QA-ING FROM START TO FINISH:

PREPARING FOR AUDIT; ALL ABOARD!

Presented by: Amanda Stanley – QAU at Symbiotic Research

PRESENTATION TOPICS

- Protocol Audits
- Critical Phase Inspections
- Raw Data / Report Auditing

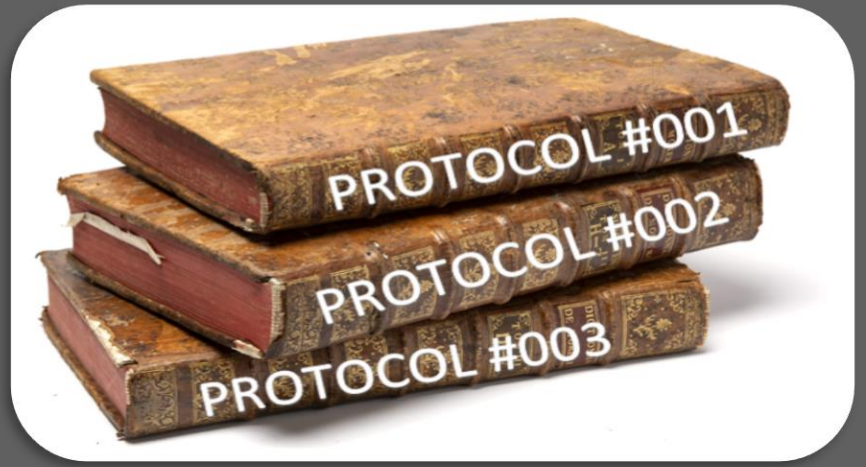
WHO ARE THE QAU?

- "Quality Assurance Professionals inspect studies/facilities and audit data to ensure that testing is being conducted in *compliance* with government regulations such as GLPs and USDA APHIS Requirements, protocols and standard operating procedures. They may be employed by field test site facilities, laboratories, management or sponsor companies or may work on a contract basis."

  - NAICC, Background

PREPARING FOR AN AUDIT

FIRST STOP: PROTOCOL



PROTOCOL

§160.120 PROTOCOL

- (a) each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain but not limited to the following information: (see next slide for details)
- (b) All changes in or revisions of an approved protocol and the reasons shall be documented, signed by the study director, dated, and maintained with the protocol

§ 160.120 Protocol.

(a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain but shall not necessarily be limited to the following information:

(1) A descriptive title and statement of the purpose of the study.

(2) Identification of the test, control, and reference substance by name, chemical abstracts service (CAS) number or code number.

(3) The name and address of the sponsor and the name and address of the testing facility at which the study is being conducted.

(4) The proposed experimental start and termination dates.

(5) Justification for selection of the test system.

(6) Where applicable, the number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

(7) The procedure for identification of the test system.

(8) A description of the experimental design, including methods for the control of bias.

(9) Where applicable, a description and/or identification of the diet used in the study as well as solvents, emulsifiers and/or other materials used to solubilize or suspend the test, control, or reference substances before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(10) The route of administration and the reason for its choice.

(11) Each dosage level, expressed in milligrams per kilogram of body or test system weight or other appropriate units, of the test, control, or reference substance to be administered and the method and frequency of administration.

(12) The type and frequency of tests, analyses, and measurements to be made.

(13) The records to be maintained.

(14) The date of approval of the protocol by the sponsor and the dated signature of the study director.

(15) A statement of the proposed statistical method to be used.

(b) All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol.

PROTOCOL

Apart from the GLPs want to review Protocol and SOPs.

Protocols can also include:

- Guideline Requirements
- Study Purpose
- References to methods
- Test Substance Retention
- If multi-site study, routing instructions for auditing
- Stability experimental design substances
- Disposition of samples
- Procedure for Protocol Amendments and Deviations

PROTOCOL

Experimental Design:

- General Test Conditions (specified as recommended from guidelines)
- Design
- Sampling (specified timepoints as recommended from guidelines)
- Analysis (radioassay, pH, Chromatography analyses, oxidative combustion)
- Data Handling and Calculations
- Calculations (Guideline specific)
- Statistical Methods and Control of Bias
- Interpretation or evaluation of results

