ONADE's Data Quality Review

Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Regulatory Affairs in Animal Health Seminar
Kansas State University Olathe
March 06, 2018

Presenter:
Ana Lazo, BS, RQAP-GLP, Quality Assurance Specialist

ONADE's Data Quality Review

- The Office of New Animal Drug Evaluation (ONADE) at the US FDA Center for Veterinary Medicine (CVM) conducts the review of new animal drug applications from initial project development to approval
- For ONADE to agree that a new animal drug is safe and effective, and therefore acceptable for approval, the submissions, study reports, and data provided to support approval must be credible
- Credibility relies on the submissions, study reports, and data being of high quality

ONADE's Data Quality Review

- ONADE reviews data with GLP and GCP studies to help demonstrate the studies are of high quality
- Studies must be adequate and well-controlled and of sufficient quality to provide substantial evidence of effectiveness or demonstrate safety.
- Evaluating submission quality and data quality has always been a part of the submission review process at CVM

ONADE's Data Quality Review

- For many years the evaluation of data quality was performed by the scientific reviewers concurrent with the scientific review
- Many of the data submissions received by CVM are not of high quality
- This led to CVM creating and presenting the 2013 Data Quality Webinar

Data Quality Webinar

- CVM/ONADE Data Quality Webinar in 2013. It:
  - Addressed feedback from industry on ONADE's lack of clarity and consistency on the expectations for data quality
  - Provided training and discussion on the factors that can impact the quality of target animal safety and effectiveness data
  - Specifically addressed expectations on data quality, raw data, compliance statements, eSubmitter, etc.

Data Quality Webinar

- After the webinar, CVM continued to review data quality. It was noted that:
  - Submission quality and data quality continued to be an issue
  - Data quality was not improving as expected
  - Consistency of data evaluation across divisions and teams was a challenge

