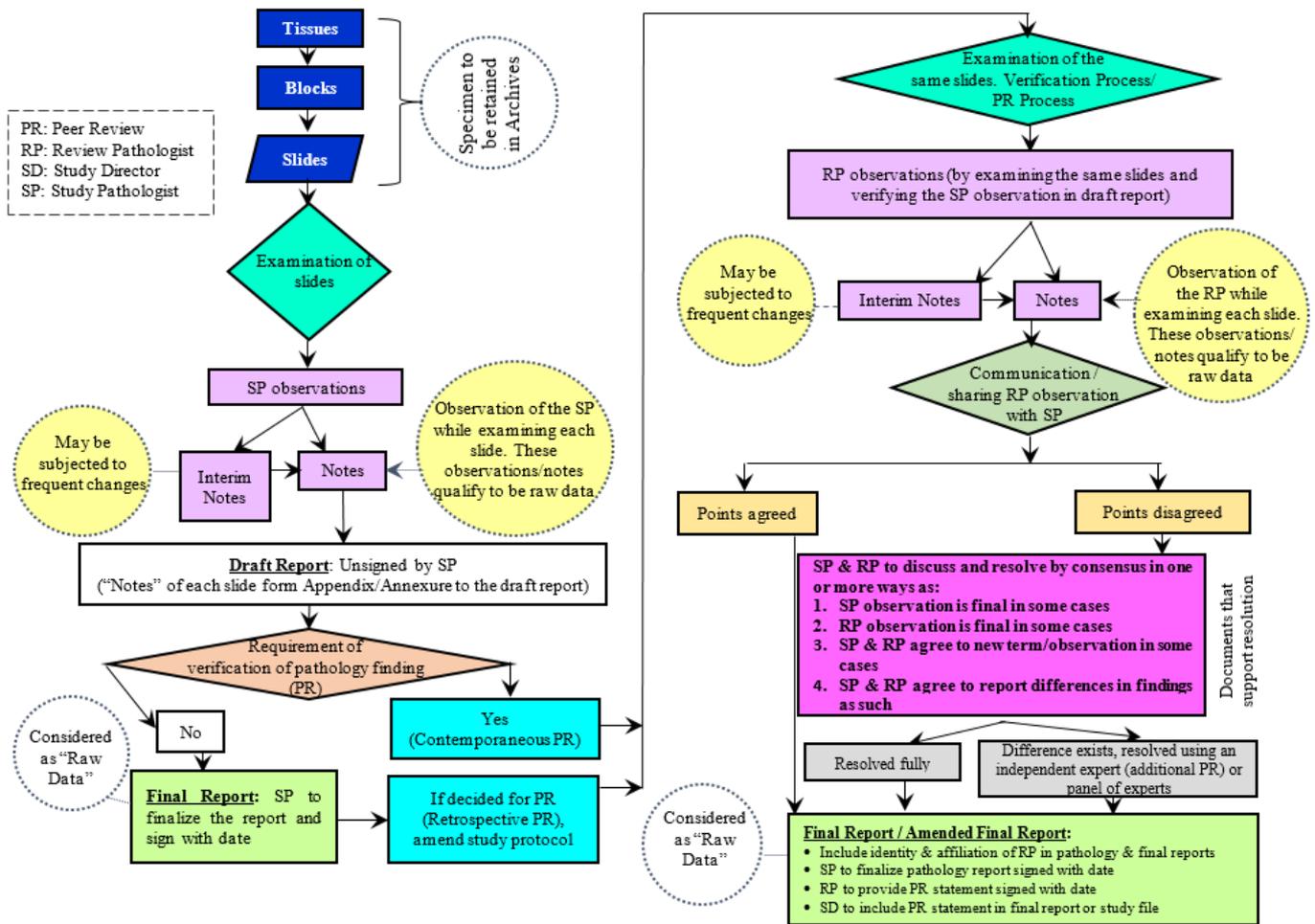


Figure 2: Process flow for histopathological evaluation by study pathologist and peer review pathologist.

ing study data (by all study personnel, including the RP); (e) archiving (of raw data and supporting material, including those applicable for PPR); and (f) reporting (in the final report of the study director, and by including reports of principal investigators or contributing scientists, RP, etc., involved in the study).

The FDA’s advance notice of proposed rulemaking in 2010 and Proposed Rule in 2016 clearly reveal its desire to have fully implemented the GLP quality system as the proper framework for building quality into planning, conducting, and reporting a nonclinical laboratory study, and strive for consistency with the relevant OECD documents wherever possible, and, at the very least, not conflict with them [32, 34].

