Pathology Peer Review and the OECD Guidance on the GLP Requirements: A Review of the Review

Jim Fikes, DVM, PhD, DACVP, DABVT
Director of Comparative Pathology
Biogen
jim.fikes@biogen.com

Dan Patrick, DVM, DACVP, DABT
Director of Pathology
MPI Research
daniel.patrick@mpiresearch.com

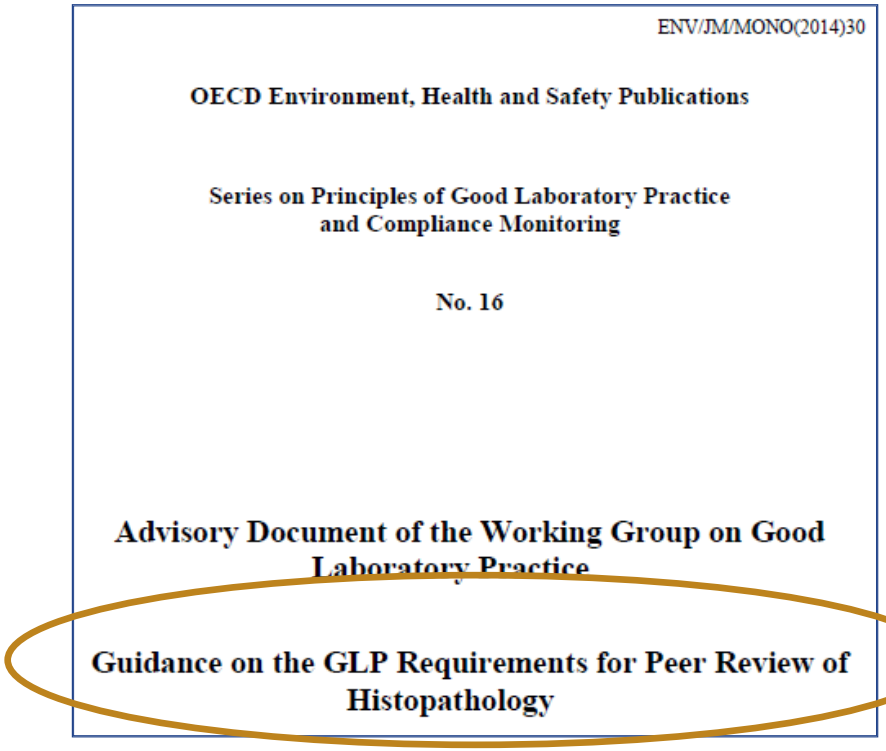
Outline

- Pathway leading to the Guidance and Review
- What is peer review (PR)
- Guidance Section 1 – Background
- Guidance Section 2 – GLP Requirements
- Guidance Section 3 – GLP Compliance of Peer review
- Questions

Evolution of the OECD Guidance on Peer Review

Purpose of the OECD Guidance on Peer Review

- "to provide guidance . . . on how the peer review of histopathology should be planned, managed, documented, and reported in order to meet GLP expectations and requirements."



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Guidance on the GLP Requirements for Peer Review of Histopathology

Why Do a Review of the OECD Guidance?

- Globally, organizations and institutions recognized need to adapt processes/SOPs to new Guidance
- Concern for varying interpretation of the Guidance & inconsistent action taken
- STP Executive Committee asked the Scientific and Regulatory Policy Committee (SRPC) to review the Guidance
  - SRPC subteam assembled
- Global stakeholders indicated a collaborative review document would be valuable
- Subteam drafted a review of the OECD Guidance with input from global community of toxicologic pathology

Intended Outcome of the Review Paper

- Provide a unified interpretation of the Guidance
- Serve as a framework for organizations to modify their processes as needed to follow the guidance

