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## Industry–Contract Research Organization Pathology Interactions: A Perspective of Contract Research Organizations in Producing the Best Quality Pathology Report

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### ABSTRACT

This article provides observations on the features of sponsor–contract research organization communication that will achieve the best quality pathology report based on our collective experience. Information on the test article and any anticipated findings should be provided, and initial slide examination should be done with knowledge of treatment group (but may be followed by blinded review of target tissues to determine no-effect levels). Only a pathologist should write or revise the pathology report or the pathology section of the overall study report. To address concerns related to undue sponsor influence, comments by sponsors should be presented as suggestions rather than directives. Adversity should be defined for each finding by the study pathologist, but the no-observed adverse effect level should not be discussed in the pathology report. Board-certified pathologists are recommended, but are not essential. Sponsors that have a particular format or report preferences should make them known well in advance. Histologic processing “to glass” of protocol-specified tissues from all dosage groups is recommended for rapid evaluation of target tissues. Telepathology is beneficial in certain situations, but it is usually more efficient for the study pathologist and reviewing pathologist to be in the same physical location to review differences of opinion and reach a consensus.

*Keywords:* preclinical safety assessment/risk management; regulatory affairs; toxicologic pathology.

### INTRODUCTION

Interactions between sponsors and study pathologists at contract research organizations (CROs) are vital to the reporting and interpretation of toxicologic pathology findings. This commentary is the result of discussions among CRO pathologists as to how these interactions can be optimized to produce a best-quality pathology report. This document describes not only typical but also suggested practices for researchers when working with toxicologic pathologists at CROs.

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### DISCUSSION

*The Debate About Whether Providing the Study Pathologist With Knowledge About the Test Article as Well as Anticipated Toxicology Findings Enhances the Quality of the Interpretation or Unnecessarily Biases the Interpretation*

There are no doubts that knowledge about the test article, including its class and pharmacological activity, helps the study pathologist and the reviewing pathologist in his or her interpretation of the findings. This information, along with anticipated clinical pathology and anatomic pathology findings, will minimize the risk of missing or misinterpreting subtle changes.

There are both positive and negative aspects to the practice of providing the study pathologist with background information. More often than not, the advantages outweigh the possible disadvantages. There have been situations in which a pathologist misinterpreted normal tissue variation as a lesion because he or she expected to see a lesion based on the pharmacological

class of the test article. However, there are many more examples of situations in which a pathologist has overlooked subtle findings or dismissed findings as not being test article related because he or she was not fully informed about the class of test article or was not provided with the expected target organs or known findings from previous studies.

Providing relevant data to the study pathologist makes communications more efficient with the sponsor and avoids irrelevant discussions when reviewing the report. This exchange of information is mutually beneficial. The information helps the study pathologist to focus on expected target tissues and lesions. The sponsor benefits in terms of an expedited report with improved scientific content, which will define the potential toxicity of the test article, will identify affected dose levels, and may lead to interpretation of the pathogenesis or mode of action of lesions associated with test article exposure. Additionally, knowledge of findings in previous studies is particularly useful in that it allows the study pathologist to harmonize the terminology for specific findings with previous studies. The use of standardized terminology for pathology observations between multiple studies facilitates the peer review process and avoids confusion when discussing findings with the sponsor.

The information that is important for the study pathologist to obtain before the initiation of microscopic evaluation includes the following:

1. Nature of the test article and known activities of this class of compounds.
2. Results of any previous toxicology studies with the test article. Whether in the same species or different species, knowledge of target organs/tissues and the types of changes previously encountered facilitates the evaluation of tissues and provides for the consistent use of terminology.
3. Metabolic, pharmacokinetic, or toxicokinetic information may be necessary for understanding patterns of changes and interpreting differences in species responses.
4. In-life data (i.e., clinical signs, body weight changes, feed consumption) from animals may greatly help in the identification of target organs and in understanding mechanisms of toxicity.
5. Clinical pathology data may add necessary perspective for the identification of target organs, contribute to an understanding of the mechanism of action, and indicate whether it is possible to clinically monitor a pathology process. Results of special assays such as hormone concentrations or enzyme induction are also important to understand the significance of some histopathologic changes.
6. Necropsy (gross) findings and organ weight changes for individual animals and dosage groups (Crissman 2004).

*Recommendation:* Knowledge about the test article, including its class and pharmacological activity and the findings from

previous studies, is crucial and helps the study pathologist in his or her interpretation of the findings. Study pathologists should have access to the same background information on the test article as is available to the sponsor.

