EDGE
Veterinary Vaccines Consulting Group, LLC

Observations from the Receiving End: What Data Package Quality Reveals about Partnerships

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My Background

- Limited to regulations for products under purview of USDA's Center for Veterinary Biologics (CVB)
  - Vaccines, diagnostic test kits, therapeutic/prophylactic antibodies, immunomodulators (some), allergenic extracts

- FDA-regulated products (drugs, devices)
- EPA-regulated products (pesticides)

Objectives

- CVB expectations for documentation and data packages
- Sponsor/CRO relationship
  - Importance of Communication
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- Impact of Sponsor-CRO relationship on Sponsor-Agency relationship and beyond

CVB's Regulatory Authority for Oversight of Records and Documents

- Virus Serum Toxin Act of 1913 as amended in 1985
- Title 9 Code of Federal Regulations (9 CFR)
  - Part 116: Records and Reports

Documentation is defined as…

9CFR 116.1 Applicability and general considerations

(a) Each licensee, permittee, and foreign manufacturer of biological products imported into the United States shall maintain, at the licensed or foreign establishment in which the products are prepared, detailed records of information necessary to give a complete accounting of **all the activities** within each establishment. Such records shall include, but shall not be limited to, the items enumerated in this part.

…the documents must be accessible….

9CFR 116.5 Reports

(a) When required by the Administrator, reports containing accurate and complete information concerning biological products, including but not limited to, product development and preparation, and market suspensions and recalls, shall be prepared and submitted to the Animal and Plant Health Inspection Service by the licensee, permittee, or foreign manufacturer (whose products are being imported or offered for importation). Unless otherwise authorized by the Administrator, records necessary to make such reports **shall be maintained in each establishment**.

…the definition of documentation is broad.

- Personnel and training
- Equipment – cleaning, sterilizing, validating
- Animals
- Research/Pre-license product development
- Production
- Testing – Section V and other testing
- Labeling
- Inventory and disposition (seeds/cells/product)
- Import permits from NIES – may also get audits from NIES
- Vendor audits

CVB has the authority to review documentation, and they will

- Complete accounting for all activities – **including** pre-license activities, records, and data
- Records kept on-site or at a CVB-approved alternate location (per 9CFR 116.1(c))
- In short, **all** establishment activities, **including work done by 3rd parties**

What is “inspection”?

- On-site physical inspection by CVB’s Inspection-Compliance Unit (IC)
- Electronic records (Administrative) inspection by IC
- Records request from CVB’s Policy, Evaluation, and Licensing Unit (PEL)
- CVB confirmatory testing of seeds/cells/final product (may request bench records for establishment’s testing of same)

Good documentation procedures are a must, even without an SOP or Training Department

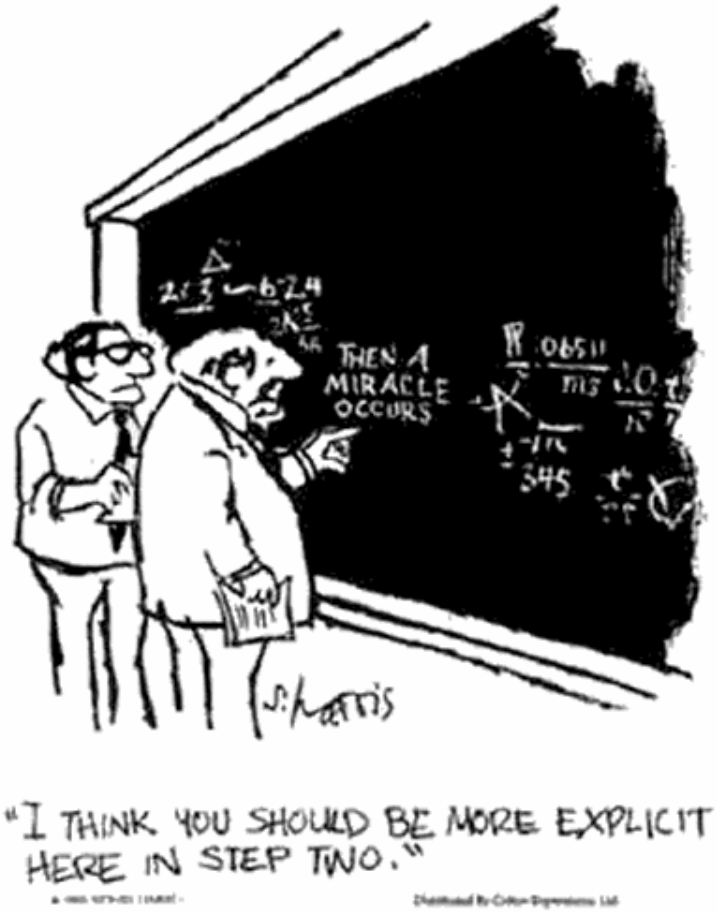
If it's not written down, it didn't happen