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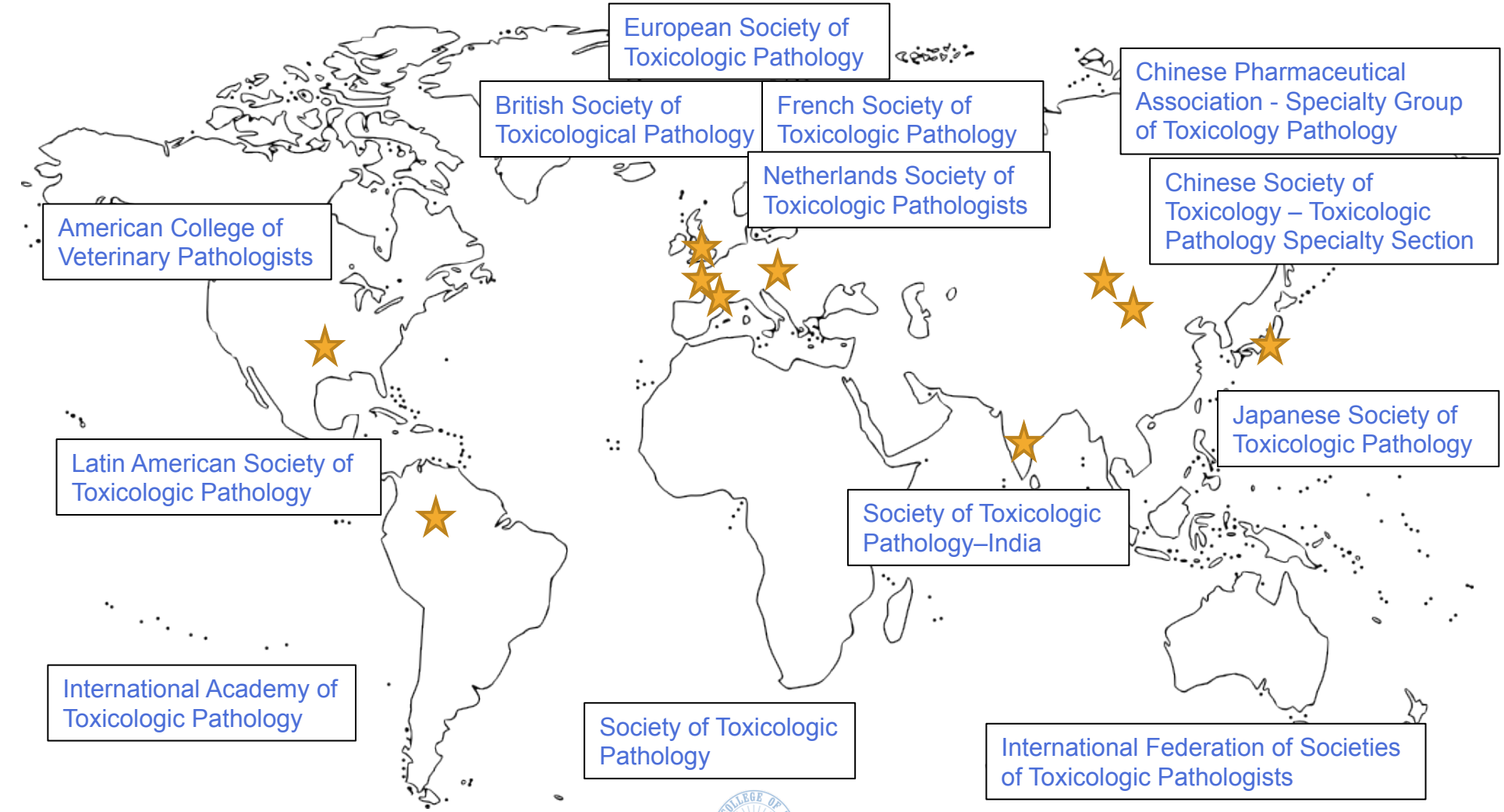
Scientific and Regulatory Policy Committee Review: Review of the Organisation for Economic Co-operation and Development (OECD) Guidance on the GLP Requirements for Peer Review of Histopathology

James D. Fikes[1*], Daniel J. Patrick[2*], Sabine Francke[3], Kendall S. Frazier[4], James F. Reindel[5], Annette Romeike[6], Robert H. Spaet[7], Lindsay Tomlinson[8], and Kenneth A. Schafer[9]

