
STP Position Paper

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Best Practices for Reporting Pathology Interpretations within GLP Toxicology Studies

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INTRODUCTION

The study pathologist provides specialized expertise to the interpretation of the toxicity and safety of pharmaceuticals, biological agents, human and animal food additives, environmental and industrial chemicals, and medical devices in animal studies. The study pathologist's findings and conclusions must be accurately and completely reflected in the study report. The pathology findings also must be integrated with other study data to provide a comprehensive discussion of toxicity and/or pharmacology of a chemical, device, or material and the relationship of toxicity to exposure. The Society of Toxicologic Pathology (STP) offers the following recommendations to help pathologists, study directors, other study personnel, management, and sponsors guarantee the quality and reliability of pathology data and interpretations incorporated within animal toxicology studies. In this paper, "pathologist" refers to both anatomic and clinical pathologists unless otherwise specified.

The Study Pathologist Should Review and Contribute to the Study Protocol

Whenever possible, the study pathologist(s) should review and/or contribute to the generation of the study pro-

col and should ensure that the pathology components of the protocol reflect appropriate scientific methods and current standards of pathology practice. If the study pathologist is not available to contribute to the protocol, it is recommended that another pathologist review the protocol prior to final approval. Although there is no regulatory requirement for the study pathologist to sign the study protocol, the pathologist's signature on the protocol can be useful to ensure agreement with the scientific objectives and methods of the study.

Authors of the Pathology Report

GLP regulations require that a study pathologist or any other scientist who generates and/or interprets anatomic and/or clinical pathology data must have the education, qualifications and experience to perform these tasks and (in collaboration with the study director) to integrate pathology findings with clinical signs, exposure information, and other study information. Study pathologists must understand the normal biology, background findings, and responses to various types of injury in the species evaluated. Although board certification in a pathology discipline is a desirable credential, the STP recognizes that many competent study pathologists are not board certified. A facility performing regulated nonclinical studies must ensure that all study personnel, including study pathologists and other scientists performing specialized pathology techniques (e.g., morphometry, ultrastructural evaluations, etc.), are qualified and competent to

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perform their assigned tasks according to prevailing regional or national standards.

Contents of the Pathology Report

Study pathologists usually evaluate gross necropsy findings, microscopic findings, and (if present) ultrastructural findings and they often evaluate clinical pathology and organ weight data. Best practices for microscopic evaluation of tissue sections have been reviewed (Crissman et al., 2004). Prior to beginning evaluation of the microscopic slides, the study pathologist(s) should have access to the study protocol and all protocol amendments, clinical signs, body weight and food consumption data, clinical pathology data, organ weight data, necropsy observations, the relevant biology of the target molecule (e.g., tissue distribution and function of the target molecule, if known), and information about expected activity and known toxicity of the test article. Pharmacokinetic data (if appropriate for the study) should be provided to the pathologist prior to the completion of the pathology report so that pathology findings can be interpreted in the context of test article exposure. Specific components that should be included in any pathology report for a GLP-compliant general toxicology study include:

- Table of contents and/or hyperlinks that allow quick and clear access to narrative sections and data tables. These components may be included in the table of contents of the final study report.
- Methods (described in the pathology report or as a reference to the protocol) including the responsibilities of the pathologist(s) and other contributing scientists. Any supplemental pathology techniques (special sectioning or staining, immunohistochemistry, manual or computerized morphometry, ultrastructural evaluation initiated in response to a microscopic finding, etc.) should be documented.
- Individual animal data and summary data tables (usually attached as appendices) for all data primarily generated or evaluated by the pathologist unless these data are presented in full as other components of the final report. Statistically significant findings should be clearly identified in the summary tables and/or in the report text. Microscopic observation summary tables should be subdivided by severity when severity information is helpful or necessary to interpret specific findings. Summary tables containing all microscopic observations subdivided by severity scores (for findings scored for severity) should be considered. When severity grading is important to the understanding of major study findings, it may be useful to provide a description of the distinguishing features of each severity grade. Supplementary tabular or graphic data representations embedded into the narrative often are useful to illustrate and summarize specific findings without requiring the reader to look up information in the regular data tables. The STP encourages the use of customized tables and/or graphic data within the narrative of the report whenever these figures contribute to a better understanding the pathology findings.
- A clear description of treatment-related findings, their significance, and their relationships to corresponding information in control animals. This description should include relationships between various significant study findings (e.g.,

