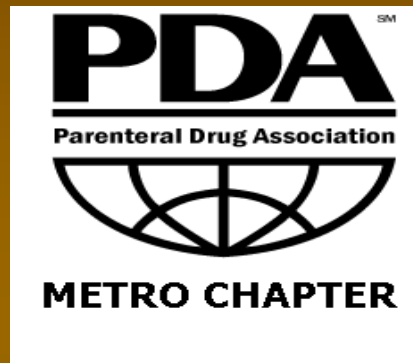



Preliminary Audit to a Pre-Approval Inspection



Chapter Day Symposium

Robert Seltzer – GlaxoSmithKline

Pre-PAI Areas of Concentration

1. Integrity of the submission via its raw data
 2. Proper conduct and content of development and validation studies
 3. GMP appropriateness of facilities and operations for clinical and commercial supply
 4. Appropriateness of all investigations on batches furnishing submission data
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Integrity of the Submission via its Raw Data

- Trace backwards to lab notebook, lab data sheet, or to electronic raw data (Part 11 compliant) a sampling of results from several development studies.
- Review the SOP(s) dealing with rules of notebook record-keeping (including corrections), peer or supervisory review, chain of custody, sample handling, and definitions of raw data.

Proper Conduct and Content of Development and Validation Studies

- Development, qualification, and validation studies, should use FDA or other generally accepted consensus std or compendial method.
- Only a few categories of process validation may be deferred till after NDA approval. Sterilization and/or aseptic process validation must precede clinical trials.
- Single drug substance lots should furnish API for a finished drug conformance, bioequivalence, or other pivotal finished drug batches.
- Laboratories/lab practices must be such as to preclude contamination or other invalidation of test results.
- Analytical methods must be validated, proven suitable (if compendial), and transferred as applicable.

Proper Conduct and Content of Development and Validation Studies

Depending on the drug product, various studies are incumbent on the developer and submission owner:

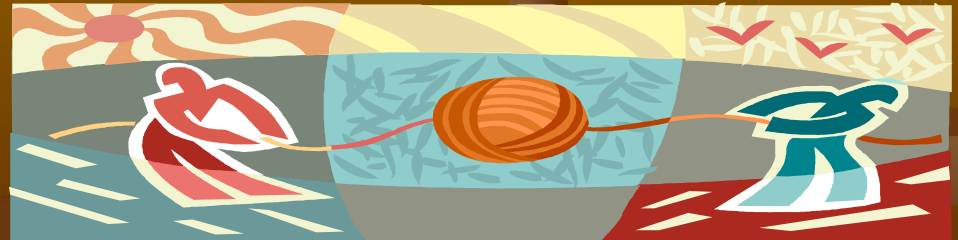
- For drugs with specified temperature storage, a shipping study is likely required (ditto for temp-sensitive API)
- If the API has a polymorph specification, then methods and rationales should exist for verifying proper polymorph at appropriate stages of manufacturing.
- Suspension products have their own host of processing issues and studies to address questions of homogeneity at re-starts, end of filling, etc.
- Manufacturing critical process parameters and critical quality attributes should be determined and their verification incorporated in batch records.

GMP Appropriateness of Facilities and Operations for Clinical and Commercial Supply

- Facilities, equipment, and instruments used to manufacture and test clinical trial, conformance, pivotal, or primary stability batches must be qualified to the same extent as a mature commercial manufacturing facility, otherwise “garbage in, garbage out.”
- One caveat to auditability/inspectability of a clinical supply manufacturing facility is that a production line, packaging/labeling line, and analytical instruments used for clinical material may not remain in place for future inspection unless they’re to be used for commercial-scale manufacturing. **There’s no such thing as “museum maintenance.”**

Appropriateness of all Investigations on Batches Furnishing Submission Data

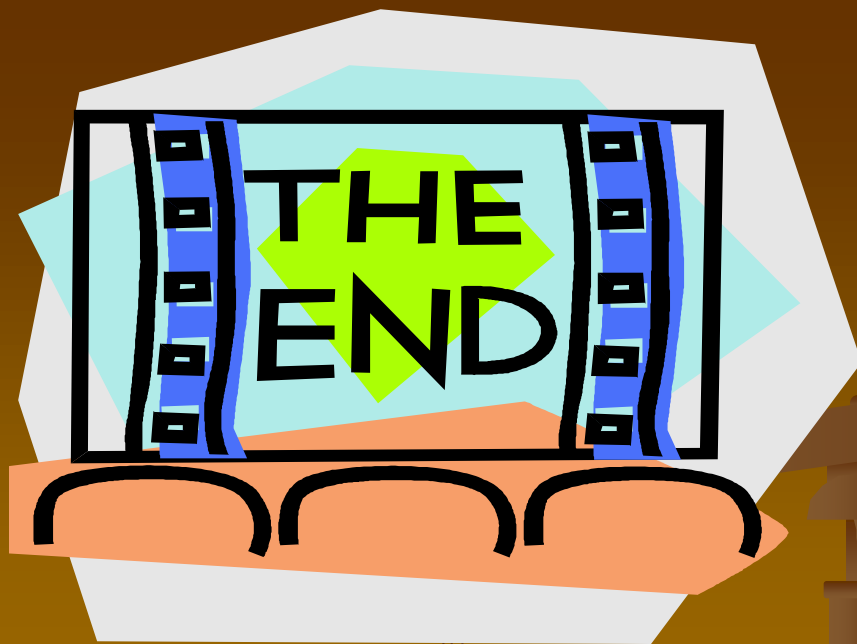
- All conformance and development batch process deviations and laboratory investigations must follow internal procedure, prove logical, answer the right questions, and be data/fact-based.
- Groupthink, project management timelines, and cost containment can ill influence what must be an unbiased, methodical, defensible investigation and subsequent conclusions and recommendations.
- A weak link in the chain of submission-supporting data, studies, and investigations can unravel the best laid plans.



Food for Thought:

Pre-PAI audit teams (1 or more) should consist of at least one research-aquainted if not a graduate-degreed scientist or engineer turned auditor.

Just as peer review is essential in research publication, it should also be an aspiration of pre-PAI audits in terms of the challenges posed by the audit questions and requests for information or rationales/justifications.



Please ask any questions

