

Demystifying the QASR Process

Presented by: Center for Veterinary Medicine (CVM)/Office of New Animal Drug Evaluation (ONADE), Quality Assurance Specialists

Ana Lazo, B.S., RQAP-GLP
DeLisa Davis, B.S.
Jordan Desilva, B.S.

Stefanie Cook, B.S., RQAP-GLP
Joo Jin, M.S., RQAP-GLP
Hong Song, M.B.A., RQAP-GLP

Objectives

- Background and Basics
- The Quality Assurance Study Reviewers (QASR) Review
 - Submission Screen
 - Full Study Review
 - Key Points
- Electronic Data Capture
- QASR Projects
- Discussion of questions from CVM



Background and Basics



CVM/ONADE and Data Quality

- CVM requires copies of raw data to be submitted with GLP and GCP studies.
- For CVM to agree that a new animal drug is safe and effective, the submissions, study reports, and data provided must be credible.
- Credibility relies on the submissions, study reports, and data being of high quality.
- Copies of raw data need to be accurate, legible, contemporaneous, original, and attributable (ALCOA).



Quality Assurance Study Review

- As of October 2015, CVM began a program for Quality Assurance Study Review to evaluate study quality and data integrity.
- The review is conducted by experienced GLP/GCP quality assurance professionals.
- Due to current resource limitations, not all data submissions are undergoing quality assurance study reviews by data quality experts.

Who are the QASRs?

- QASRs are Quality Assurance Study Reviewers.
- QASRs are quality assurance (QA) professionals with extensive QA experience and backgrounds at regulated research organizations.
- Have expertise in various fields, such as toxicology, analytical chemistry, histopathology, computerized systems validation, electronic data capture systems (EDCs), etc.
- QASRs have 50 plus years of combined industry QA experience.
- Work with sponsors, and other divisions within ONADE, the CVM Office of Surveillance and Compliance, and other Offices within CVM.
- Provide expertise in regulatory compliance in support of new animal drug approvals.



QASR Team Members

- Michelle Kornele, D.V.M., Team Leader
- Ana Lazo, B.S., RQAP-GLP
- Stefanie Cook, B.S., RQAP-GLP
- DeLisa Davis, B.S.
- Joo Jin, M.S., RQAP-GLP
- Jordan Desilva, B.S.
- Hong Song, M.B.A., RQAP-GLP