#### 4. Pathology Peer Review Processes and Conditions

Considering the industry practice for decades and the requirements of the OECD guidance document [20], the expectation of regulatory agencies when performing PPR is that (a) the sponsor, test facility, and test site covered in the study protocol, and all personnel, including the RP, need to comply with the GLP quality system requirements; (b) the organizations performing the PPR must have SOPs describing its processes; and

(c) the specific study protocol or its amendment must describe the PPR process applicable for the study [20, 34]. Figure 2 depicts the complete process flow of the PPR process to aid in understanding complexities and applying GLP conditions for each activity. While the process described in Figure 2 could be similar in most organizations, it is possible that some may adopt a slightly different process. To effectively adopt the GLP quality system requirements of the OECD, FDA, and EPA for the PPR process, the common concept of applying Five Ws and one H (5W1H - viz., why, what, who, where, when and how) from planning to reporting is deemed appropriate. The ‘why’ part is the fundamental GLP quality system requirement, according to the OECD, FDA and EPA for any activity performed for a GLP-compliant study or study phase. The remaining parts (4W1H) provide ways and means for understanding the conditions and achieving the compliance requirements. Accordingly, Table 1 provides a detailed account of the application of 4W1H to major GLP processes and describes conditions applicable for PPR. The information could be directly applied as directed by a study protocol or study protocol amendment. If there is any regulatory requirement for peer review by a pathology working group, then the concepts could be applied as directed by the

Process	Condition				
	What	Who	Where	When	How
Planning	PPR <sup>a</sup>	SD <sup>b</sup> , SP <sup>c</sup> and RP <sup>d</sup> (RP as per sponsor approval). Test Facility Management and Test Site Management, when engaged, have roles to play	In study protocol or study protocol amendment (by SD at TF <sup>e</sup> )	Any time indicated below: <ul style="list-style-type: none"> <li>• Prior to study initiation (signing of study protocol)</li> <li>• Prior to or after finalizing (signing) pathology report but prior to finalizing study report.</li> <li>• After study completion (signing study report)</li> </ul>	In study protocol or study protocol amendment, identify RP; GLP status of RP's facility, (QAU <sup>f</sup> ) audit, describe the PPR process covering extent of peer review, data collection, use, method of resolving and reporting difference in observations if any, archiving of data, records and report/statement of RP, and indicate how such report/statement would be used by either SP in pathology report or SD in study report, etc.
Performing	Review of draft/final pathology report and re-evaluation of slides and providing observations to SP, and participate in resolving differences	<ul style="list-style-type: none"> <li>• SP (sharing draft or signed report and slides)</li> <li>• RP (can be from TF, TS, external pathology consultancy organization or independent consultant pathologist)</li> </ul>	<ul style="list-style-type: none"> <li>• TF (External RP visiting TF for PPR)</li> <li>• TS <sup>e</sup>, when pathology phase is part of multi-site study (External RP visiting TS for PPR)</li> <li>• External facility / Sponsor / Consultant RP's place</li> </ul>	<ul style="list-style-type: none"> <li>• When SP completes draft pathology report and makes it available (before or after QAU review) to RP along with slides</li> <li>• After completion (signing) of pathology report by SP (but SD not yet completed the study report) and SP provides the signed pathology report to RP</li> <li>• After completion (signing) of final pathology report by SP and study report by SD</li> </ul>	The common practice is un-blinded slide evaluation (RP knowing SP's observations). <ul style="list-style-type: none"> <li>• Review draft/final pathology report</li> <li>• Re-examination of microscopic slides as outlined in study protocol or study protocol amendment and SOP</li> <li>• Seek additional slides or fresh slides from paraffin blocks or tissues for evaluation, if needed</li> </ul>
Monitoring	Review of draft study protocol and/or study protocol amendment, inspection of PPR activity, and audit of data and reports of RP and SP	QAU at TF (also at TS or external pathology consultancy organization, or other places, as applicable)	At all locations, as applicable: <ul style="list-style-type: none"> <li>• TF</li> <li>• TS</li> <li>• Pathology consultancy organization / Sponsor</li> </ul>	<ul style="list-style-type: none"> <li>• When draft study protocol / study protocol amendment is received from SD</li> <li>• When in-life phase of PPR is in progress</li> <li>• When data (summary table), and draft and final pathology reports are received from SP</li> </ul>	<ul style="list-style-type: none"> <li>• Review of draft study protocol / study protocol amendment</li> <li>• Inspection during in-life phase of PPR</li> <li>• Audit of data (summary table) and draft report prior to or after finalization of RP report/statement</li> <li>• Audit of final pathology report, and draft and final study report</li> </ul>
Recording	<ul style="list-style-type: none"> <li>• Microscopic observations (points concurred and those differed with SP's observations)</li> <li>• How differences were resolved, including any correction to the data on diagnosis by SP</li> </ul>	<ul style="list-style-type: none"> <li>• RP</li> <li>• SP</li> </ul>	<ul style="list-style-type: none"> <li>• On paper</li> <li>• In electronic system</li> </ul>	<ul style="list-style-type: none"> <li>• While reevaluating slides under microscope (every time, when each slide or set of slides is evaluated)</li> <li>• During preparation of draft/final report/statement by RP, it is possible to go back for re-evaluation of slides and to make changes to the notes / observations</li> <li>• While making any correction to data on diagnosis after consensus</li> </ul>	<ul style="list-style-type: none"> <li>• Record observation (raw data) of microscopic evaluation of each slide directly, promptly and accurately on paper or in electronic system. Also, record legibly when written on paper</li> <li>• If change to any recorded data is needed, make changes by adopting audit trail requirements</li> <li>• In case of entry in electronic system, ensure that the system maintains audit trail automatically</li> </ul>
Archiving	All data including PPR observations and details of resolution of differences, if any, between RP and SP. Specimen and reports (peer review report / statement, pathology report, and study report)	<ul style="list-style-type: none"> <li>• SD/SP/RP (as specified in study protocol or study protocol amendment)</li> <li>• SD is primarily responsible for transferring data, specimen and report to archives</li> </ul>	As covered in study protocol or study protocol amendment (at TF, TS or other location)	Archive PPR related data, report/statement, communication, etc., as specified in study protocol or study protocol amendment, taking into consideration organization's SOP, which needs to be based on: <ul style="list-style-type: none"> <li>• After completion of study (signing of final report by SD) as per OECD (1998) [4]</li> <li>• During or at the close of the study as per FDA (1987) [14] and EPA [15]</li> <li>• The proposed rule of FDA (2016) [19] provides timeframe up to 2 weeks after study completion</li> </ul>	<ul style="list-style-type: none"> <li>• All data recorded on paper as well as signed peer review report/statement of the RP, pathology report of SP, and study report of SD</li> <li>• When data are captured in electronic system, retain them in e-archive system</li> <li>• Specimen, including blocks and slides, appropriately labeled and retained</li> </ul>
Reporting	<ul style="list-style-type: none"> <li>• Statement / report of RP, pathology report of SP and study report of SD</li> <li>• Discuss in the report how significant differences that lead to changes to the findings of SP were handled</li> <li>• Identity and affiliation of RP</li> </ul>	RP, SP and SD	<ul style="list-style-type: none"> <li>• RP's statement / report (in study file or report)</li> <li>• Pathology report</li> <li>• Study report</li> </ul>	<ul style="list-style-type: none"> <li>• RP's statement or report either before or after finalizing pathology report</li> <li>• Finalize pathology report when all significant differences in the findings, if any, between SP and RP are resolved (that is, no need for an independent expert or panel of experts).</li> <li>• Finalize study report after pathology report is signed</li> </ul>	<ul style="list-style-type: none"> <li>• Simple statement or report by RP covering list of animal tissues from different treatment groups examined, findings agreed or resolved with SP, and RP's agreement on the conclusion of the pathology report</li> <li>• Some regulatory agencies or PWG <sup>h</sup> may require separate reports of RP and SP</li> <li>• Significant differences in findings that lead to changes to the SP's findings need to be discussed in pathology and/or study report</li> <li>• See Table 2 for more details</li> </ul>