PROTOCOL

Test, Control, and Reference Substances:

- Purity Determinations and limits of purity (≥95%)
- Test substance solubility → how will test substance be prepared, which type of solvent?
- Test Substance, Stock Solutions, Dilution storage
- Any additional reference substances used will be added by a protocol amendment?
- Preparation and Administration of Dosing Solutions.
- Reserve samples from each batch of test, reference substances
- Purity and stability testing (stability and, when relevant to the conduct of the study the solubility of the test, control, and reference substances under conditions of administration)
- Preparation and Administration of Test Substances

PROTOCOL

Test System:

- Description and source of supply
- Storage
- Acclimation

PROTOCOL

Sample Instruction (protocol or SOP driven):

- Sampling Instruction and Interval
- Sample Preparation and Handling
- Shipping of Samples (storage, shipped frozen on dry ice)
- Total Number of Samples
- Sampling naming instruction
- Sample Storage stability

LOOK BEYOND

Having a GLP Protocol check list is a tremendous auditing tool; but its not the only tool that QAU auditors have.

- Consult Study Guidelines
- Consult Standard Operating Procedures
- Think Big Picture (how will this be accomplished?)
- Identify any potentially “avoidable” protocol deviations
- Ask Study Directors and Sponsors questions!!!

PREPARING FOR AN AUDIT:

SECOND STOP: CRITICAL LABORATORY PHASE INSPECTIONS

CRITICAL PHASE INSPECTIONS

- §160.35 (b)(3) Inspect each study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve an existing problems, and any scheduled date for re-inspection. Any problems which are likely to affect study integrity found during the course of an inspection shall be brought to the attention of the study director and management immediately.

QAU AND THE PHASE INSPECTIONS

- QA will inspect for both study-specific and facility GLP compliance.
- QA will ensure that the study protocol is being followed, data is entered appropriately, test/control/reference substances have proper labels and are not expired, all purity and chain of custody documentation is available, equipment logbook entries are properly recorded, SOPs are followed and study personnel have appropriate training documentation.

DETERMINATION OF CRITICAL PHASES

Determining critical phases is typically dependent on the study type and duration

Typical Critical Phases for Inspection:

- Test Substance (receipt, storage, preparation)
- Test Substance Application
- Test System (e.g., receipt, storage, preparation)
- Specimen Activities (various analyses)

INTERVALS OF CRITICAL PHASES

Phase Inspection Intervals – the frequency of phase inspections will be dependent on the type, size, and duration of the study, and whether or not it has been contracted to an additional facility.

Consider long term studies, set a time requirement for phase inspections. Phase Inspections should be performed approximately XXX for long-term studies, at SOP or protocol directive.

PLANNING A PHASE INSPECTION

- Plan Ahead- discussions with Study Director / PI for phase inspection expectations and to discuss dates, preferably at the time of protocol approval.
- Study Director / Principal Investigator should give advance notice of the exact dates of critical events so that the in-process phase inspections can be performed.
- Plan a schedule but be flexible. Consider the need for a critical phase inspection. QA should be able to perform additional unannounced and spot inspections of any study performed, if needed.

PRIOR TO QA ARRIVAL

- Read the protocol
- Identify relevant SOPs and review
- Prepare checklists or forms to collect information during the inspection. Use the protocol and SOPs to guide.
- Review personnel training records
- Copies of procedures available

STUDY SPECIFIC INSPECTION

- Protocol Focused
- QA will inspect to determine that no deviations from approved protocols or SOPs were made without proper authorization and documentation.
- Urgent Findings: Any problems which are likely to affect study integrity found during the course of an inspection shall be brought to the attention of the study director and management immediately.
- Inspections with significant GLP findings will be sent immediately to the Study Director and Study Director's Management.

SUPPLEMENTAL DATA (FACILITY RECORDS)

- Chain of custody documentation for Test Substance
- Sample shipping records / chain of custody
- Correspondence (printed copies of emails, phone logs, any documents required to reconstruct the activities of the study).
- List of SOPs used in the study
- Copies of chemical storage temperature records
- Copies of sample storage temperature records
- Personnel: CVs / Training Records
- Equipment Use / Maintenance Logs

PHASE INSPECTION REPORTS

- Showing the date of the inspection (include on cover page)
- The study inspected (include on cover page)
- The phase or segment of the study inspected (include on cover page)
- The person performing the inspection (include on cover page)
- Make audits detailed but easy to follow. Provide enough detail so that the finding is easily understood.
- Positive and Constructive findings are key.