#### *Requests for Blinded Initial Histopathologic Evaluation*

Blinded evaluation of slides (evaluation without prior knowledge of treatment) is occasionally requested by sponsors (and some regulatory officials) with the goal of reducing study pathologist bias. Blinded analysis, a common laboratory practice, is extensively used in clinical trials of candidate pharmaceutical products. Although blinded evaluation certainly has a place in toxicologic pathology, there are distinct negative aspects to blinded evaluation in the primary examination of tissues from toxicology studies. Without knowledge of treatment groups, the study pathologist is not able to use the controls to define the threshold of background lesions. Practical issues including preparation of slides, recording of findings, and decoding, to name a few, may complicate the process. In addition to extending the time required to perform histopathologic evaluation, an initial blinded evaluation may negatively affect the quality of the assessment.

There is a consensus among pathologists not to perform blinded evaluation for the initial examination because the positive aspect (prevention of bias) of the blinded evaluation of an entire study will certainly not outweigh the negative attributes. Since knowledge about the test article, treatment groups, and anticipated findings is believed to assist the study pathologist in his or her examination, using blind evaluation may cause the study pathologist to miss subtle changes. However, blinded evaluation of target organs, once identified, is a recommended common practice that helps to avoid diagnostic drift, reduces the potential for bias in the histopathologic evaluation, and assists in the identification of no-effect levels.

*Recommendation:* Blinded evaluation should not be performed for the initial histopathology evaluation and should be restricted to the evaluation of target organs once identified.

#### *Practices That Contribute to a Productive Peer Review*

The primary objective of a pathology peer review is to ensure the consistency and accuracy of diagnoses as well as to confirm that all target tissues are identified, all of which leads to increased quality of the final pathology diagnoses and interpretations. Despite the lack of mandated requirements for pathology peer review, both sponsors and regulatory agencies acknowledge that collaborative review by more than one pathologist increases confidence in the accuracy of the pathology diagnoses and the quality of the pathology interpretations.

The pathology report should be available to the reviewing pathologist. It is beneficial for the reviewing pathologist to examine the report and the tables prior to the peer review. The reviewing pathologist should also be aware of the background information associated with the test article or other test articles with a similar mechanism of action.

The reviewing pathologist should be experienced in how to conduct a peer review (i.e., follows Society of Toxicologic Pathology guidance).

The objectives of a formal histopathology peer review (prospective or retrospective) are several: (1) determine accuracy and consistency of nomenclature (i.e., survey for the presence of incorrectly diagnosed or inaccurately described treatment-related lesions); (2) determine completeness (i.e., survey for the presence of undiagnosed treatment-related lesions); (3) determine the appropriateness of the no observed effect level (NOEL) or no observed adverse effect level (NOAEL) by reviewing all target tissues and organs; and (4) review the correctness of the textual interpretation derived from those data. The intention of the peer review is not the corroboration of every detail of every histology finding; rather, it is to ensure that test article-related findings are properly identified, consistently diagnosed, and correctly interpreted (Crissman 2004).

It is most beneficial to have an experienced reviewing pathologist, whether internal or external, whose aim is to determine whether the study pathologist identified all test article-related findings and whether there is consistent use of terminology, particularly for test article-related findings. Therefore, it is helpful when the reviewing pathologist has access to the terminology used in previous studies to ensure consistency between studies. The reviewing pathologist should concentrate on findings that have an impact on the study outcome rather than minor differences in thresholds of recording changes. The reviewing pathologist should refrain from cataloguing incidental lesions or biological variation. These are not pertinent to the primary goal of the peer review, which is to identify test article-related findings and affected dose levels.

Appropriate time should be allocated to perform the pathology peer review. Peer review takes place soon after the initial evaluation by the study pathologist. The reviewing pathologist should have a standard means of documenting any disagreements, discuss them with the study pathologist over the microscope if necessary, and ensure that the study pathologist provides a written response. After the review, if there are some substantive differences in pathologic interpretation with the study pathologist, it is more efficient to be in the same physical location to review the comments and slides than discussing them by phone or mail. Although telecommunication is feasible, when there are substantive remarks, it is time-consuming and the review of selected slides is obviously more difficult without a multi-head microscope (telepathology using digital images may be beneficial).

*Recommendation:* The reviewing pathologist should be aware of the background information associated with the test article. As he or she should be experienced in how to conduct a peer review, he or she should concentrate on findings that have an impact on the study outcome rather than minor differences in

thresholds of recording changes. Appropriate time should be allocated to perform the pathology peer review phase of the study.