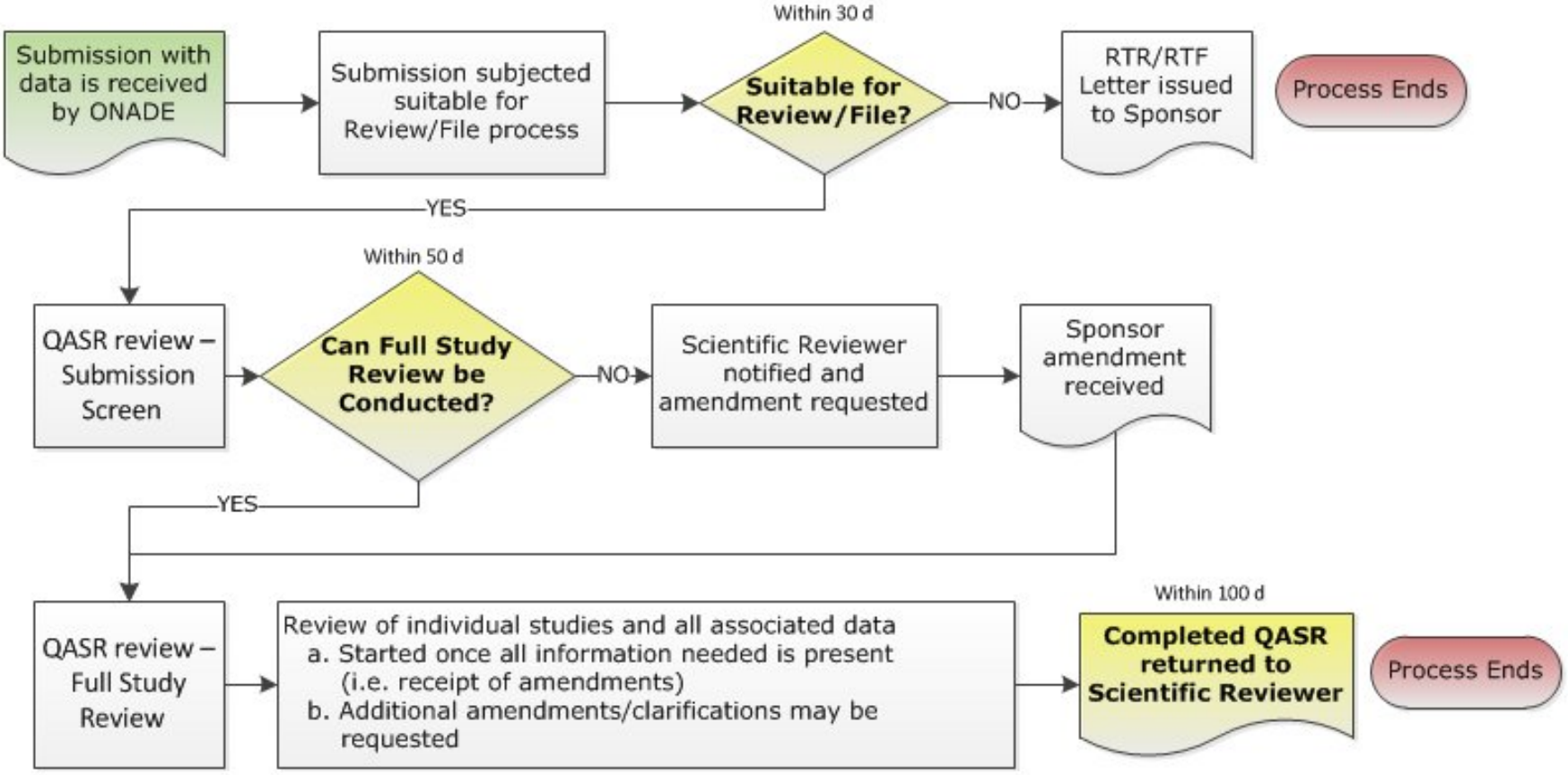
Data Quality Review

- In 2015, CVM/ONADE introduced internal changes to the way data quality was reviewed in an effort to build consistency across multiple divisions and teams in the evaluation of data quality
  - The Quality Assurance Study Review

Quality Assurance Study Review

- As of October 2015, Quality Assurance Study Reviews began on data submissions to evaluate the quality of data contained in these submissions
- Due to resource limitations, not all data submissions are currently undergoing formal quality assurance study reviews by members of the QA Team; all data submissions are reviewed for quality
- The Quality Assurance Study Review is conducted by a Quality Assurance Study Reviewer (QASR). They are experienced GLP/GCP quality assurance professionals

Workflow to Assess Quality



What is the QASR Process?

- The QASR:
  - reviews the submission for data quality and study integrity issues
  - assesses the quality and credibility of the data and final study report (FSR)
  - is in regular communication with other members of the review team
- Two parts to the Quality Assurance Study Review – Submission Screen and Study Review

Quality Assurance Submission Screen

- General recommendation of submission contents are directed by 21 CFR 514.110 (New Animal Drug Applications)
- Looks at overall submission quality and is an initial screen of data quality for each study in the submission
- Examples of what these are:
  - Table of contents: properly organized and indexed
  - GLP compliance statement (for GLP studies)
  - Complete and accurate final study report
  - Complete and accurate English translation of foreign language

Quality Assurance Submission Screen

- Determines if all documents and data are present to continue with a full data quality review
  - Reviews the FSR and protocol to determine what information and contributor reports should be included in the submission
  - Identifies what data were collected, the method of collection, and what copies of raw data are included in the submission
- If required items are missing, an amendment is requested or the submission is found incomplete
- Completed by Day 50 (target) of the review clock (180d)

Common Findings of the Submission Screen

- Poor organization of submission; lack of a good (or any) table of contents
- Critical information can't be located; study documents are not well organized
- Missing or inadequate translation of data in languages other than English (i.e. forms and reports)
- Files can't be opened or do not have data
- The submission contents are not consistent with previous discussions/agreements

Common Findings of the Submission Screen

- Contributing scientist reports are not included in the submission
- Duplicate copies of data or data repeated in multiple files
- Information in eSubmitter is missing, incorrect, vague, or conflicts with the contents of the submission
  - CVM plans to continually improve the structure of eSubmitter to help users build submissions and reviewers find information and evaluate submissions more efficiently.
    - For example, the scientific review staff will be able to identify areas within various submission types, and determine how best to organize the data. The eSubmitter template will reflect these changes in an effort for a more structured format and a better way to organize the data.