- Legible and indelible –NO pencils, NO white-out!
- Clear and understandable
- Verified by initials/ signature and date

Good documentation practices

- Document when actions performed (not before or after)
- Only document what was actually done; never falsify
- Clearly record observations; define any codes
- Explain inconsistencies
- Make certain all records correct—check and double check
- Ensure you validate (sign and date)

Good documentation practices



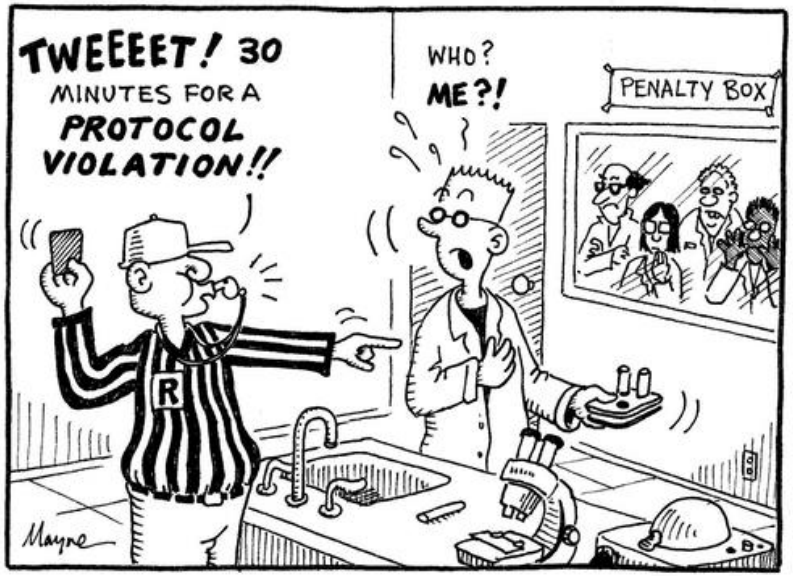
Good documentation of study results is a given, but documentation for methods, materials used, media and solutions, reagents, storage conditions, material disposition, etc., are also critically important

Good data packages

Contain data generated from reviewed protocols

- CVB publishes detailed guidance for study design–read this first!
- Don't assume your protocol is suitable—submit to the CVB for review and comment before starting study