#### *Practices That Can Be Implemented to Minimize the Amount of Editing Needed on Draft Toxicology and Pathology Reports*

As mentioned above, the study pathologist will eventually need to know the biological activity of the test article before she or he can make meaningful interpretations of findings. Providing this information earlier in the process will make report preparation and review more efficient. If sponsors have a particular format or preferences for reports (e.g., report order, tabulation), they should make those preferences known to the CRO well in advance of report preparation. Ideally, those preferences would be provided to the CRO no later than the date the study protocol is signed.

During the review of the draft toxicology/pathology report, which is the CRO's deliverable, the sponsor should focus on content, not writing style. Changes to the pathology data/report that are not relevant to the toxicity of the test article should be avoided. Redirecting the emphasis to the incidental or non-test article-related findings instead of test article-related changes should also be avoided. The CRO scientists should write in clear English, business style, and be trained on basic rules of reporting of regulatory toxicity studies (e.g., OECD 2002). In many cases, too much time is wasted on writing style. Most CROs have procedures in place to accommodate sponsor-specific formats and preferences, but it is not possible to accommodate the personal preferences of the myriad of individual reviewers. An internal review by senior scientists within the CRO is highly recommended prior to sending the draft report to the sponsor.

For the final toxicology report, which includes the pathology report, the sponsor study monitor should compile the sponsor comments before they are sent to the CRO study director and contributing scientists for their consideration. If there are several sponsor scientists involved, it is more efficient to group and send all their comments at the same time, and not individually, to avoid unnecessary repetition or contradictory comments. Waves of comments from the sponsor are inefficient, since the CRO is often working under short timelines. Although scientific input from reviewers is always welcome, it is considered inappropriate and unacceptable for anyone other than a pathologist to rewrite the pathology section of the report.

*Recommendation:* If sponsors have a particular format or preferences for reports (e.g., report order, tabulation), they should make those preferences known to the CRO well in advance of report preparation. The sponsor should focus on content, not writing style. The sponsor study monitor should compile the sponsor comments before they are sent to the CRO study director and contributing scientists for their consideration. To avoid unnecessary repetition or contradictory comments, it is more efficient to group and send all the comments at the same time and not individually.

### *Common Practices of Sponsors That Detract from Receiving a High-Quality Pathology Interpretation in a Timely Manner*

As discussed above, sponsors that require studies to be reported with no information on previous studies or the biological activity of the test article are more likely to receive a lower quality pathology report that may require revision of reports and/or re-examination of slides. Also, repeated stylistic changes to verbiage will likely result in unnecessary delays. This is the reason we recommend that the sponsor's reviewing pathologist be involved both with the writing of the study protocol and early in the slide reading to aid in nomenclature development.

The sponsor's intention to lower costs required for histologic processing and subsequent evaluation can influence the quality of pathology reports and an increase in project duration. It is common practice for protocols to require histologic processing and histopathologic examination of tissues from high-dose and control animals prior to histologic processing of tissues from intermediate-dosage groups. This practice, though it curtails costs to a minor degree, inevitably leads to: (1) delays in completion of the study; or (2) processing and examination of target organs in haste, with the attendant increase in errors and overtime labor costs for the CRO; and (3) possible reduction in overall study quality. Histologic processing and slide preparation of tissues from all dosage groups at the onset of the histology phase is recommended whenever financially feasible.

By their very nature, target tissues may not be known at the start of a study. Once target tissues are identified by the study pathologist and approved by the study director and sponsor, there is a rush to process, examine, and incorporate findings into the pathology report by a predetermined report date. In the interest of reducing overall pathology turnaround time, it is often desirable to have slides from high-dose and control tissues sent to the study pathologist for examination during the same time period the intermediate dosage group tissues are processed through histology. As a result of this practice, the intermediate-dose target organs are typically available to the study pathologist immediately after completion of the high-dose and control group examination.

Eliminating the delays in histologic processing and histopathologic examination of target organs can easily save one to two weeks in overall study completion time. Processing of intermediate dosage group tissues to block stage rather than slide stage is also helpful in situations in which financial or other constraints prohibit preparation of glass slides from all protocol-specified tissues at the onset of the histology phase. Having paraffin blocks available immediately upon identification of target tissues allows the study pathologist to examine target tissues within one to three days of target tissue identification, as compared to one to two weeks if the histology team must start from scratch when target tissues are identified.