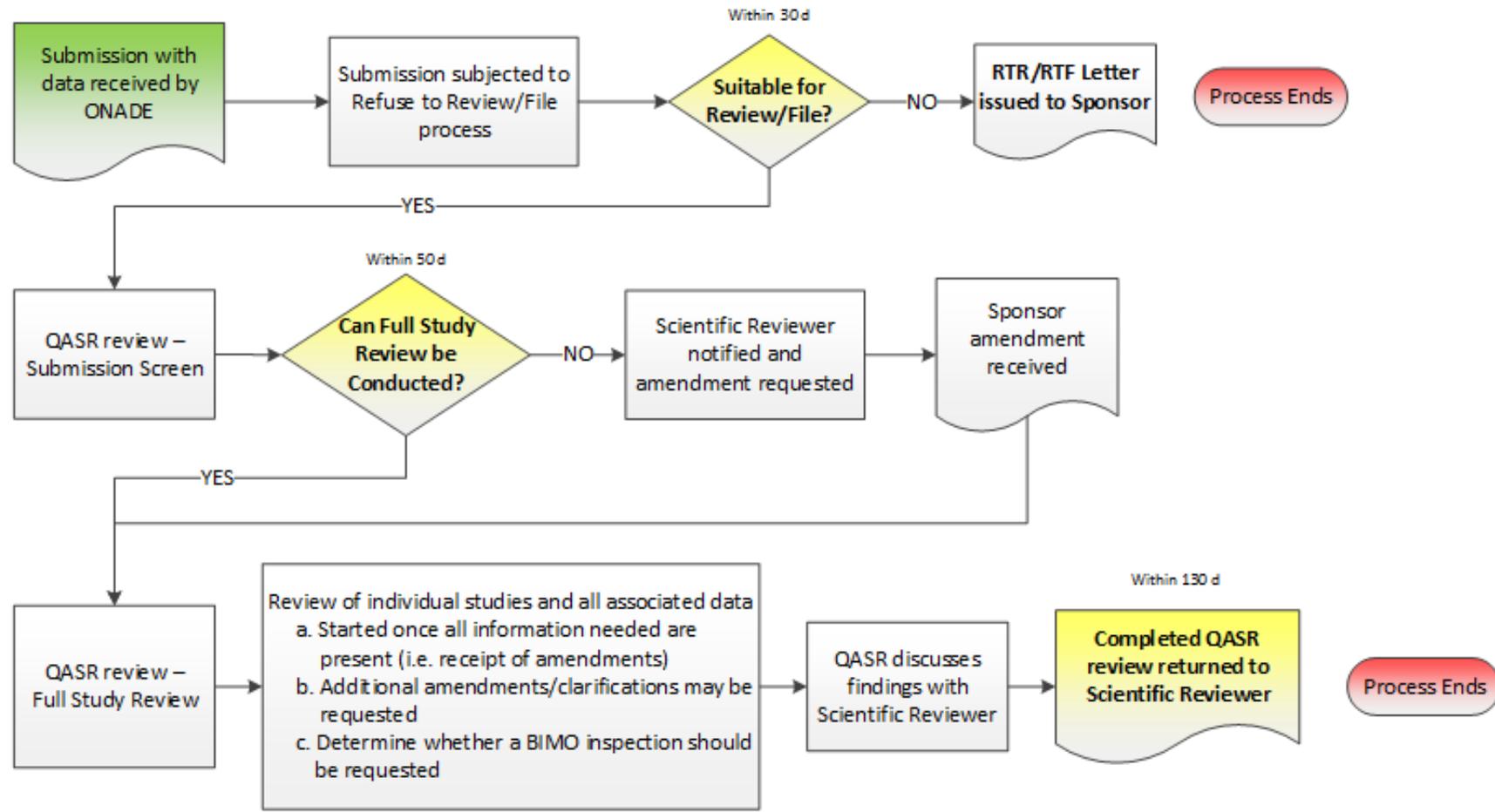


The QASR Review

Studies Undergo Quality Assurance Study Review

- A submission may contain multiple studies/sites.
- Only studies submitted with data in support of CVM decision-making are consulted for QASR review.
- The QASRs currently accept consults of the following study types:
 - Effectiveness
 - Safety (target animal and human food)
 - Bioequivalence

Workflow to Assess Quality



Study Screen

- Commences after the RTF (refuse to file)/RTR (refuse to review) assessment has been completed by the home review division. RTF/RTR is a brief initial review for submission completeness.
- Comprehensive screen to confirm all information is present for the full study review.
- Conducted to confirm all necessary documents and data that will be used to support scientific and regulatory decisions are included.
- If significant deficiencies are identified, transmit to sponsor comments will be provided to the primary scientific reviewer to request an amendment.
- Completed by Day 50 of the review clock.



Submission Screen

- In a submission, we expect
 - Final study report
 - Signed protocol and amendments
 - Copies of raw data to support protocol requirements
 - Including audit trails if collected in an EDC system
 - Sponsor compliance statement
 - README file and table of contents

Submission Screen – Examples of deficiencies

- Files contain entries in a foreign language.
 - Full translations are not provided.
 - Translations are not required to be certified but are expected to be accurate per the commitment of the sponsor via signature in eSubmitter.
- Sponsor GLP compliance statement is not provided for GLP studies.
- Categories of copies of pertinent raw data are not provided.
- The XML electronic data files only contain the final data points and date; audit trails aren't provided.
- Missing or insufficient README File.

Full Study Review

- The full study review is an in-depth review of the apparent quality of each included study with data in the submission. Study review confirms:
 - That the final study report (FSR) accurately describes the conduct of the study, including the standard of conduct.
 - That the submitted copies of raw data support the content of the FSR and the FSR accurately reflects the raw data.
 - That the study was conducted in accordance with the protocol & protocol amendments with any deviations documented.