International Endorsement of the Review Paper



OECD Guidance Document - Outline

- Section 1 – Background
  - Focus on processes to organize, perform and record PR
- Section 2 – GLP Requirements
  - Process and interactions between the PR and Study Pathologist
- Section 3 – GLP Compliance of Peer Review
  - PR at non-GLP versus GLP facility & Study Director responsibilities
- Section 4 – Summary of Expectations

What is Peer Review

- Toxicologic pathology assessments have two critical steps*
  1) Diagnosis and recording of all pathology findings
  2) Integrated interpretation of all pathology information within the study to identify and characterize treatment-related findings
- Pathology data is qualitative by nature
- Peer review is a process where a 2nd pathologist reviews the study pathologist's evaluation by examining the data and a subset of tissues
- Routinely practiced by CROs and biopharmaceutical companies

**Morton et al, Toxicol Pathol, 2010*

Purpose of Peer Review

- Quality check – helps ensure accuracy, consistency, and completeness
- Accurate identification of Target organs and Effect Levels (e.g. NOEL, NOAEL)
- Correct interpretation of pathology results
- Contributing to overall increased confidence in the results of the pathology evaluation
- Concludes with issuance of a PR memo
  - Summarizes what was done (e.g. animals, tissues reviewed)
  - States that there was consensus

Section 1. Background – Key Themes

- Guidance focused on PR processes (1.1, 1.2 and 1.3.)
- PR in non-GLP compliant facility may be necessary (1.4)

Guidance focused on PR processes (1.1-1.3)

- 1.1. Histopathological assessment is a key endpoint
- 1.2. Recognizes PR as a tool practiced in tox path to ensure quality and accuracy of diagnoses and interpretations
- 1.2. No absolute requirement for peer review in GLP principles, but regulators tend to expect some level
- 1.3. Guidance concerned with the processes used to organize, perform and record the results of the PR
- 1.3. Augments current recommended practice on how to conduct path peer review

PR in non-GLP compliant facilities (1.4)

- Sponsor may require some or all slides to be peer reviewed by specific pathologist
- Relevant expert not always employed by GLP facility
- May not always be possible to perform the PR in a GLP compliant facility

Section 2. GLP Requirements – Key Themes

- What is histopathology raw data? (2.6)
- How the PR process is directed/guided (2.1 and 2.2)
- Role/activities of the peer review pathologist (2.3)
- Documentation/archival requirements of PR conduct/ notes/correspondence (2.4 and 2.5)
- When disagreements occur (2.7, 2.8, and 2.9)
- Documentation of PR outcome (2.10, 2.11, 2.12)

What is Histopathology Raw Data?

2.6: *Slides and blocks are specimens rather than raw data and must be archived*

- Consistent with US FDA (1987 Final Rule) and Japanese MHLW (1997 MHW Ordinance 21)
- Pathology raw data is not established until the anatomic pathology report is signed
- Raw data is only altered if changes are made to a finalized pathology report

What is Histopathology Raw Data?

Contemporaneous PR

Study Pathologist completes initial read & draft report

PR Pathologist reviews subset of slides

Finalized path report (raw data exists)

PR Pathologist shares comments & differences with Study Pathologist

PR and Study Pathologist work toward consensus

Study Pathologist finalizes pathology report (creates raw data)

Any changes reflected in amended path report issued by Study Pathologist

PR Pathologist issues peer review memo

Retrospective PR

What is Histopathology Raw Data?