Sponsors may request preliminary data from one or two organs, but they need to understand that some results may change within the context of the full evaluation. In nonrodent studies, sponsors may request that the first evaluation be

performed only in control and high-dose animals. Thus, interpretation of findings or incidence is more difficult because of the low number of animals. Similarly, piecemeal or partial reports for information sharing that have not been subjected to in-house quality control review are also prone to late-stage changes. In studies that have interim and final sacrifices, the release of interim results prior to the final audited pathology report may also lead to some differences when the final pathology report is issued. Sponsors must understand that pathologists ultimately evaluate studies, not individual tissues or animals.

Time to delivery of the pathology report is also a critical consideration. Many CRO study pathologists already face a shortened time period to evaluate slides owing to previous study delays, but there is still an expectation to maintain high quality. Timelines that become shorter and shorter generally have an adverse affect on the overall quality of the product. These issues commonly come to a head with regard to target tissue examination and incorporation of peer review findings into the pathology report. A large histology facility typically can handle two to five target tissues in an expedited fashion, presuming the targets are not bones or teeth from large animals, but identification of twenty-five to thirty target tissues can result in consternation.

Delays in pathology report completion also result from the common practice of performing cytologic examination of bone marrow smears only upon detection of histopathologic alterations in sections of bone marrow. Cytologic examination of bone marrow is very labor intensive and should not be attempted in haste at the time the pathology report is near completion. The requirement for cytologic examination of bone marrow smears should be incorporated into the study protocol whenever known pharmacologic action or results of previous studies suggest a bone marrow effect.

*Recommendation:* Histologic processing of tissues to blocks or slides from intermediate-dose groups should be performed along with tissues from high-dose and control animals, particularly if the potential target tissues are known or suspected from prior studies. This practice, though it increases costs to a minor degree, leads to: (1) shortened study completion time, (2) processing and examination of target organs in a timely manner, and (3) possibly increased overall quality. Cytologic examination of bone marrow smears should be included in the original study protocol whenever there is suspicion of bone marrow effects. Since pathologists ultimately evaluate studies, not individual tissues or animals, sponsors must understand that preliminary data are for information only and are subject to change prior to the final audited pathology report.

### *Study Pathologist Involvement in Authoring and Review of the Integrated Toxicology Report*

In laboratories that use an independent, "stand-alone" pathology report, the study pathologist should author the pathology report and have full responsibility for the content of that report. The study pathologist should be consulted by the

study director on any issues relating to pathology and should provide input on conclusions drawn from the pathology data. Study pathologists should not be placed in the role of auditor to ensure that their interpretations are accurately incorporated into the overall study report. The study director is responsible for determining that reports of contributing scientists, including the pathology report, are accurately translated into the study report.

In laboratories that use “integrated” reports, in which pathology is discussed along with other aspects of the study, and the study pathologist signs the overall study report, the study pathologist is responsible for ensuring pathology interpretations are accurately reflected in the overall study report. Experience suggests that integrated reports have a distinct potential for errors in translation; therefore, sufficient time and resources must be available for the study pathologist to perform a thorough review of the study report before signing the report.

*Recommendation:* The study pathologist should author the pathology report and have full responsibility for the content of that report. If the pathology report is a separate signed pathology subreport, the study director is responsible for ensuring appropriate incorporation into the toxicology report, and the study pathologist should not be requested to sign the toxicology report. If the pathology report is integrated into the toxicology report, the study pathologist should be asked to cosign the toxicology report and should be given appropriate time to review the report.

#### *Appropriate Current Use of Digital Pathology or Telepathology in Pathology Peer Reviews*

The use of virtual slides (scanned digital images) has a distinct place in the conduct of peer reviews. Most pathologists agree that digital pathology will eventually be preferred to shipped slides. The benefits of using digital pathology include decreased shipping cost, faster turnaround time, and elimination of fear of losing or breaking slides. In addition, with the time saved on travel, it should be possible to identify randomly selected animals for full-tissue peer review at any time after the slides are prepared so the peer review of those slides can take place before the review of target organs. Owing to a variety of technical and regulatory considerations, virtual slides are not yet appropriate for first examinations in Good Laboratory Practice (GLP) studies. That is anticipated to change as improved technology allows for faster scans and regulatory decisions are reached regarding the acceptability of data based solely on examination of virtual slides. Many pathologists agree that the entire peer review of a large study is inefficient using scanned digital images. A review of selected slides for a targeted discussion during peer review, for example, would be more appropriate. Even though it is recommended to have a face-to-face discussion over a microscope, often minor differences can be resolved with a brief teleconference between the study and reviewing pathologists.