What the Quality Assurance Study Review is not:

- A pre-approval, desktop BIMO; the review is focused on the accuracy of FSRs and the copies of raw data submitted to support the protocol and FSR in addition to regulatory compliance.
- An expectation from CVM for “perfect” studies; no study is “perfect”.
- A simple QC check; verification of transcribed data copies submitted as XML files is a small portion of the QASR review.



Key Points for QASR Review



Key Areas of Focus

- Five areas of focus for data integrity
- The final study report
- Sponsor GLP compliance statement (for GLP studies)

Five Areas of Focus

- QASR transmit to sponsor comments are focused on the following five critical areas, which are also the five areas of focus during the study review:
 - Drug accountability
 - Dosage to animal
 - Animal accountability and enrollment
 - Study endpoints and critical variables
 - Adverse events
- Other comments may be provided, as agreed upon by the review team

Drug Accountability

- Points to consider when preparing your submissions:
 - Documentation of
 - Chain of custody
 - Drug storage
 - Drug use
 - Disposition
 - Specifics of documentation will be determined by the standard of conduct and the protocol.

Drug Accountability – Common Deficiencies

- Amount of TA (test article)/IVP (investigational veterinary product) received, usage, return and disposal
 - Accountability throughout the study not properly or poorly documented.
 - Amounts used throughout the study don't match up.
- Reconciliation of TA/IVP
 - Amounts don't match.
 - Vials or amounts previously “lost” (such as a broken vial or spilled amount) appear in final amounts.
 - “Lost” amounts are not properly documented at the time of occurrence or not documented at all.
 - Drug usage is not properly documented.

Drug Accountability – Example

- No documentation of the receipt and disposition of the test article.
 - We could not determine whether the documentation was not located because it was created and not submitted or not documented during the study.
 - It is important that the documentation of the test article receipt and disposition are provided to us because we verify that all test article can be reconciled based on the amount received, the amount used, and the amount remaining.
 - Accountability permits us to determine if the correct dosing occurred.
- As a result, the sponsor was asked to provide us with the copies of test article and disposition record via an amendment to the submission.

Dosage to Animal

- Points to consider when preparing your submissions:
 - Documentation of
 - Each dose administered (per protocol)
 - Dosage amount
 - Treatment administered (test article or control)
 - Route of administration
 - Time administered (if required by protocol)
 - Identity of treatment administrator and data recorder (if different)
 - Mis-dosing, re-dosing, and other dosing issues
 - Any special equipment used



Dosage to Study Animals – Common Deficiencies

- Animals were not dosed per protocol.
- Documentation doesn't support protocol dosing method (syringe size, route of administration).
- Can't verify TA/IVP administration or the amount administered due to poor documentation.
- Notification and documentation of mis-dosing:
 - Not reported in timely manner.
 - Less than thorough assessment on impact to the study.

Dosage to Study Animals – Example

- There was no documentation of which product was administered to each animal and whether dose was administered subcutaneously in the designated area. Also, animals not intended for dosing were documented as being dosed.
 - We could not confirm that the animals received the intended product (control or IVP) via appropriate route of administration. Also, non-compliance to the protocol occurred because animals that were not supposed to receive dosing were documented as dosed.
 - This study had other numerous documentation issues, gaps in documentation, and non-compliance issues. Therefore, we determined that the study was not an adequate and well-controlled study. We recommended that the primary reviewer not use the study in support of regulatory decision-making.
 - The primary reviewer agreed with the QASR's assessment that the study was not considered adequate and well-controlled due to compilation of concerning GCP issues. The study was concluded as not acceptable for evaluation of effectiveness.

