NAICC Annual Meeting
New Orleans, LA
QA Track IV
"A Preamble Ramble – Early Expectations and Current Procedures"

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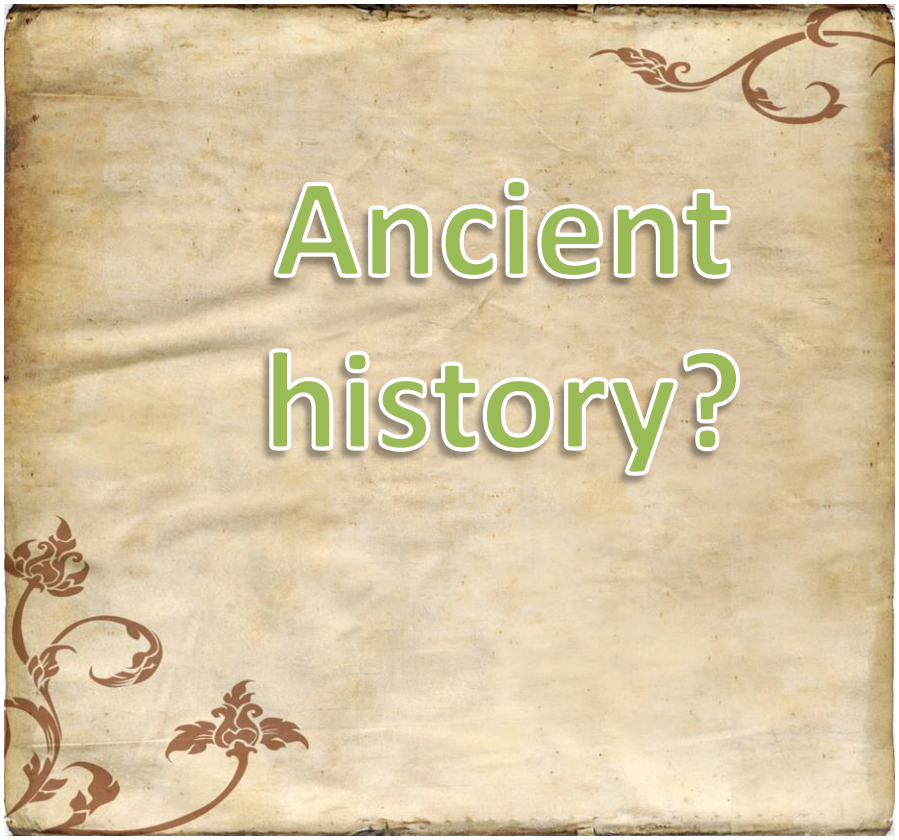
Presentation Details

- We will have two short presentations, the first using the first GLP Final Rule from the FDA. Please use the handout, or the PDF of the whole publication, as shown on each slide. You will also be provided with a complete overview of the contents of this valuable document, for your continuing education and support of GLP compliance.
- The second presentation will address gaps commonly found in the study file and raw data for Magnitude of the Residue studies, to help improve your facility SOPS and QA auditing techniques. We'll close with group discussion of two situations and leave time for other questions.

Why We Need to Know GLP History, and Understand Agency Reasoning When GLPs were First Introduced

Highlighting: FDA's (and EPA's) Authority;
QA Public Comments & the Decisions by FDA

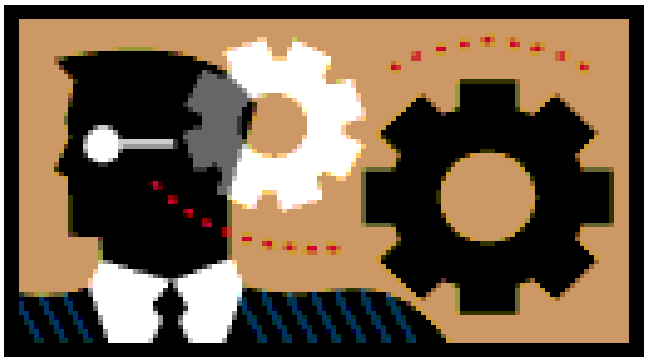


Use the Preamble PDF or Handout

- **Navigaton:** See top of each page for the Federal Regulation [FR] Page number (e.g., #59986, and the text columns for Paragraph number.
- **Start at** the Final Rule designation and paragraphs 1 & 2 – The Commissioner explains why the GLPs would not have been sufficient as guidelines.
- **Move to FR page 59990, paragraph 17,**
- The Definitions section generated many comments, so they are important for everyone to know and use consistently. Staff training on all levels should always include Definitions.
- **Move to FR page 59992, paragraphs 34, 35, 36**
- So many comments were received on QA that the reader is referred to **FR page 59996, beginning with paragraph 75 – please move there.**