Telepathology is useful for discussions of a few selected slides—for example, during the reading of a study, prior to completion, when a highly significant, possibly test article–related change is discovered. Sponsor study monitors may prefer photomicrographs that can easily be used for internal presentation. These photomicrographs should be clearly labeled as being for illustration only, and not for interpretation. Without telepathology, when a sponsor requests photomicrographs of unexpected or interesting lesions, it may require an excessive amount of the study pathologist’s time; with telepathology, once the slides are digitized, it is easy to send images to the sponsor or, better yet, allow sponsors to have remote access to the virtual slides so they may review slides as they wish.

*Recommendation:* The use of scanned digital images may reduce the shipping costs of peer reviews and may hasten their completion, but the entire peer review of a large study is currently inefficient using scanned digital images. A review of selected slides for a targeted discussion would be more appropriate. As technology improves, virtual slides may be more appropriate for peer review or even first examination of large GLP studies.

#### *Pathology Reports Containing Interpretive Versus Descriptive Language or Conclusions*

Pathology reports should be carefully segregated into Results versus Discussion sections. The Results section, which is based on the underlying lesion records, should be entirely factual and descriptive, with as little interpretation as possible (e.g., hepatocellular vacuolation, not vacuolar degeneration). This is the purely technical area of the pathology effort, and it must be very accurate and as precise as possible. However, the Discussion section, with its interpretations, proposed pathogenic mechanisms, discussion of adversity, and relation of lesions to the pharmacology of the compound, is the area in which a well-trained pathologist can make the most substantial contribution to the report and the overall effort of the toxicology study. In most cases, the organ weights, clinical pathology, and histopathology alterations are clearly evident, but what these alterations may mean with regard to human risk is another matter.

Based on the descriptive data, the study pathologist must relate the findings to the administration of the test article, stress associated with test article administration, or to background spontaneous findings; he or she will provide an interpretation on the adversity of findings. If the pharmacology is known, findings could be related to the test article’s activity, including the exaggerated pharmacologic effects. Additional interpretative comments, including pathogenic mechanisms, should be included if they are based on the study data and not speculative assumptions. The study pathologist needs to be cautious when writing interpretative comments if the information provided is incomplete or missing; sponsors should not request that the study pathologist speculate unreasonably. The study

pathologist should be comfortable making interpretative comments regarding pathogenesis of test article-related observations if it is an area in which he or she has particular expertise. Study pathologists should refrain from textbook or literature suggestions of possible pathogenesis unless the cited literature is directly applicable to the study.

Since pathology is a subjective science that uses variable descriptive terminology rather than rigid data, it is very important that the study pathologist who generates the descriptive data is the one who interprets the data and puts them into perspective rather than leaving it to the CRO study director, who is often a toxicologist and who may not be familiar with the subtle nuances of the pathology terminology and grading. Pathogenesis of lesions caused by test articles that are more likely to be speculative and unpublished should not be part of the pathology report. Well-characterized background findings may be discussed if cited in the literature. Adversity of a specific finding can also be discussed, as guidelines have been published (Lewis 2002; Dorato and Engelhardt 2005).

The NOAEL is a studywide concept that incorporates, in addition to pathology, clinical observations, clinical pathology, and other toxicological end points; this should not be discussed in the pathology report. Regarding the identification of NOEL/NOAEL or exaggerated pharmacology, the CRO study director should take into account all of the study data. Discussion about the mechanism of action or pathogenesis of the lesions may require the sponsor's input, since the sponsor should have more extensive knowledge about the test article or similar test articles.

*Recommendation:* The Results section, which is based on the underlying lesion records, should be entirely factual and descriptive, with as little interpretation as possible. The pathologist receiving comprehensive information about the test article is in the best position to interpret the findings in a section clearly labeled as Discussion, not Results. The NOAEL for the entire study should not be discussed in the pathology report; any discussion of NOAEL should be limited to the context of the pathology findings.