<sup>a</sup>PPR = pathology peer review  
<sup>b</sup>SD = study director  
<sup>c</sup>SP = study pathologist  
<sup>d</sup>RP = (peer) review pathologist  
<sup>e</sup>TF = test facility  
<sup>f</sup>QAU = quality assurance unit  
<sup>g</sup>TS = test site  
<sup>h</sup>PWG = pathology working group

Table 1: Pathology peer review to comply with GLP processes and conditions.

regulatory agency. In addition to the information provided in Table 1, highlights of key requirements and responsibilities are provided in the following sections.

#### 4.1. Basic Information

Generally, the decision to conduct PPR for a study that is new (to be initiated), ongoing (in progress, wherein the pathology report may or may not have been finalized and signed by the SP) or was completed (final pathology report signed by the SP), is taken by the sponsor, who also identifies the RP in consultation with the SP, study director, and test facility management. Key aspects are (a) criticality of the toxicology study, including likely mode of action of the test article; (b) expertise and experience of the RP; (c) whether the latter is working in a GLP-compliant facility, in a non-GLP facility or as an independent consultant; (d) location where the PPR will be performed; (e) extent of review of slides from control and treatment groups, with possible extension to additional slides or new slides from paraffin blocks/tissues; (f) method of capturing the RP's notes and observations; (g) the mechanism of resolution of differences between the study and review pathologists; and (h) reporting of findings, including the RP's statement, etc. This basic information is an important prerequisite for the study director to incorporate them suitably in the study protocol or study protocol amendment.

#### 4.2. Study Protocol and its Amendment

The study protocol is the only document approved by the sponsor and subsequently by the study director that can mandate a formal peer review, contemporaneously or retrospectively. All activities, including those applicable to the PPR (refer to the "basic information" given in Section 4.1), when stated in the study protocol or protocol amendment and claimed for GLP compliance, need to be performed in compliance with GLP. Any of the activities that are not carried out in compliance with the GLP quality system warrant documentation of deviations and impact assessment on the integrity of the study's outcome.

#### 4.3. Responsibilities

All study personnel, including the RP, need to comply with GLP requirements. The OECD indicates that "*all personnel involved in the conduct of the study must be knowledgeable in those parts of the principles of GLP which are applicable to their involvement in the study*" [17]. Study conduct implies performance or involvement of identified personnel, as directed by the study protocol. It does not exclude the involvement of a RP in PPR if there is an intent in the study protocol. By virtue of putting the RP's name in the study protocol, it allots responsibility and accountability for generating information for the study. A question is whether the RP is a study person or not. The OECD advisory guidance indicates, "*Because the reviewing pathologist is interpreting data and not generating data it would be appropriate for them to be considered as a contributing scientist*" [20]. The same guidance also defines raw data as

those that include all documentation (e.g. "*identity of the tissues that were reviewed, when the tissues were reviewed and by whom*") and "*all correspondence [ . . . ], including minutes of teleconferences between the sponsor and the test facility.*" Also, when any difference of interpretation results in a significant change leading to change in the SP's original diagnosis, then the origin of such data is the RP. Accordingly, it is appropriate to state that the RP is indeed generating data while performing PPR for confirming the findings of the SP and/or improving the quality of the pathology report.