- The PR memo and communications do not meet the definition of raw data
  - Define the process and should be maintained in the study file and archived
- In a retrospective PR, appropriate to maintain the pathology table changes and versions of signed reports
  - Allows for reconstruction of the process and transparency

How the PR Process is Directed/Guided

2.1: Peer review should:

- *be clearly described in the study plan (including whether the PR will be performed contemporaneously or retrospectively)*
- *include information on how the pathology PR will be planned, managed, documented, and reported*
- *if some or all of the above information is documented in an SOP, a reference to the current version of the SOP is acceptable*

How the PR Process is Directed/Guided

- While the detailed methods for conducting a PR could be detailed within the protocol, more common practice is to describe in a peer review SOP
- *"a reference to the current version of the SOP is acceptable"*
  - If the SOP of the peer reviewer's organization will be used then additional references to the specific SOP not required
  - Not recommended to list specific SOP numbers in the protocol

How the PR Process is Directed/Guided

2.2: The study plan should allow reconstruction of how tissues will be selected for peer review while allowing sufficient flexibility to react to unexpected findings

- More common for SOPs to define the minimal materials for an appropriate PR while also allowing for flexibility
  - Recommendations have been previously published (Morton et al., 2010)
- The specific materials, including a list of tissues that were evaluated, are documented within the PR memo

Role/Activities of the PR Pathologist

2.3: The PR pathologist is a contributing scientist rather than a Principal Investigator, they are not generating data, and the study director maintains ultimate responsibility for ensuring that the PR is GLP compliant

Role/Activities of the PR Pathologist

- Does not generate raw data or contribute as an author to the final report
- The PR pathologist should be identified in the study protocol, amendments, and/or other study documents
- Study pathologists are responsible for the interpretation of pathology study data

Documentation/Archival Requirements of PR Notes/ Correspondence

2.4: Details of how the PR was conducted (tissues reviewed, when they were reviewed, and by whom) should be documented and retained within the study file. Notes made by the PR pathologist do not have to be retained

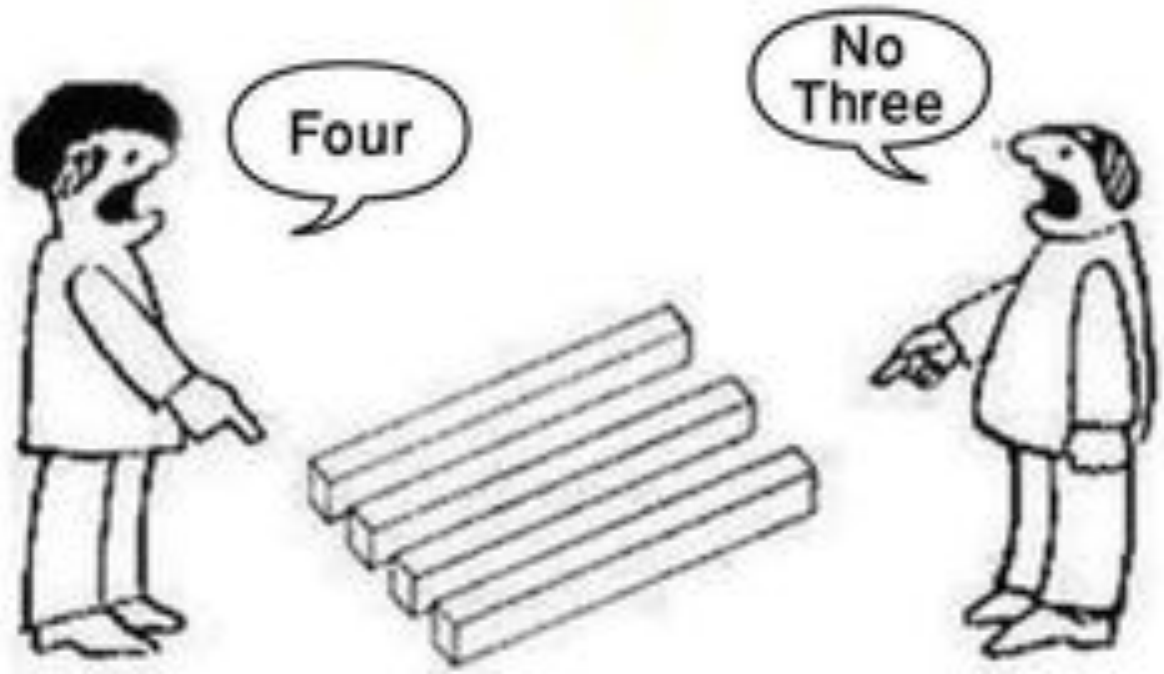
- The details are captured in the PR memo
  - Retention in the study file with appropriate archival is adequate; however, some facilities prefer to also include it in the study report
  - Contains the peer reviewer name, tissues/data reviewed, and dated signature by the PR pathologist
- No requirement to retain any peer review notes or discussions between the PR pathologist and study pathologist