QAU Comments - Paragraphs 75-92

- Of 135 comments, **100** objected to *all* of the proposals in 58.35 – so… nothing much has changed!
- We need to understand how FDA viewed the QA unit to develop QA SOPs



- Preamble Focus Points:
  - Direct reporting to Management by QA
  - Eliminating conflicts with respect to "independence" of QA in small businesses
  - SOPs to govern QA operations
  - SOPs to govern other op's
  - Independence of *each* study
  - Raw Data as foundation
  - Ability for study reconstruction from raw data – whether "used" or not, it needs to be available.

Standard Operating Procedures

- FDA found serious flaws in all aspects of "study conduct" – SOPs can *standardize operations among diverse operators*
- This is why we need to compare training records to operators as part of an inspection, or based on a finding from a raw data/report audit.
- Who is operating equipment, applying test substance(s), or taking specimens?
  - Who is recording raw data during these operations? Are they represented in the data by initial/date, or other information such as their role (Scribe, Time-keeper, etc.)?

- **RED ALERT:** The EPA presently finds many GLP departures from SOPs – check the facility's "governing SOPs" against what you see in practice. Be sure to inform Mgt.

Choosing the Critical Phase Inspection (CPI)

- Review of the protocol for the study & facility
- Selection of phase(s)

based on QAU SOPs and other factors that may influence your choice(s)

[Call out factors that would influence your CPI selection, **and/or frequency**]

- Does the staff have all appropriate information and equipment?

- Are you serving as the facility QA, or coming in as a Sponsor QA?
- Is the method a familiar one, or will there be a validation phase to create a working method?
- What are the protocol's communication requirements?

Status Reports

FR 59998, Parag. 88 [EPA's 160.35 (b) (4) is the same]
This section gives us a better framework for what should be part of a Status Report. Content is related to problems found and actions taken during inspections and audits, and to inform that action is still necessary. The SD may not have the authority to address all findings; some may have to be handled by Mgt.

The frequency of these reports may be determined by Management , but they are submitted to the SD and Mgt.

During your "normal" inspections, the SD and Mgt. must be immediately informed "**of any problems which are likely to affect study integrity"** (160.35 (b) (3).

Critical Phase Inspections & Status Reports

- Findings from a Study **CPI** (SD & MGT)
  - Equipment log not completed for the inspected operation (SD directs action; OK at re-check)
  - Equipment log has several years of records in the binder (SD replies, "Noted.")

- Items for **QA Status Reports** (MGT action)
  - You continue to find instances where direct entry is not done
  - Older data is still in the log, not archived (risk)
  - Other logs for *replaced* equipment have not been archived (risk)

Standard Operating Procedures

- Be sure that your own QAU SOPs reflect what the GLPs require –
  - Your own operations need to be made standard for new QA training, as well as for guiding the procedures and answering the occasional question
- FDA & EPA never intended a CPI to be a quick, single-focus event, but comprehensive monitoring and reporting to the Study Director and testing facility Management

Let's prove that statement

- **Move to FR 59998, paragraph 87**
- Again, since EPA/FDA cannot be everywhere, so we stand in the gap.
- We inspect operations, and review the SOPs that govern them, to assure consistency
- Safety, for example, is related to training
- Passwords are related to that also, plus data security
  - Where are intersections?

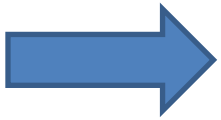
- Protocols & Changes
- Consider harvest – if the protocol "allows" a large fruit to be sectioned, is that the same as "directing"?
- Here, the field site needs to be aware of what will happen in the laboratory. **How can the protocols be improved?**

Make Preamble Rambles More Routine

- OK, it's a given that this is not very exciting...
  - But EPA Investigators' reactions to GLP non-compliance can be MUCH more exciting than we'd like

The FDA & the EPA Preambles offer valuable resources for your education, refresher training, and also gives you the ability to answer the question:

"Where does it say <u>THAT</u> in the GLPs??"



PUT THEM ON YOUR READER or DESKTOP WHEN YOU GET HOME – use them to educate & study.