The Proposed Rule of the FDA defines, "*Contributing scientist means an individual responsible for the conduct, interpretation, analysis, or any other service for a phase of a non-clinical laboratory study. An individual expert or specialist who is an independently employed contracted person, as defined in this section, is an independent contributing scientist*" [34]. The new regulation proposes to replace existing terms like "*individual scientists or other professionals involved in the study*" with the term "*contributing scientist*" for reporting study results. It is therefore appropriate to state that the RP, who is an expert or specialist independently employed as contracted person is responsible for the specific service of review and interpretation of data from the pathology phase of a study, and hence, deemed fit to be a contributing scientist with responsibilities such as complying with GLP. Also, the FDA rule states that the contributing scientists must comply with GLP and document, maintain, and update information about their education, training, and experience related to their responsibilities for a particular phase. Additionally, it requires that the independent contributing scientist assigned with specific responsibility needs to, "*date and sign the study protocol to indicate agreement to comply with protocol requirements for all phases of the nonclinical laboratory study the independent contributing scientist will conduct and the applicable requirements of this part*" (21 CFR Part 58) [34]. Thus, the responsibility of a RP, who is considered as a contributing scientist, goes much beyond what may be minimally stated in a study protocol or organizational SOPs relating to PPR. The OECD (2014) lists several responsibilities of the RP [20]. Overall, the SP is responsible for the pathology report, including corrections in audit trail as applicable, and the study director holds ultimate responsibility for ensuring that the PPR process is conducted in accordance with the requirements of GLP. The latter also needs to make a statement in the final report concerning the extent to which a study including PPR complies with GLP.

#### 4.4. GLP Compliance Status of Facilities for Peer Review

The OECD states that, "*there is an expectation that the peer review should be conducted in compliance with GLP*" [20]. It also recognizes that relevant experts for PPR are not always employed by all GLP test facilities or sites. Hence, for PPR to be of scientific value, it has to be conducted by acknowledged experts who may not work within a GLP-compliant facility or site or may be independent pathology consultants. When a decision is to be made for performing such review in a non-GLP facility, then the options are: (a) justify use of such non-GLP facility or independent expert consultant within the study protocol or

Type of formal peer review	Difference of opinion/finding between SP and RP		
	(A) No significant difference	Significant difference resolved	
		(A) Retain SP's finding	(B) Change SP's finding
Contemporaneous (Before signing the pathology report by the SP)	Simple statement by RP that the pathology report presents the agreed findings	<ul style="list-style-type: none"> <li>Discuss in final report (see Note 2) how differences of interpretation were handled and changes made by the SP</li> <li>A separate statement by the RP that the pathology report presents the agreed findings is expected</li> </ul>	<ul style="list-style-type: none"> <li>Amend the study protocol for using another independent expert (second RP) or panel of experts for resolving differences.</li> <li>Document the joint conclusion of the SP, RP and the second RP or the expert panel in the final report (see Note 2)</li> <li>A separate statement/report covering how the SP, RP and the second RP resolved their differences or separate report of the expert panel is expected</li> </ul>
Retrospective (after signing pathology report by the SP) (Adopt Note 3)	<ul style="list-style-type: none"> <li>Same as above point</li> <li>Amend pathology report to also include agreed non-significant differences</li> </ul>	<ul style="list-style-type: none"> <li>Same as above points</li> <li>Amend pathology report to include agreed non-significant and significant differences</li> </ul>	<ul style="list-style-type: none"> <li>Same as above points</li> <li>Amend pathology report to include agreed non-significant difference and the resolution and conclusion of the SP, RP and the second RP or the report of the expert panel</li> </ul>
Retrospective (after signing study report by study director) (Adopt Note 3)	<ul style="list-style-type: none"> <li>Same as above points</li> <li>Also, amend study report</li> </ul>	<ul style="list-style-type: none"> <li>Same as above points</li> <li>Also, amend study report</li> </ul>	<ul style="list-style-type: none"> <li>Same as above points</li> <li>Also, amend study report</li> </ul>

**Note:**

1. A, B and C refer to three categories of differences in interpretation between the SP and RP leading to resolution or no resolution.
2. Final report normally means the final study report of the study director. However, in this case, it is necessary to discuss or present matter in the pathology report and in the final report as appropriate.
3. Amend the study protocol for retrospective peer review and complete the peer review.

Table 2: Approach for resolving differences of opinion between study pathologist (SP) and peer review pathologist (RP) for different types of formal peer review.

study protocol amendment and final report, and (b) consider facilitating a RP to perform PPR at the test site or facility that conducted the study or phase. In the latter option, the RP would receive an appropriate level of training on the facility or site procedures prior to performing the review. Essentially, the sponsor, test facility or site, (in case of multi-site study involving pathology as a study phase [18]), study director, SP (who can be the principal investigator as well in a multi-site study), RP and the quality assurance unit (of all applicable facilities) need to value the GLP requirements and support for overall compliance by the PPR process.

4.5. Quality Assurance Activities

In a GLP study involving PPR, the role of the quality assurance unit extends to monitoring the review activities, which may include audit of premises and equipment used by the RP and review of documents covering raw data and statement/memo/report as per OECD (2014) [20]. Also, the FDA proposes that, “the quality assurance unit must audit all contributing scientists’ reports and any report amendments to ensure they include a report of all data and reflect the protocol, and amendments, and applicable SOPs. This requires that all data generated during the study are included and discussed, which is essential for the full transparency necessary for reconstruction of the study” [34]. Additionally, it requires oversight by the lead quality assurance unit, including audit of reports and amendments of independent contributing scientists and any persons conducting a phase of the study lacking either a principal investigator or a quality assurance unit or both.