Documentation/Archival Requirements of PR Notes/Correspondence

2.5: All correspondence between the sponsor, test facility, and the PR pathologist regarding the evaluation of the slides used for the PR should be retained, including minutes of teleconferences between the sponsor and the test facility

- Essential correspondence to retain are the particular communications that reflect the processes, plans, and expectations **directly linked to the slides** used in the PR
- Should not be interpreted to mean that any possible type of correspondence needs to be retained
  - Anything regarding preliminary observations and the draft pathology interpretation are considered pathology working notes

When Disagreements Occur



When Disagreements Occur

2.7: A clear, transparent, and unbiased process should be implemented to resolve differences; and this process should be documented within the facility's SOPs

2.9: If agreement cannot be reached, an independent expert or panel of experts may be used to resolve the issue and the conclusions should be clearly documented in the final report

When Disagreements Occur

- Important to note that consensus is usually reached
- If consensus not achieved, additional processes to resolve should be defined in SOPs and/or the protocol
  - Differences of opinion may be resolved through consultation with other pathologists/subject matter experts, or by convening a pathology working group
  - PWG methods (Mann and Hardisty, 2013; Morton et al., 2010)

When Disagreements Occur

2.8: Where the PR pathologist's findings were significantly different from the original interpretation of the study pathologist, a description of how differences were handled and changes made to the study pathologist's original interpretation should be discussed in the final report

- Contemporaneous peer reviews
  - Original interpretation (finalized pathology report) has not yet been generated, thus, no changes to discuss
- Potential for disagreements regarding the raw data restricted to retrospective peer reviews
  - Changes subject to audit trail and must be captured in a report amendment

Documentation of PR Outcome

2.10: Not necessary to report in detail the outcome of the PR in the pathology or final report; a simple statement that it was conducted and that the pathology report presents the agreed upon findings suffices

2.11: No requirement for the PR pathologist to sign the pathology or final report, however, there is an expectation that the PR pathologist will sign the statement which should be retained in the study file

2.12: The identity and affiliation of the PR pathologist should be listed in the final report

Documentation of PR and Outcome

- Simple statement regarding PR outcome = PR memo
  - Lists the materials and that the peer review pathologist agrees with the study pathologist's interpretation
- PR memo is generally signed and dated after the pathology report is finalized
- The identity and affiliation of the PR pathologist can be included in the pathology and/or study report
  - If the PR memo is included in the final report, further listing isn't necessary