Animal Accountability and Enrollment

- Points to consider when preparing your submissions:
 - Documentation of
 - Each animal from receipt to final disposition, including enrollment and randomization
 - Animal history if relevant to meet protocol requirements
 - Method of animal identification
 - Correlation of animal identification methods and numbers (if multiple methods are used)
 - Housing/pen/cage diagram, if applicable

Animal Accountability and Enrollment – Common Deficiencies

- Number of animals received, enrolled and removed
 - Accountability can't be verified from animal arrival to the end of the study.
 - There is poor or no documentation of animal accountability and enrollment.
 - Animal ID's switched then corrected without supporting documentation or after completion of the study.
- Species, gender, age, body weight, inclusion, and exclusion criteria
 - Ages of animals are not within the protocol requirements.
 - Body weights are not within the protocol requirements.
 - Animals enrolled meet/have an exclusion criteria.
 - No documentation provided to support or meet the inclusion or exclusion criteria.

Animal Accountability and Enrollment – Example

- Protocol required 20 animals to be examined for ticks prior to study start, but only 16 animals were examined.
 - The number of animals to be examined for ticks did not meet the protocol requirement. Also the protocol required the 16 animals with the highest tick count be enrolled on the study.
- Deviation was not written for not examining the protocol required amount of animals.
 - Possible exclusion of this site for not meeting the protocol enrollment inclusion/exclusion criteria.
 - Possible RTR if there wasn't enough animals to draw conclusion.

Study Endpoints and Critical Variables

- Points to consider when preparing your submissions:
 - Documentation of
 - Endpoints and critical variables in a clear and concise manner
 - Units (per protocol)
 - Procedures used
 - Sample collection, chain of custody, processing and evaluation
 - Who did what and when

Study Endpoints and Critical Variables – Common Deficiencies

- Observations and measurements
 - Not collected/documented per protocol.
 - Improper sample storage and handling.
 - No sample stability for repeat thawing and refreezing.
 - Poor or no documentation.
 - Late entries or corrections after the study.
- Masking
 - Personnel not masked per protocol.
 - Masked personnel performing tasks that could unintentionally unmask those personnel.

Study Endpoints and Critical Variables – Example

- In a flea effectiveness study, flea combing times were significantly less or more than protocol requirement and flea counting was conducted out of order. Some infestation times were recorded within the same minute or a minute after the previous animal's infestation time, however, only one person was identified for multiple functions and animals were not in close proximity (i.e. the next animal in different room).
 - We could not determine whether the same amount of fleas would have been observed if the time spent for combing would have been per the protocol. And, because the flea counting was not conducted in order, it could not be determined if any bias was introduced. Also, the data collected interfered with CVM's ability to confirm that the data are attributable, original, accurate, contemporaneous, and/or legible.
 - This study had several other issues with overall study quality and data integrity and we could not have confidence that the study was adequate and well-controlled and of sufficient quality to provide substantial evidence of effectiveness.
 - The primary reviewer agreed with the QASR's assessment and concluded that the study should be considered invalid due to lack of evidence for the adequate and well-controlled study.

Adverse Events

- Points to consider when preparing your submissions:
 - Contemporaneous documentation of:
 - Each occurrence
 - All assessments, procedures, testing, and results
 - Notification of appropriate personnel within appropriate timeframes

Adverse Events – Common Deficiencies

- Documentation, notification, and investigation of adverse events (AEs)
 - Little or no documentation of the AE
 - Notification is not in a timely manner
 - Little or no investigation
 - Less than thorough assessment
- Final Study Report verification
 - FSR does not match the AE documentation
 - Not all AEs reported in the FSR

Adverse Events – Example

- Numerous serious AEs, including animal death, were not reported to the sponsor within 24 hours as required per the protocol. Many of these serious AEs were reported weeks to months later.
 - This study had other numerous documentation issues, gaps in documentation, and non-compliance issues. Therefore, we determined that the study was not an adequate and well-controlled study. We recommended that the primary reviewer not use the study in support of regulatory decision-making.
 - The primary reviewer agreed with the QASR's assessment that the study was not considered adequate and well-controlled due to compilation of concerning GCP issues. The study was concluded as not acceptable for evaluation of effectiveness.

The Final Study Report

- The Final Study Report should:
 - Clearly state the standard of conduct.
 - Accurately reflect the conduct of the study.
 - Accurately reflect the data generated during the study.
 - Contain signed contributor reports.
 - Fully address any issues that may have impacted the outcome of the study.