in-life findings, gross findings, body weight changes, organ weight changes, clinical pathology changes, and microscopic findings). Conventional (film-based) or digital images of characteristic gross, microscopic, or ultrastructural findings may be included in the report, but are not required.

- Clear reasons for deciding that specific observations are not related to treatment or are not biologically and/or toxicologically meaningful. Whenever supporting information is available, scientific references and/or study data should be used to support these conclusions.
- When possible, integrated mechanistic or pharmacologic explanations of the physiologic and/or pathologic relationships of specific findings.
- A concise summary identifying the major pathology findings and/or target organs that guide risk assessment and the doses or exposures at which these findings occur.
- Appropriate references from scientific literature that support the interpretations and conclusions based on study information. References that link specific findings to pharmacologic or toxic mechanisms or support conclusions that findings are not adverse should be provided whenever possible. If historical control data are described within a report, these data should be included in the report.
- The signature of the study pathologist(s). If more than one study pathologist contributes to the evaluation of pathology data, the contributions of each should be clearly identified and each must sign the report containing his/her contributions. The peer review pathologist is not required to sign the report (see Pathology Peer Review section next).
- Other documentation (quality assurance statement, compliance statement, etc.) required by GLP regulations unless this information is provided in the final study report.

Pathology Peer Review

The STP recommends that selected microscopic slides from pivotal general toxicology studies should be reviewed by a second pathologist prior to the signing of the pathology report (Society of Toxicologic Pathologists, 1991). The STP further recommends that the entire pathology narrative should be peer reviewed. If a formal pathology peer review is performed, this peer review should be documented in the study report (Society of Toxicologic Pathologists, 1997). The peer review pathologist is not required to sign the study report, but should prepare and sign a peer review statement clearly describing all materials reviewed, indicating that major discrepancies have been resolved, and reflecting the general agreement of the peer review pathologist and the study pathologist on the interpretation of the pathology findings.

The Study Pathologist Must Sign a Separate Pathology Report or an Integrated Report Containing the Pathology Narrative

The pathologist(s) who performs the primary analysis and interpretation of pathology data should be identified in the study protocol and/or report and must sign a report that includes the data generated and evaluated and the pathologist's interpretations. The study pathologist's signature on the report reflects concurrence with the study

data and interpretations for which the pathologist takes responsibility.

The Form of the Pathology Report

Toxicology laboratories generally issue either (1) an integrated final study report that is signed by both the study director and the study pathologist(s) or (2) a separate pathology report signed by the study pathologist that is appended to the final study report. With either report format, it is essential that the pathologist and other contributing scientists provide an integrated assessment of significant study findings including clinical findings, clinical pathology information, organ weight data, anatomic pathology findings, and pharmacokinetic data. The STP believes that either integrated study reports (which contain contributions of the study director, pathologist(s), and perhaps other expert contributing scientists) or separate, appended pathology reports can be accurate, comprehensive, and GLP compliant. Either form of report should provide the necessary individual animal data tables, summary data tables, pathology narrative containing integration of pathology findings with all other study data, and clear accountability for primary evaluation and interpretation of pathology data. Regardless of the methods used to report pathology findings, the reporting process must preserve the integrity of the interpretation of morphologic and clinical pathology findings.

It has been suggested that a separate signed pathology report appended to the final study report provides for better individual accountability for interpretation of pathology data (Vishwanathan, 2005). A separate pathology report does not preclude an integrated assessment of all study information. If a separate signed pathology report is created, the STP recommends that the study pathologist(s) also should contribute to the final study report to ensure that all treatment-related pathology findings are accurately described and correlated with other study information.