Section 3. GLP Compliance of Peer Review – Major Points

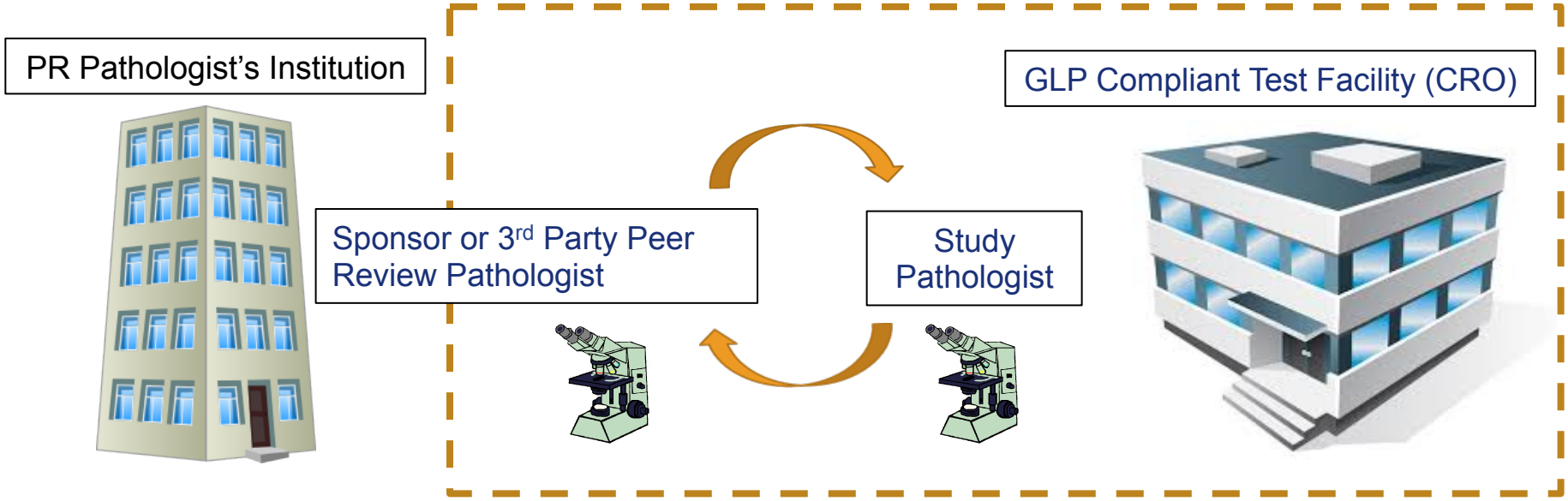
- PR at GLP versus non-GLP facility (3.1)
- Study Director's responsibilities (3.1, 3.2, and 3.3)

PR at GLP versus non-GLP facility (3.1)

- Expectation that PR is conducted in compliance with GLP
- Guidance recognizes, for scientific value, PR may have to be conducted at non-GLP facility
- Should consider conducting PR at GLP-compliant test facility to make review GLP compliant

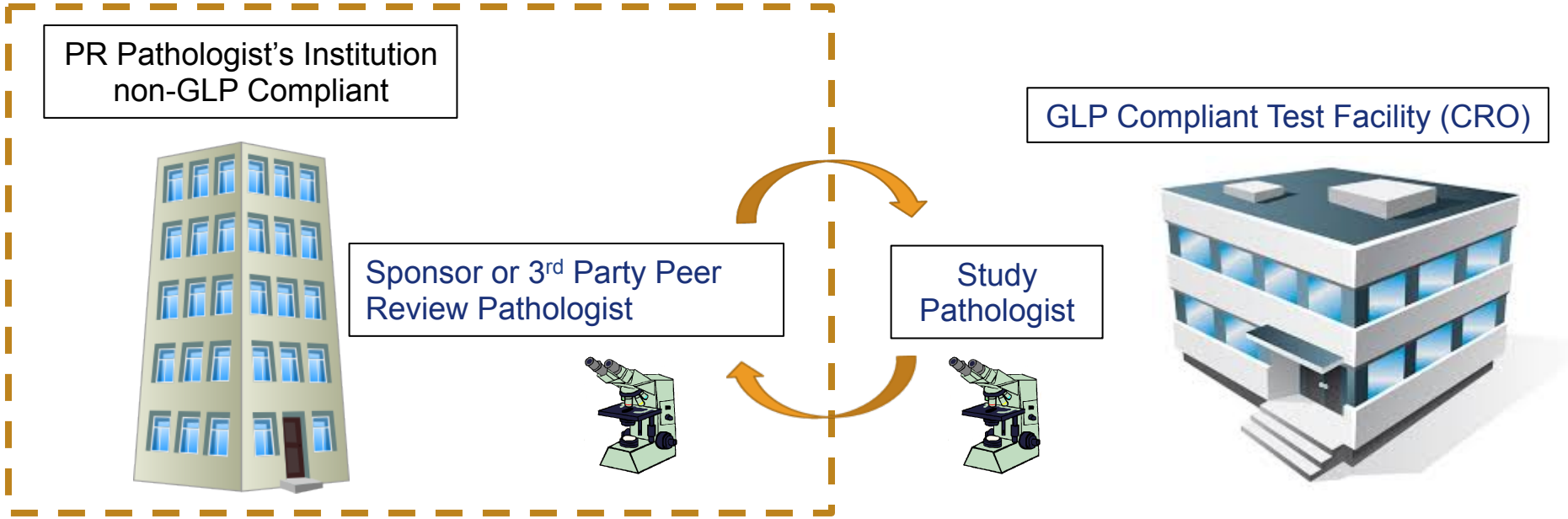
Example of Peer Review at GLP Facility

- Sponsor/3rd party PR pathologist travels to GLP compliant test facility
- PR pathologist has relevant training and follows SOPs