Quality Assurance Study Review

- In-depth review of the apparent quality of each study with data in the submission
- Evaluates compliance of the study to the protocol
- Evaluates the completeness and quality of any copies of raw data submitted with studies to support the approval of a new animal drug
- Confirms the submitted copies of raw data support the content of the FSR
- Evaluates adherence to ALCOA (attributable, legible, contemporaneous, original, and accurate) in the copies of raw data

A Quick Note About Protocols

- Protocol concurrence from CVM indicates that we "fundamentally agree with your proposed design, execution, and analyses".
- Protocol concurrence doesn't convey evaluation or agreement with the format or presentation of the final study report.
- The sponsor is responsible for assuring compliance with GLPs and GCPs. All deviations should be discussed in the final study report or GLP compliance statement (for a GLP study).

Quality Assurance Study Review

- Provides the review team (primary and consulting reviewers) with an assessment of the quality and completeness of the data and FSR prior to scientific and regulatory decisions being made.

- Of particular concern are QASR findings regarding:
  - Drug accountability
  - Dosage to study animals
  - Animal accountability
  - Endpoints being measured
  - Adverse events

Examples of Critical Data Quality Issues

- Drug accountability
  - Documentation of the receipt, distribution and disposal allow for the reconciliation of quantities of test article/IVP throughout the study. For example:
    - Improper test article/IVP and control product handling, administration and documentation
    - Poor documentation of test article administration/accounting
    - Poor documentation of storage conditions and/or stored under improper conditions
    - **IMPACT: Unable to determine if drug was maintained appropriately to maintain activity or if study animals were administered correct treatment dose, and therefore, no way to determine the impact of improper storage or dosing errors on study results.**

Examples of Critical Data Quality Issues

- Animal accountability
  - Account for all animals (disposition documented), especially those removed from study
  - Data to support the inclusion/exclusion criteria
  - Trace all animals from the beginning of a study all the way through study completion. For example:
    - An animal removed at the beginning of the study is recorded as alive throughout the study duration
    - An animal that died and received necropsy half way through the study was never removed from the study and had in-life observations recorded up to the end of study.
    - **IMPACT: Resulted in accountability and data integrity gaps**

Examples of Critical Data Quality Issues

- Dosage to study animals
  - Documentation of the amount of TA/IVP given to animals substantiates that the animals received the correct dose at the correct frequency. For example, medicated feed:
    - The same quantity of hay was not provided to all replicates on the same date at Site A
    - According to records, one replicate did not receive hay for over a month, despite days when snow cover would have limited access to grazing
    - Site B did not consistently document when hay was fed and did not record quantity
    - **IMPACT: Unable to determine if intake of free-choice medicated feed provided inferential value to the population.**

Examples of Critical Data Quality Issues

- Endpoints being measured
  - Were the critical end points measured correctly and by the right people? For example: In a residue depletion study the dose or withdraw period was not substantiated:
    - Feeders not checked at appropriate intervals or not enough information provided in study report to fully document when animals finished consuming the medicated feed
    - Study report stated all medicated feed had been consumed, however submitted raw data did not support the statement. In addition, the report did not include any deviations to the protocol or how the amount of feed consumed or dose was determined.
    - **IMPACT: Cannot calculate a withdrawal period if unable to determine if animals received correct dose and/or when treatment period ended.**

Examples of Critical Data Quality Issues

- Adverse events
  - All known and unknown adverse events are recorded in the data and reported in the final study report. For example:
    - Inadequate Adverse Event monitoring of sites in canine field effectiveness study
    - Serious adverse events (SAEs) were not reported
    - Adverse events reported in owner diaries were not included in the final study report
    - Dogs were not managed per protocol when adverse reactions occurred
    - **IMPACT: These deviations were not caught by the monitor and corrected, therefore the issues continued to occur.**

Examples of Critical Data Quality Issues

- Adverse events
  - All known and unknown adverse events are reported in the final study report. For example:
    - Inadequate Adverse Event monitoring a field effectiveness study
    - Increased AEs in treated group *vs* control without explanation or discussion
    - Inconsistent recording of AEs
    - AEs not reported to sponsor within timeframes
    - Incomplete necropsy records on dead animals
    - **IMPACT: Unable to determine if AEs and deaths were treatment related.**

Common Findings of the QASR Review

- GLP Sponsor Compliance Statement
  - Statement should affirm that each study was conducted in compliance with US FDA GLP (21 CFR Part 58) regulations or provide a brief statement of the reason for non-compliance.
  - For studies conducted under OECD GLP, the statement should include a description of each item of non-compliance with regards to the US FDA GLP and the impact of that non-compliance on the study.