4.6. Documentation

Document requirements for peer review are similar to those applicable for a GLP study. The OECD requires documentation of the entire process of peer review and related records such as, (a) evidence of experience/expertise of the RP; (b) agreement

that the RP will use the test facility or site SOPs, if chosen to perform PPR at the test facility or site; (c) chain of custody of slides, if shipped out of the test facility or site for PPR; (d) security of samples and documents while at the RP’s facility; (e) validation status of computer systems, if applicable; (f) quality assurance audits; and (g) all correspondence and minutes of meetings and teleconferences among related parties. The OECD further indicates that, “It is important that the original plan for the review process include a joint review by the original and reviewing pathologist of the two sets of results to explain or resolve apparent differences, should they occur. The results of the peer review should be documented and archived and any differences of opinion resolved through consensus” [19]. The expectation of “the two sets of results” and assessment of “apparent differences” could be possible only when the RP’s observations (results of peer review) are independently documented. A regulatory pathologist’s perspective on PPR of preclinical safety studies with respect to submission to the FDA for verification of data quality, accuracy and integrity was provided by Francke and Mog, who summarized the importance of documentation as, “we cannot judge peer review if it is not documented, if peer review is in the protocol – document it”, and “your peer review efforts are to us only as clear as your documentation” [7].

4.7. Resolving Differences of Opinion on Pathology Observations and Interpretation

Differences in diagnosis of microscopic slides by the study and review pathologists can be possible both in contemporaneous and retrospective peer reviews, leading to discussion between them for possible resolution. The OECD (2014) guidance describes two types of differences, viz., “no significant difference” and “significant change” without specifying any criteria [20]. Fikes *et al.* considered that the term “significant” in this context is not related to statistics but refers to a meaningful or impactful difference in the histopathologic diagnosis

and/or interpretation, for example, change in no observed effect level (NOEL), no observed adverse effect level (NOAEL) and/or target tissue with test article effect [6]. Applying such criteria would indeed be helpful to develop SOPs for resolving differences and reporting in pathology and study reports. However, the consideration of Fikes *et al.* that the term “raw data” (defined as those covered under points 2.4 and 2.5 of the OECD, 2014 [20]) is not applicable to contemporaneous peer review is difficult to comprehend, since the OECD guidance does not make or imply any difference in the definition of raw data between contemporaneous and retrospective peer review processes [6]. Extensive coverage of “raw data” compliance to GLP quality system relating to histopathology evaluation and PPR has been delineated in the previous article by this author [22].

The OECD guidance [20] describes handling and resolution of “no significant difference” and “significant change” between the SP and the RP in PPR process. The method of resolution can be categorized as A, B and C, as summarized below:

- A. No significant difference: “*Not necessary to report in detail the outcome of the peer review in the pathology report or the final report.*”
- B. Significant change/difference resolved by making changes to the SP’s original observation or interpretation: “*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.*”
- C. Significant difference not resolved or agreement cannot be reached: “*An independent expert or panel of experts may be used to resolve the issue. The conclusions of the panel should be clearly documented in the final report.*”

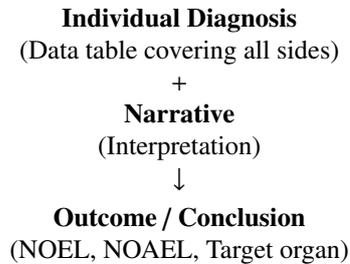
In most cases of PPR, category A is believed to be applicable while resolving differences of interpretation. It is also possible that sometimes either the categories A and B together or the category B alone, could be applicable for resolving differences of interpretation between the SP and RP. While category C is considered to arise infrequently, one cannot rule out such a possibility, and in such case, some points of category A and/or B could also be present for resolution. Table 2 provides a process approach for resolving the three categories of differences of opinion between the pathologists in contemporaneous and retrospective PPR. When addressing differences that fall under category B, greater sensitivity to changes will become apparent, especially when (i) the direction of change of NOEL and/or NOAEL is towards higher value and/or, (ii) the RP is from the sponsor organization. Hence, from a quality system point of view, the extent of documentation and audit trails should demonstrate data integrity and unbiased reporting in the pathology report while deriving conclusions after PPR.

#### 4.8. Data Locking

Neither the OECD nor the FDA cover anything about data locking explicitly. The only expectation of all GLP regulations