Many toxicology laboratories and product sponsors favor the use of an integrated study report because they believe that the integrated report written jointly by the study director, study pathologists (anatomic and/or clinical), and other contributing scientists provides the most comprehensive, consistent, and accurate interpretation of all study data. The contributors to an integrated report share the construction of the report's discussion, conclusion, and abstract (executive summary). Since the report abstract (executive summary) and tabular summary (CTD tables) often are used in isolation by sponsors and regulators to quickly understand and summarize study findings, the pathologists' contributions to these report components improve the study report and ensure that the study pathologists' interpretations are accurately reflected in all study documentation. If the pathology report is integrated into the final study report and no separate pathology report is prepared, the same data tables, pathologist's interpretations, and pathologist's conclusions that would exist in a separate pathology report must be included in the integrated report.

Best Practices for Pathology Report Generation

In order to ensure the integrity and accurate interpretation of pathology data within study reports, the STP recommends that:

- Whenever possible, the study pathologist(s) should contribute to generation of the study protocol.
- It is a management responsibility of the organization conducting the study to ensure that individual accountability and responsibility of all study personnel including the study pathologist(s) are clearly defined in the study protocol and/or final report. When 1 study pathologist interprets clinical pathology data and another interprets anatomic pathology data, or when 2 pathologists share the evaluation of the anatomic pathology data, the roles of each should be clearly described.
- The study pathologist(s) should have primary responsibility for interpretation of assigned pathology data (including necropsy findings, microscopic findings, and ultrastructural findings and usually clinical pathology and organ weight findings).
- The study pathologist should have access to the study protocol and all protocol amendments, all study data including the intended pharmacologic target and mechanism of action, in-life study data, clinical pathology data, organ weight data, necropsy findings, toxicokinetic information, and (when possible) data from previous studies with the same test article.
- The study pathologist should carefully review all pathology individual and summary data tables that she or he is responsible for generating and interpreting.
- Either an integrated study report containing the pathology narrative and tables or a separate pathology report can provide appropriate accountability and integration of all study data. Clear and open communication between the study director and the study pathologist(s) is the key to accurate interpretation and integration of study data.
- The study pathologist should assist the study director in writing and/or reviewing the final study report, including the discussion, conclusion, and abstract (executive summary), to ensure that pathology findings and interpretations are accurately presented. When feasible, integration of pathology findings with other study data should be done jointly by the pathologist, study director, and/or other contributing scientists.
- The study pathologist must sign a separate pathology report or an integrated study report. If two individuals have primary responsibility for evaluating different data sets (e.g., clinical and anatomic pathology data), both must sign a report (separate or combined) that includes their assigned contributions. If a pathologist creates a separate pathology report and contributes to the final study report, the pathologist must sign the separate pathology report. The STP suggests that the study pathologist(s) who contributes to both separate and integrated reports also sign the final study report, however this signature is optional because the study pathologist's findings will be clearly documented in the separate report. The pathologist's signature on either type of report signifies that the pathologist approves all pathology-related data tables and the narrative sections for which the pathologist is primarily responsible, including correlation of pathology data with other study information in all sections of the report. The STP suggests that the meaning of the pathologist's signature on the integrated report be described on the signature page of the report and/or in the study protocol.

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REFERENCES

- Crissman, J. W., Goodman, D. G., Hildebrandt, P. K., Maronpot, R. R., Prater, D.A., Riley, J. H., Seaman, W. J., and Thake, D. C. (2004). Best practices guideline: toxicologic histopathology. *Toxicol Pathol* **32**(1), 126–131.
- Society of Toxicologic Pathologists (1991). Peer review in toxicologic pathology: some recommendations. *Toxicol Pathol* **19**(3), 290–292.
- Society of Toxicologic Pathologists (1997). Documentation of pathology peer review. *Toxicol Pathol* **25**(6), 655.
- Vishwanathan, C. T. (2005). FDA perspectives on current issues in GLP. Presentation at Society for Quality Assurance Regulatory Forum, Baltimore, MD.