Common Findings of the QASR Review

- Unreported Deviations
  - A deviation has occurred and should be documented any time, after the protocol has been signed and when the conduct of a procedure diverges from the protocol
  - At a minimum, the following information should be captured when documenting a deviation
    - Date the deviation occurred
    - A full description of the deviation
    - Any appropriate corrective or mitigating actions taken
    - The impact of the deviation on the study
    - Documentation meets the basic standards we expect for all raw data, e.g., attributable, legible, contemporaneous, original and accurate (ALCOA)

Common Findings of the QASR Review

- FSRs don't accurately reflect the submitted raw data
- FSRs lack sufficient clarity, information, and detail
- Critical study documentation is missing
- Numerous deviations written after study completion

Common Findings of the QASR Review

- No discussion of circumstances that may have impacted the quality and integrity of the study in the FSR
- Lack of documentation to demonstrate appropriate sample handling
- Lack of documentation to verify study personnel were adequately trained
- Inadequate monitoring/QA

Other QASR Objectives

- The QASRS are members of the review team and collaborate with the review team to make decisions regarding the outcome of the submission
- Will continue to monitor overall quality of investigators, contract research organizations, and sponsors
- Will continue to request BIMO inspections and may participate in BIMO inspections
- Will continue to develop tools for outreach to maintain communication with stakeholders regarding data quality standards and expectations

Copies of Raw Data Submitted to CVM

Two different types of raw data are submitted to CVM

- Manual data
  - Collected via hand-writing with indelible ink on paper and copies of manual raw data
  - If submitting to CVM, submit as scanned copies in PDF format
  - Examples: animal receipt records, test article accountability logs, analytical standard and QC preparations, paper data capture forms
- Electronic Data Capture
  - Collected via entry into an electronic system in electronic form Examples: automated hematology records, mobile device data entry platform, etc.
  - Note: EDC is not a topic of focus for this presentation but may be addressed in a future presentation

CVM Review of Data

- **Ultimate goal: The final study report should fully and accurately reflect the raw data. CVM needs confidence in the data to make appropriate regulatory decisions.**

- We need to be able to navigate data files in order to locate data that correlates with protocol required activities, time points, treatments, etc.

Final Study Report: How can you help us?

- Include in the final study report
  - Clearly identify data collected manually vs. electronically
  - Identify data collected manually and later transcribed for review and the QC procedures used to verify the accuracy of the transcription
  - Names of data acquisition systems used and the data collected by each system
  - A statement indicating the instruments(s) and/or equipment were validated and/or calibrated as appropriate (i.e. thermometers, balances, and pipettors.
  - Ensure PDF copies of submitted raw data are fully legible

*** We will continue to work on where we want to be by identifying what crucial data needs to be submitted and what would be the best way to get it.**

Principles for Maintaining Data Quality

- Compliance with data quality principles must be maintained throughout the data lifecycle. Be sure that you are thinking of the following:
  - Data collection
  - Changes to the data
  - Submission to CVM
  - Archival

Signs Data Quality is Improving

We are starting to see an improvement in submission and data quality

- Better and more complete documentation of study procedures
- Better explanations of events impacting the outcome of the study
- Better descriptions of data collection methods used, types of data collected via those methods, and QC procedures used to ensure data quality

Submission/Data Quality Relevant Resources

- Not a comprehensive list but examples of some of the most important for data quality:
  - 21 CFR 58 (Good Laboratory Practice)
  - 21 CFR 514 (New Animal Drug Applications)
  - CVM GFI #85 (VICH GL 9) – Good Clinical Practice
- Other relevant GFIs as per the individual study type, e.g.,
  - Bioanalytical Method Validation (2013 draft)
  - GFI #3 – General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food Producing Animals
  - GFI #185 – Target Animal Safety for Veterinary Pharmaceutical Products

Submission/Data Quality Relevant Resources

- The Data Quality Webinar and Q & A document are excellent resources on data quality and can be found here: *http://wayback.archive-it.org/7993/20170111100024/http://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm348902.htm*
- If you have questions about CVM/ONADE's data quality program please contact the Quality Assurance Team Leader:

Michelle.Kornele@fda.hhs.gov

Thank You!


FDA
U.S. FOOD & DRUG
ADMINISTRATION