is that “*all data generated during the conduct of a nonclinical laboratory study must be accurate, legible, contemporaneous, original, and attributable (ALCOA)*” [34]. Additionally, all regulations allow changes to any entry made (whether on paper or captured electronically) by study personnel so as not to obscure the original entry and must indicate: (a) who made the change, (b) when the change was made, and (c) the reason for such change, which together simply means maintaining audit trail. There has been no stated exception to this requirement so far for histopathology-related data (notes, observations or whatever other terms one can use for the study or review pathologists’ findings), although there have been several opinions and contradictions expressed or recommendations and suggestions made [6, 12, 15, 23]. The OECD states that any computerized system used for data collection or to store histopathology data should be GLP compliant and should have a variety of security measures to ensure data integrity throughout the process of histopathology data collection and reporting, and that any changes made after the pathology contribution has been locked are recorded and audit trail kept [19]. Although the two points are not mutually exclusive, they appear to be conveying a contradictory meaning. For computerized system-related data integrity and audit trail, it is necessary to comply with the requirements of the FDA and OECD [31, 21]. It has been well recognized that histopathological diagnosis recorded on paper or captured electronically initially for slides by the same pathologist would possibly undergo several changes during the course of evaluation, and therefore, no one would doubt integrity or motives of the individual who makes such changes. The concept of data locking is primarily aimed to apply audit trail when the histopathology diagnostic finding of each slide is captured or changed in computerized system during the course of evaluation. The current data capture applications being used for histopathology recording generally apply two types of audit trails when a diagnosis is changed: (1) prior to data locking – to maintain two of the three conditions of GLP requirements ((a) and (b) above), and this is similar to corrections made in track change mode by the same or different people during review of a Word document, and (2) after data locking – to maintain all the three conditions of GLP requirements for audit trail ((a) to (c) above). The key question is when to apply the data locking provision to histopathological evaluation of slides. Should it be before sending the draft pathology report to the quality assurance unit for review, which is expected to precede the sending of the draft report for contemporaneous PPR or after resolving differences between the study and review pathologists in contemporaneous PPR? The Japanese regulatory authorities expect data locking prior to sending the draft report – or worksheet signed and dated by SP (raw data) – to the external/sponsor PPR [8]. Engelhardt *et al.* viewed that “locked” versus “unlocked” really does not matter, as long as events are recorded and retained to maintain transparency in the process [4]. From a quality system perspectives, it is considered appropriate to lock the data even before sending the draft report or summary table for review by the quality assurance unit because if there are inspection observations necessitating change, then there is a logical documentation of reason for change in the system. Cer-

tainly, such data locking is expected before sending the draft report for PPR 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 (see category B described section 4.7 of this paper) [20]. Also, the derived outcome of a pathology report is expected to depend primarily on individual diagnosis of slides (independent parameter) and narrative of interpretation as given below:



If there are any significant changes (category B) to the derived outcome of a study as a result of the PPR, then there is a high probability of change in at least some individual diagnosis. Accordingly, to meet the requirement of the OECD (2014) guidance, the data need to be locked before sharing the draft report with the RP even for contemporaneous PPR [20]. The FDA and the OECD require maintenance of complete audit trail throughout the documentation process, including corrections and changes made, regardless of applicability of the PPR for a study [31, 21].

#### 4.9. Reporting

When PPR is performed as directed by the study protocol or its amendment, the responsibility of reporting information in the pathology report rests with the SP and in the study report with the study director. When peer review is performed after submission of study report to a regulatory agency (retrospective PPR), the EPA asks for independent reports by the SP and the RP along with the original slides for review by a pathology working group [27]. The OECD (2014) guidance states that there is no requirement for the RP to sign the pathology report or final report [20]. It also states that in the absence of signature, there is an expectation that the RP will issue a signed statement for the study file, implying that the RP can also sign the pathology report if the study protocol specifies such a requirement. In the Proposed Rule of the FDA (2016), there is an expectation of an independent report from the RP (contributing scientist, “an individual responsible for conducting, interpreting, analyzing, or performing any service for a phase of a nonclinical laboratory study”) and such a report needs to be appended to the pathology or final study report [34]. Also, the FDA proposed to be consistent with the EPA GLP regulations (40 CFR 160.185(a)(12) and 792.185(a)(12)), which states, “The signed and dated reports of each of the individual scientists or other professionals involved in the study, including each person who, at the request or direction of the testing facility or sponsor, conducted an analysis or evaluation of data or specimens from the

study after data generation was completed” [26]. The expectation is, therefore, that a signed and dated report of each identified individual who conducted an analysis or evaluation of data or specimens from a study after data generation for that activity is completed by that individual. Overall, the FDA proposes, “this addition to provide transparency regarding the review of study findings and the development of conclusions submitted in the final study report” [34]. Accordingly, it is appropriate to describe clearly the reporting requirements of the PPR in the organizational SOP in general, as well as in the specific study protocol or study protocol amendment, in compliance with GLP quality system requirements.

#### 5. Conclusion

Pathology peer review, considered valuable by the community of pathologists, industry, test facilities, and regulatory agencies for the purpose of improving the quality of histopathological evaluation, interpretation and reporting, has been of diverse types, and is more often carried out contemporaneously than retrospectively. Considering that peer review can lead to changes in the interpretation of slide examination and the outcome and conclusions of a study, the OECD published an advisory guidance document in 2014. This document warrants compliance to GLP processes when PPR is performed in a GLP or non-GLP testing facility or test site, or by an independent consulting pathologist. The study director needs to include an appropriate statement of compliance or non-compliance to processes adopted for peer review as part of the GLP compliance statement in the final report of the study. The detailed account of GLP processes and conditions applicable for PPR described in this paper would be of value for developing or modifying organizational SOPs, and for preparing study specific protocol or protocol amendment. The Proposed Rule of the FDA on GLP published in 2016 sets an overall quality system framework for nonclinical studies consistent with the OECD GLP, as well as certain approaches and definitions in 21 CFR Part 820, makes several changes, including several definitions, and also brings in peer review of any phase, not necessarily only the PPR. There is an expectation that the Proposed Rule of the FDA when finalized would bring in progress towards harmonization with OECD principles of GLP. The requirements of 21 CFR Part 11 and of the OECD (2016) advisory document on computerized systems do not justifiably support several contrary views on audit trail and timing of locking pathology data. Resolution of differences between the study and review pathologists requires documentation, and if such differences result in significant changes to the original observation of the SP, then the pathology report and/or the final report need(s) to discuss how the differences have been handled, regardless of the type of formal peer review. Although some aspects of reporting of peer review findings by the peer review pathologist is covered in the OECD (2014) guidance document, the expectation of the FDA could be interpreted differently if the Proposed Rule is finalized and becomes effective in the current form. This review paper has dealt with these points in detail, considering data generation by histopathology evaluation and that peer review