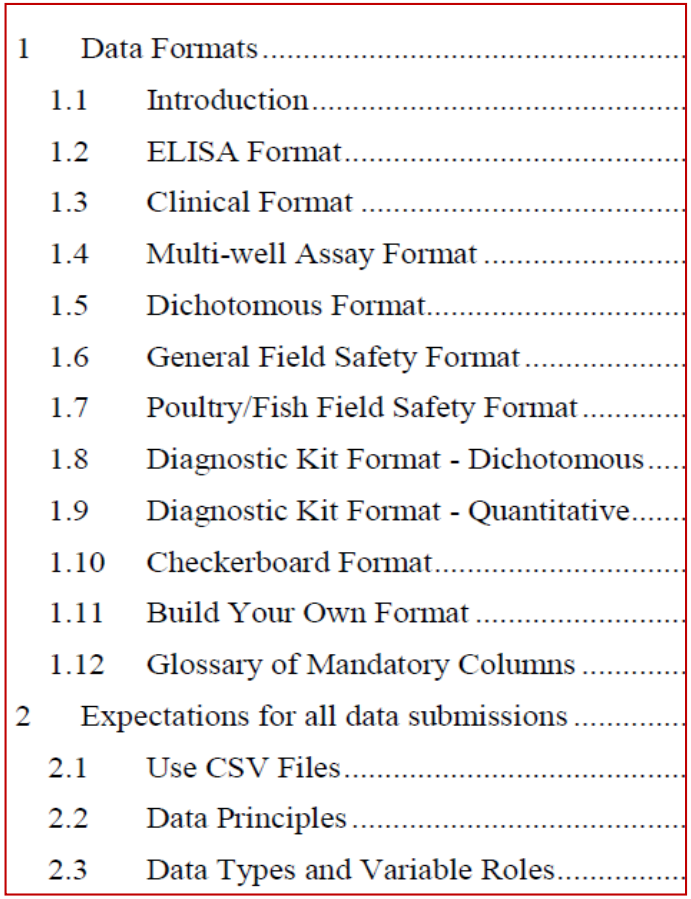
- Suitable protocol ≠ guarantee regulatory acceptance of all possible outcomes, but it does reduce risk of having to repeat the study
- Follow the written protocol when conducting the study



Good data packages

Follow agency guidelines for report format

- CVB guidance on submitting electronically
  - Ensures submissions are routed properly and are amenable to electronic review
  - Specific expectations for electronic data formatting—Use CVB-supplied templates to enable machine reading and processing, even if electronic files are delivered by regular mail



Getting started with a Sponsor-CRO relationship

- Put CDA/NDA in place
- Agree upon Statement of Work/Protocol
  - Have complete/detailed study protocol available and agreed upon well in advance of initiating work
  - Ideally, input from applicable regulatory agency
  - Agree upon level of participation and oversight by study sponsor
  - Develop method to communicate revisions to protocol

Define Quality Expectations

- Does CRO have a Quality Management System?
- Is the study expected to be GxP compliant?
- Will the Sponsor's Quality group be auditing the CRO?
- Who is responsible for QC of the data?
- What are the training and training documentation expectations?
- What is the role of the Study Monitor?

Define Responsibilities

- Determine level of validation or qualification of the CRO's lab methods (needs can vary depending on regulatory agency)
- Duplicate clinical samples
  - Are they expected?
  - Who will maintain and how
- Chain of custody documentation (shipment & receipt)
- Cold chain documentation, if applicable

Define Responsibilities

- Preparation of vaccine material—clarify and agree upon handling instructions
- Quantification of vaccine dose at beginning and end of vaccination phase(s)
  - Who will do?
  - Use of sample from actual vaccine vial or representative samples held in lab?
  - # of replicates?
  - Quantification method—ideally done with validated potency assay
- Same considerations apply to challenge material

Define Responsibilities

- Progress reports--frequency and level of detail
- Determine how unexpected developments be communicated
- General animal welfare expectations
- Determine responsibility and management for any DEA-controlled substances

Sponsor Responsibilities

- Fully understand the agency's expectations
- Clearly communicate expected deliverables
- Fully understand CRO's capabilities ***and*** limitations

High quality records and reports leave the Agency with a favorable impression of the Sponsor and the CRO

If you don't take the time for proper documentation, regulatory approval is delayed (at best)

Agency review process halts every time there is a question/need for clarification

Agency Interactions

Incomplete records damage the credibility of both the Sponsor and the CRO:

- “We can’t find it” does not sit well with any agency
- Consequences:
  - Integrity of CRO is called to question
  - Integrity of Sponsor is called to question
  - “If they were negligent here, where else did they mess up?”
  - Increased regulatory scrutiny for everything in which the Sponsor and CRO is engaged

Agency expects the person at the end of the phone can answer questions

Sponsor MUST be able to answer questions about ALL studies

"Sign here to indicate you have no idea what you've signed."

Summary

- Rushing into the work can lead to costly errors
- Careful planning is paramount
- Clear roles can smooth the way
- Communication throughout the process is critical


Question
Time!