OTHER KEY POINTS TO CONSIDER

- If you don't understand something, ASK!!!
- Communication is key!
- QAU is here for guidance and not criticism

- EPA Standard Operating Procedure SOP NO.: GLP-C-02
  - Were periodic QA inspections conducted for the study? What phases were inspected? Were the number of inspections and choices of phases appropriate and were they adequate to ensure the integrity of the study?

PREPARING FOR AN AUDIT:

FINAL STOP: RAW DATA & REPORT

DATA QCED AND QA READY?

- Were data recorded promptly, and directly onto appropriate forms or into study notebooks, were all data recorded?
- Data should be peer reviewed and ready for QA Audit
- Spreadsheets available? Any transformed data ?
- Any data being marked as DNU, Do Not Use, with justification / reasoning.

REPORT AUDIT CHECKLIST BASED

Report Check List

- Use §160.185 Reporting of Results
- Use Study Protocol
- Use Relevant SOPs

PROTOCOL REQUIREMENTS

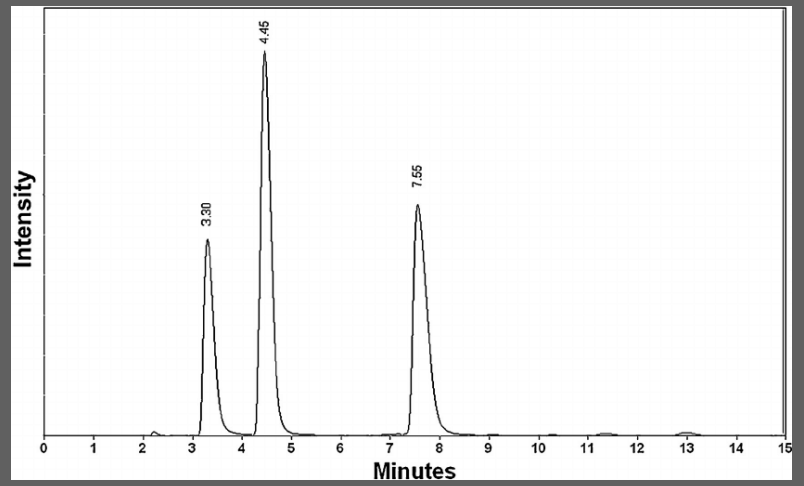
- Was the study conducted in accordance with the protocol and its approved amendment(s)?
- Audit the report and the protocol next to each other.
  - Dose at 2.5 mg/kg of soil?
  - Acceptance criteria met?
  - Was the study purpose met?

REQUIREMENTS

- **GLP Compliance Statement**
- §160.12 Statement of Compliance or non-compliance
  - A statement that the study was conducted in accordance with this part; or
  - A statement describing in detail all differences between the practices used in the study and those required by this part; or
  - A statement that the person was not a sponsor of the study, did not conduct the study, and does not know whether the study was conducted in accordance with this part.
- **QA Statement**
  - §160.35 Quality Assurance Unit (7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.

PRESENTATION OF DATA

- Data can be in found in tables
- Figures
- Graphs
- Present transformation of data
- Summarized