is equivalent to any other activities that are normally covered in a study protocol, with all flexibility as to the design, extent of peer review and reporting. The views expressed in this paper could be challenged based on difficulties, complexities and special status needed for histopathological evaluation. However, it is to be recognized by all stakeholders that the various aspects delineated in this paper simply emphasize the need for adoption of uniform practice of data recording, making corrections to the data or observations, as provisioned in GLP, resolving differences explicitly in reports, and taking full responsibility for every activity covered in the study protocol by those identified individuals. Adoption of such uniform practices would not only bring out complete transparency to the entire pathology peer review process but also possibly move towards ending the long-standing controversies.

Considering the complexities and diverse nature of pathology peer review processes as well as certain inclination towards “person-oriented” approach when describing peer review pathologists’ responsibilities and compliance requirements, there is indeed a need for greater harmonization among GLP regulations. The complexities presented in this article would help evolving policies and guidelines for uniform adoption by various stakeholders viz., regulatory agencies, sponsors, test facility managements, study directors, principal investigators, study pathologists, peer review pathologists, quality assurance units and others connected with GLP compliant studies.

## 6. Declaration of Conflicting Interest

The author declares that there is no conflict of interest.

## 7. 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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## 10. References

- Crissman, J. W., Goodman, D. G., Hildebrandt, P. K., Maronpot, R. R., Prater, D. A., Riley, J. H., Seaman, W. J., & Thake, D. C. (2004). Best Practices Guideline: Toxicologic Histopathology. *Toxicologic Pathology*, 32, 126-131.
- Dua, P. N., & Jackson, B. A. (1988). Review of Pathology Data for Regulatory Purposes. *Toxicologic Pathology*, 16, 443-450.
- Eighmy, J. J. (1996). Study Pathologist Perspective of Pathology Peer Review. *Toxicologic Pathology*, 24, 647-649.
- Engelhardt, J. A., Hardisty, J. F., & Mann, P. C. (2013). Regulatory Forum Opinion Piece: Pathology Peer Review – To Lock or Not to Lock, Is That Really the Question? *Toxicologic Pathology*, 41, 1051-1052.
- European Commission. (2016). *EU Legislation with Good Laboratory Practice (GLP) Provisions* (Version March 2016). Retrieved from [http://ec.europa.eu/DocsRoom/documents/16846/attachments/1/translations/en/renditions/native&GLP\\_provisions\\_EU-legislation\\_Mar2016](http://ec.europa.eu/DocsRoom/documents/16846/attachments/1/translations/en/renditions/native&GLP_provisions_EU-legislation_Mar2016)
- Fikes, J. D., Patrick, D. J., Francke, S., Frazier, K. S., Reindel, J. F., Romeike, A., Spaet, R. H., Tomlinson, L., & 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. *Toxicologic Pathology*, 43, 907-914.
- Francke, S., & Mog, S. (2014, November). *Peer Review of Preclinical Safety Studies – A Regulatory Pathologist’s Perspective* [Webinar]. Presented at IATP-STPI Seminar on Pathology Peer Review, Bengaluru, India.
- Harada, T. (2012, September). *Current Situation for Pathology Peer Review in Japan*. Presented at 10th ESTP Congress, Stresa, Italy. Retrieved from [http://www.japantopath.org/ja/related/peerreview/peerreview20120911\\_2.pdf](http://www.japantopath.org/ja/related/peerreview/peerreview20120911_2.pdf)
- Her Majesty’s Stationery Office (HMSO). (1999). *The Good Laboratory Practice Regulations 1999*. Retrieved from [http://www.legislation.gov.uk/uk/si/1999/3106/pdfs/ukSI\\_19993106.en.pdf](http://www.legislation.gov.uk/uk/si/1999/3106/pdfs/ukSI_19993106.en.pdf)
- Japanese Ministry for Health and Welfare. (1997). Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs, Ordinance No. 21 (as last amended by the Ordinance of the Ministry of Health, Labour and Welfare No.114 of June 13, 2008). Retrieved from <https://www.pmda.go.jp/files/000153713.pdf>
- Japanese Ministry of Agriculture, Forestry and Fisheries. (1999). Notification on the Good Laboratory Practice for Agricultural Chemicals. Retrieved from <https://www.acis.famic.go.jp/eng/glp/GLPmain.pdf>
- Leininger, J. R., & Parker, G. A. (2014). Regulatory Forum Opinion Piece: What Are Pathology Raw Data? *Toxicologic Pathology*, 42, 469-471.
- Mann, P. C. (1996). Pathology Peer Review from the Perspective of an External Peer Review Pathologist. *Toxicologic Pathology*, 24, 650-653.
- Mann, P. C., & Hardisty, J. F. (2013). Peer Review and Pathology Working Groups. In W. M. Haschek, C. G. Rousseaux, M. A. Wallig, B. Bolon, R. Ochoa, & B. W. Mahler (Eds.), *Handbook of Toxicologic Pathology* (pp. 551-564). New York: Elsevier.
- McKay, J. S., Barale-Thomas, E., Bolon, B., George, C., Hardisty, J., Manabe, S., Schorsch, F., Teranishi, M., & Weber, K. (2010). Commentary on the Process of Peer Review and Pathology Data Locking. *Toxicologic Pathology*, 38, 508-510.
- Morton, D., Sellers, R. S., Barale-Thomas, E., Bolon, B., George, C., Hardisty, J. F., Irizarry, A., McKay, J. S., Odin, M., & Teranishi, M. (2010). Recommendations for Pathology Peer Review. *Toxicologic Pathology*, 38, 1118-1127.
- 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. Retrieved from [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem\(98\)17&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en)
- Organisation for Economic Co-operation and Development. (2002). OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 13. *Consensus Document of the Working Group on Good Laboratory Practice, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies*, ENV/JM/MONO(2002)9, 1-17. Retrieved from [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono\(2002\)9](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2002)9)
- Organisation for Economic Co-operation and Development. (2012). Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Testing Guidelines 451, 452 and 453, 2nd edition. Retrieved from <http://www.oecd->