#### *Board-Certified Versus Nonboarded Pathologists*

Occasionally, sponsors specifically request, and sometimes insist, that a board-certified pathologist read their studies. Board-certified pathologists are recommended, but are not essential for the reading of regulatory toxicology studies (Crissman 2004). In North America, for example, certification is typically earned by examination after three years in a residency training program in anatomic pathology, which is not specifically focused on laboratory species or experimental disease. The skills and knowledge needed to interpret the results of preclinical safety assessment studies require additional training and experience, gained over a period of several years working in an industrial setting under the mentorship of an experienced toxicologic pathologist. Certification in anatomic veterinary pathology, in and of itself, is not, therefore,

synonymous with competency in toxicologic pathology. The number of years the pathologist has evaluated slides and interpreted data in an industrial setting and the quality of the mentorship he or she has received during this time may be better predictors of competency than formal pathology certification. Sponsors that insist on using only board-certified pathologists may unknowingly be denying themselves the expertise of a highly qualified pathologist and effectively forcing the CRO to assign their studies to a pathologist who may have passed the board exam, but who may not yet have the experience necessary to handle that particular study.

To remain competitive, CROs have to retain high-quality pathologists. In the future, perhaps all North American- and European-trained toxicologic pathologists will be American College of Veterinary Pathology (ACVP) or European College of Veterinary Pathology (ECVP) certified, but in today's environment, there are many competent toxicologic pathologists practicing in North America and Europe who are not certified but may have many years of experience. Sponsors are usually more willing to work with noncertified pathologists after they have developed long-term relationships with CROs and gained confidence in the work they generate.

Ideally, the sponsor should give the CRO management the flexibility to select the most qualified or appropriate study pathologist for the study or project. In pairing a pathologist with a particular study, CRO management must be free to consider the technical and scientific expertise of the pathologist for the particular route of administration (e.g., inhalation, infusion, dermal administration, or intravitreal injection). They must also consider the pathologist's in-depth knowledge of the targeted organ system for the test article to be administered, prior interactions with the client, prior experience with the client's test article or with test articles that have a similar mode of action, as well as the workload and training of the individual pathologists.

We would recommend that sponsors ask more specific questions about how the CROs train and evaluate their pathologists. Each CRO has its own training program, which is basically intensive, on-the-job experience in the practice of toxicologic pathology under the direct supervision of an experienced senior pathologist(s). Mentoring and coaching of toxicologic pathologists, both young and old, should continue throughout their careers. The tools most frequently used by CRO management are in-house peer review of slides and pathology reports by senior scientists. Slide sessions at the multi-headed scope, journal clubs, regional one-day scientific meetings, and scientific conferences are additional opportunities for continuing education. These experiences are important in the development of a pathologist's skills and should be considered by sponsors when they evaluate a CRO's pathology services.

Sponsors also occasionally request a board-certified pathologist to be present at necropsy for all animals from regulatory toxicology studies. In this capacity, the study pathologist is on hand to examine gross lesions, give guidance on how to record the findings, and ensure that subtle changes are not overlooked by the necropsy technicians. Equally important, it is the study pathologist's responsibility to ensure the description of

variation in the normal appearance of tissues, including size and color, are not included as diagnoses, since doing so often results in meaningless microscopic correlations. Although the desire to have a pathologist attend necropsies is understandable, the use of board-certified or highly experienced pathologists in this capacity is more costly and not always necessary. These functions may be adequately and economically performed by veterinarians who have necropsy experience, but who are not board-certified toxicologic pathologists. However, experienced toxicologic pathologists should be readily available to the necropsy team should questions arise. "Readily available," in this context, would mean within the same building as the necropsy unit, though not necessarily in the same room.

A sponsor's request for a necropsy pathologist may be successfully fulfilled by employing veterinary pathologists after their post-residency years, while they can divide their time between attending necropsies and studying for boards. It is also possible that a clinical veterinarian with industry experience and some pathology training could also serve in this capacity in consultation with, and under the direct supervision of, an experienced toxicological pathologist.

*Recommendation:* Board-certified pathologists are recommended, but are not essential for the reading of regulatory

toxicology studies. During necropsies, experienced or board-certified toxicologic pathologists should be readily available to the necropsy team should questions arise, even if they are not necessarily in the same room.

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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**, 126–31.
- Dorato, M. A., and Engelhardt, J. A. (2005) The no-observed-adverse-effect-level (NOAEL) in drug safety evaluations: use, issues and definition(s). *Regul Toxicol Pharmacol* **42**, 265–74.
- OECD (2002). *Guidance Notes for Analysis and Evaluation of Repeat-Dose Toxicity Studies*, OECD Series on Testing and Assessment, No. 32, OECD Publishing. doi: 10.1787/9789264078482-en.
- Lewis, R. W., Billington, R., Debryune, E., Garner, A., Lang, B., and Carpanini, F. (2002). Recognition of adverse and nonadverse effects in toxicity studies. *Toxicol Pathol* **30**, 66–74.