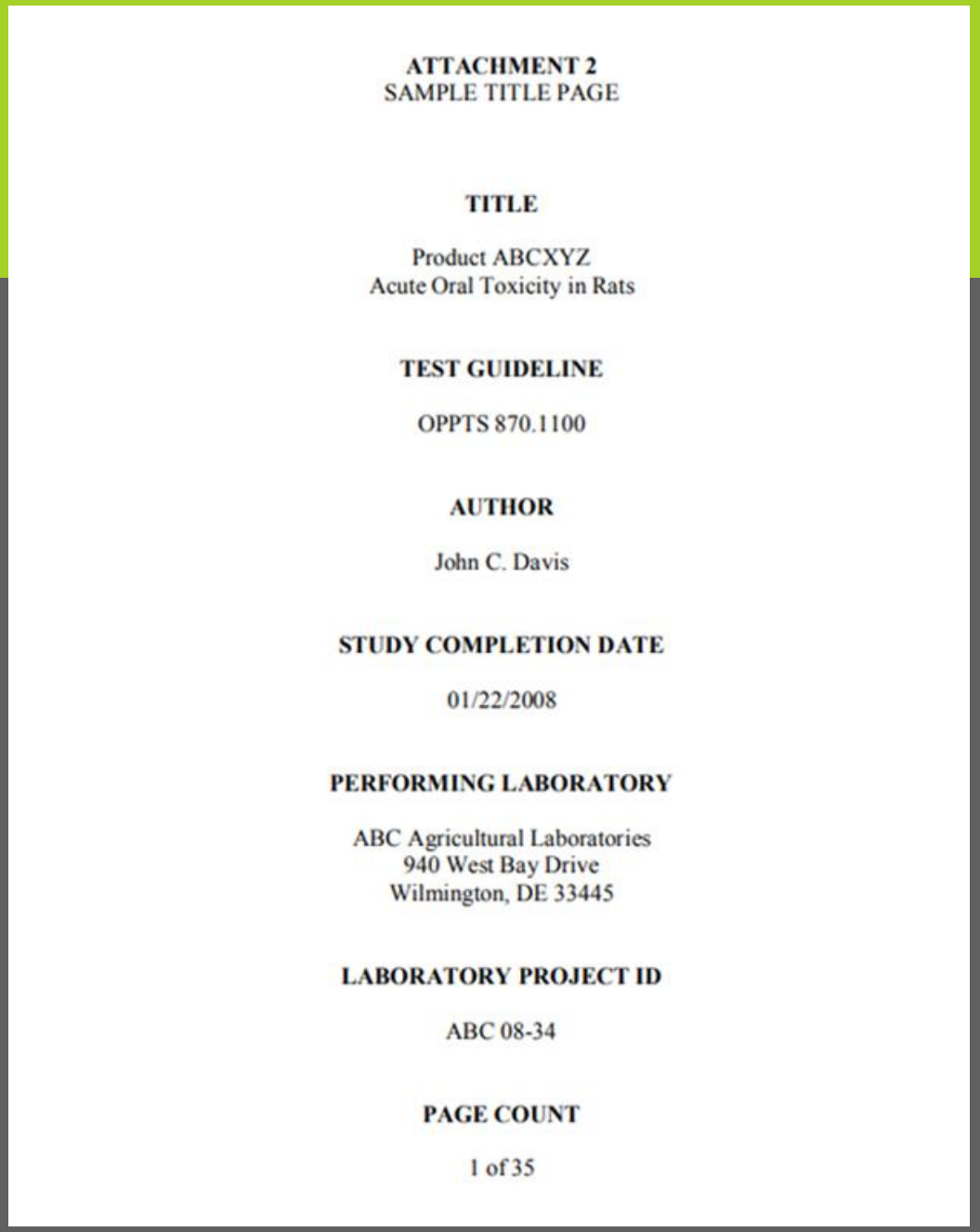


RETENTION OF RECORDS

- Are records being retained according to GLPs and Protocol requirements?
- Physical address located within the report is a GLP Requirement
- Standard Operating Procedures for archiving and retention of records
- Facility Records to support study
- Notify EPA if moving archive location

PR NOTICE 2011-3

- Standard format for Data Submitted under FIFRA and Certain Provisions of FFDCA PR Notice 2011-3 applies to all data that are submitted to the EPA to support any application, or submission intended to persuade EPA to grant, modify, or leave unmodified a registration or other approval required as a condition of sale or distribution of a pesticide.



ATTACHMENT 2
SAMPLE TITLE PAGE

TITLE

Product ABCXYZ
Acute Oral Toxicity in Rats

TEST GUIDELINE

OPPTS 870.1100

AUTHOR

John C. Davis

STUDY COMPLETION DATE

01/22/2008

PERFORMING LABORATORY

ABC Agricultural Laboratories
940 West Bay Drive
Wilmington, DE 33445

LABORATORY PROJECT ID

ABC 08-34

PAGE COUNT

1 of 35

THANK YOU!!

Please, hold for questions until the end of this session ☺