- library.org/docserver/download/9714361e.pdf?expires=1499796237&id=id&accname=guest&checksum4=93CF16D9F5350A1D8807BFCDAE83868D
- [20] 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](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)30&doclanguage=en)
- [21] Organisation for Economic Co-operation and Development. (2016). OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 17. *Advisory Document of the Working Group on Good Laboratory Practice, Application of GLP Principles to Computerised Systems*, ENV/JM/MONO(2016)13, 1-33. Retrieved from [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)13&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)13&doclanguage=en)
- [22] Settiagounder, N. (2017). Histopathology Evaluation and Peer Review for Nonclinical Studies: Raw Data Compliance to GLP Quality Systems. *Journal of Regulatory Science*, 5(2), 45-55.
- [23] Tuomari, D., Elliott, G., Kulwich, B., Yarrington, J., Fouillet, X., Geoly, F., & Long, P. (2004). Society of Toxicologic Pathology Position on Histopathology Data Collection and Audit Trail: Compliance with 21 CFR parts 58 and 11. *Toxicologic Pathology*, 32(1), 122-123.
- [24] U.S. Environmental Protection Agency. (1983). Toxic Substances Control; Good Laboratory Practice Standards; Final Rule. Retrieved from <https://cdn.loc.gov/service/ll/fedreg/fr048/fr048230/fr048230.pdf>
- [25] U.S. Environmental Protection Agency. (1987). *Notice to Pesticide Applicants, Registrants and Petitioners* (PR Notice 87-10).
- [26] U.S. Environmental Protection Agency. (1989). *Good Laboratory Practice Standards*, 40 CFR § 160 & 792. Retrieved from <https://www.ecfr.gov/cgi-bin/text-idx?SID=e5f53f9ca071b342c182f09a9f961eda&mc=true&node=pt40.26.160&rgn=div5> and <https://www.ecfr.gov/cgi-bin/text-idx?SID=e5f53f9ca071b342c182f09a9f961eda&mc=true&node=pt40.35.792&rgn=div5>
- [27] U.S. Environmental Protection Agency. (1994). *Requests for Reconsiderations of Carcinogenicity Peer Review Decisions Based on Changes in Pathology Diagnoses* (PR Notice 94-5). Retrieved from <https://www.epa.gov/pesticide-registration/prn-94-5-requests-reconsiderations-carcinogenicity-peer-review-decisions>
- [28] U.S. Food and Drug Administration. (1976). Nonclinical Laboratory Studies Proposed Regulations for Good Laboratory Practice. Retrieved from <https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133725.pdf>
- [29] U.S. Food and Drug Administration. (1978). Nonclinical Laboratory Studies – Good Laboratory Practice Regulations. Retrieved from <https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133728.pdf>
- [30] U.S. Food and Drug Administration. (1987). Good Laboratory Practice Regulations; Final Rule, 21 CFR Part 58. Retrieved from <https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133730.pdf>
- [31] U.S. Food and Drug Administration. (1997). Electronic Records; Electronic Signatures, 21 CFR Part 11. Retrieved from <https://www.gpo.gov/fdsys/pkg/FR-1997-03-20/pdf/97-6833.pdf>
- [32] U.S. Food and Drug Administration. (2010). Good Laboratory Practices for Nonclinical Laboratory Studies (Advance Notice of Proposed Rulemaking), 21 CFR Part 58. Retrieved from <https://www.gpo.gov/fdsys/pkg/FR-2010-12-21/pdf/2010-31888.pdf>
- [33] U.S. Food and Drug Administration. (2016). *Considerations for Use of Histopathology and Its Associated Methodologies to Support Biomarker Qualification, Guidance for Industry*. Retrieved from <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285297.pdf>
- [34] U.S. Food and Drug Administration. (2016). Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule, 21 CFR. Part 16 and 58. Retrieved from <https://www.gpo.gov/fdsys/pkg/FR-2016-08-24/pdf/2016-19875.pdf>