There's time for a stretch break before we move on to the next topic

Gaps commonly found in the study file: SOME ROOT CAUSES

- COMMUNICATION
- ✓ In-between protocol signing by the SD, and his/her signing of the final report (or protocol amendment for termination of the study), the project is active and subject to GLP compliance

- Gaps generally come from change, and from a few sources
- What does the test facility determine to be "raw data"?
- How does it control and capture the changes that may impact study conduct? Auditing?

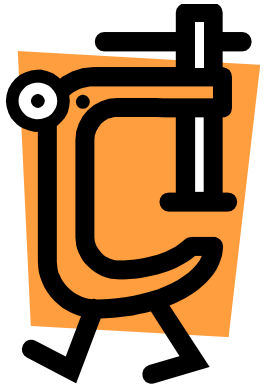
"Back in *my* day…"

- Technology has given agriculturally-based QAU's a lot more to consider than just paper
  - Text and voice/phone messages
  - Email
  - Cloud storage
  - Ipad, Iphone
  - Remote drives, USB
- It's a lot more than a notepad in the researcher's pocket IRL

Although, there may still be one in use!

- QA's role – be sure you are asking questions about how "the study file" and "raw data" contents are handled

Guidance and Tools



Be sure there that the facility guides Personnel into creating documentation that will be GLP-compliant. This means it must be direct, or identified as a transcript, copy or “from memory.” Let the EPA handle the fine points of data adequacy.

Work with the testing facility to find sturdy solutions that work for them – given that agreeing to some changes is part of the bargain! Create good SOPs based on team work.

The Basics

- Who, What, When, Where and Why
- Describe in words
- Consider allowing the use of words, instead of exclusively using codes, to explain changes in raw data
- At the end of the day, could another technician understand what happened, who decided what, and when, and know the status of any situation still “open” for tomorrow?

The Basics

- If something is different, explain what you see
- Check the protocol and be sure all of its changes (amendments, deviations) are in your possession
- Write it down! If in pencil, copy or transcribe that original raw data (retain that).
- Ask!!
- Be supportive of questions, slow down, check

Data Handling SOPs

- Adequate for Personnel *and* Study Director
- Where does the paper all go? Initial/date?
- When are emails expected to be printed, initial/date, and made part of the study file?
  - Good auditing clues – when you see where a technician or Lab Director made a note to "check with the SD," be sure the documentation exists.
  - Are all of the protocol's directions followed?
  - If study Personnel change, is the data file given to the next person in charge?

Bridging the gaps with questions, analysis

- ✓ Look for points of change during a CPI, such as a change of a column and/or other equipment during an analytical method process

What does the SOP say – is the data being recorded as stated in the procedure?

If not, is there some "practical" reason?

- ✓ What about points of change in the method itself because of unanticipated circumstances?

To what extent, or when, does communication with the Study Director occur? Who decides when?

Standard Operating Procedures

- Since the role of SOPs is to produce a consistency of operation among diverse “operators,” there should be instruction for unforeseen events, results, etc.
  - This is at the very root of GLP compliance, according to the Preambles: an unbroken (patching is OK) trail of raw data and study file contents from point A to point B.

Other areas

- **Sample Handling**

What is the receipt, ID, point-to-point specimen handling procedure (or set of them)?

How does storage equipment (freezer, refrigerator, cold room, ambient area) temperature get monitored, how often, and what is the weekend procedure, if no constant monitoring system?

- Do unit ID's match forms?

- "When the power goes out"
  - Are there alarms for the major sample holding area(s), and how complex is notification system?
  - Are there "back up" thermometers?
  - Do records show month, date, and year (Year can be part of heading only)
  - Is documentation adequate to explain exactly what happened, the duration of the event, etc?

Sample Handling in the Lab, con't.

- Inventory Logs
  - Check SOPs, forms
  - How many years are in the binder? Does the SOP address archival of Freezer maintenance, inventory and other logs?

  Good Status Report item

- Processing
  - Yes, it's a grind! But QA should be there now and then, to observe the crop processing. It's important!
- What happens when a specimen received is very dirty, or is large and frozen solid (cantaloupe)?
  - Do Personnel's Raw Data training include addressing hazards or questions?
  - What's in the protocol?

Discussion of Situations

- Time to practice some gap-filling skills.
- Please refer to the first “situation” – time will be allowed for reading, then group interactive discussion will follow.