Example of Peer Review at Non-GLP Facility

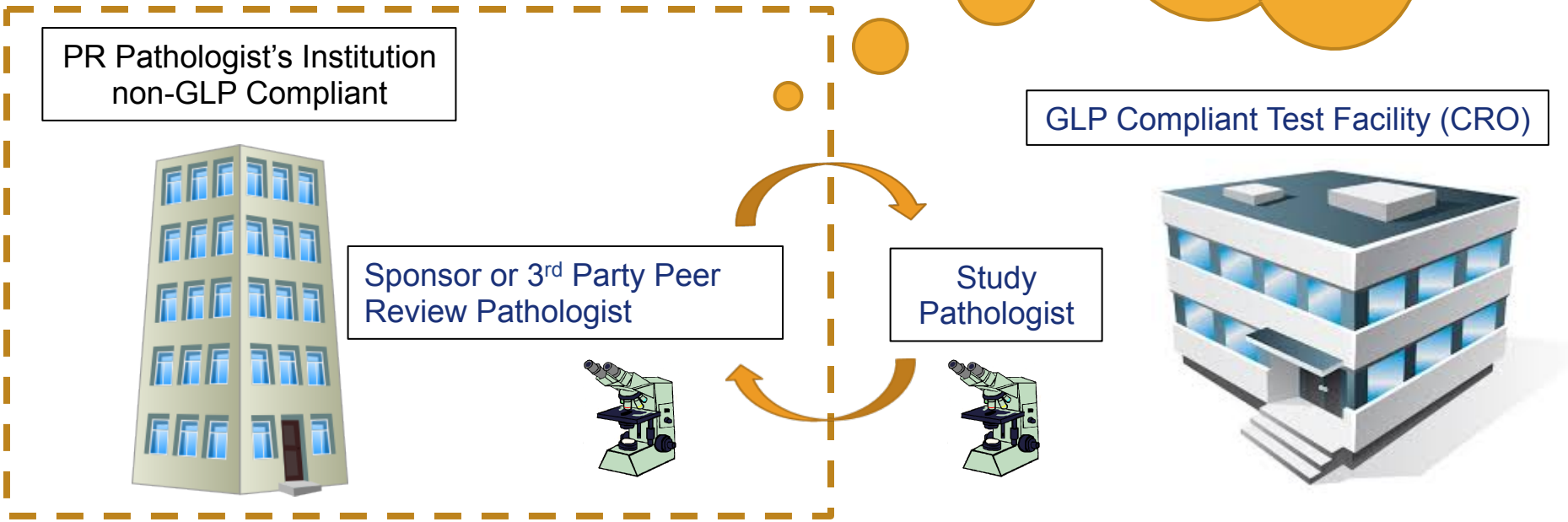
- Slides and pathology data transferred to Sponsor/3rd party PR pathologist
- PR pathologist's site non-GLP compliant



Peer Review at Non-GLP Facility

- Slides and pathology data transferred to Sponsor/3rd party PR pathologist
- PR pathologist's site non-GLP compliant

To avoid this, Guidance stresses to consider performing PR at test facility under their GLP Quality System umbrella



Study Director's Responsibilities (3.1, 3.2, and 3.3)

- 3.1. PR in non-GLP facility justified in and recorded in study plan and final report
  - Update protocol by amendment if needed
- 3.2. Study Director must be satisfied PR process is sufficiently managed
- 3.3. Non-GLP PR should be documented within the Study Director's statement

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Questions?

jim.fikes@biogen.com

daniel.patrick@mpiresearch.com

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