Final Study Report – Common Deficiencies

- Missing or not signed contributor reports
- Does not accurately reflect the raw data
- Does not accurately describe the QC procedures in place for the transfer of data to a contributing scientist (or necessary personnel)
- Deviations not reported to the study director (SD) and the impact on the study not addressed
- Analysis validation plans not defined or amended into the protocol
- EDC systems not clearly defined or listed
- Data transcribed into an EDC system not clearly identified
- How ALCOA was maintained in the EDC systems used on the study not clearly indicated in the FSR
- Archival of data collected using an EDC system not reported
- Validation and or calibration of equipment not described

Final Study Report – Example

- The FSR did not meet requirements of 21 CFR Part 58 (GLPs)
 - It lacked the contributor reports.
 - No description of circumstances that may have impacted the quality and integrity of the data was included.
 - The FSR did not have sufficient detail to fully and accurately summarize the conduct and outcome of the study.
 - An amendment may have been requested.
 - Could indicate lack of study oversight or adherence to GLP's.

Sponsor GLP Compliance Statement

- For a GLP study, we expect the contents below to be included in the compliance statement:
 - This statement must affirm that each such study was conducted in compliance with the GLP regulations or provide a brief statement of the reason for the non-compliance as described below.
 - Describe all deviations and GLP exceptions noted in the study director's FSR with the impact assessed.
 - For studies conducted using standard other than FDA GLPs:
 - Describe how you did not comply with FDA GLPs in your study.
 - Describe how studies complied with the FDA GLPs and why the non-compliance to FDA GLPs did not affect the outcome of the study results.
 - The statement should be signed/dated by the sponsor representative(s) responsible for making these assurances.
 - Statement should be reviewed by the QAU.

Sponsor GLP Compliance Statement – Common Deficiencies

- The sponsor GLP compliance statement is not present.
- There is a lack of clarity in the role of the individual signing the statement.
 - Is the signature authority an employee of the sponsor that has direct knowledge of the conduct of the study, understanding of GLPs and able to appropriately assess the impact that any deviations may have on the study?
- Items of non-compliance are not identified in the statement.
- Includes a listing of the differences between OECD and FDA GLPs. This should not be included in this statement.
 - We need to understand the specific non-compliance to FDA GLPs that occurred for your study and what impact it has on the quality of your data submitted to CVM.



Sponsor GLP Compliance Statement – Example

- Sponsor GLP compliance statement claims OECD GLP compliance and doesn't address exceptions to FDA GLPs.
 - The sponsor was requested to amend the sponsor compliance statement to clearly indicate what exceptions to the FDA GLPs (21 CFR 58) occurred during each study. Exceptions include any practices used during the study that may have been in compliance with OECD GLPs but that deviated from the FDA GLPs.

Additional Common QASR Observations

- Final Study Report does not accurately reflect the raw data.
 - Cut and paste from protocol and only changes tense and possibly adds amendment without clarification or explanation of what occurred.
- Unreported deviations:
 - Numerous deviations written after study completion.
- No discussion of circumstances that may have impacted the quality and integrity of the study in the FSR.
- Documentation issues:
 - Notes to file (NTF) written at the end of the study to document protocol requirements without supporting documentation.
 - Lack of documentation of sample handling from necropsy to freezing (residue studies).
 - Non-contemporaneous recording of data and protocol required procedures.

Additional Common QASR Observations

- Data does not support that adequate personnel were involved in the study.
- Test article/IVP not able to be reconciled.
- Animal accountability, especially for those removed from study.
- QA inspection reports not reported to the SD and Test Facility Management (TFM) in a timely manner.
- Contributing scientist reports not appended to the FSR or included in submission (mixture assays).
- Equipment issues:
 - Calibration and verification didn't bracket the actual ranges.
 - No current calibration records to show the equipment was maintained and suitable for use for the duration of the study.

Benefits of the QASR Process

- More transparency and consistency through a standardized quality assurance study review by QA professionals.
- More efficient review by the scientific reviewers.
- More predictable application of standards to sponsors and more consistency between the divisions.
- Better communication of CVM's expectations with sponsors and consistency across all divisions within ONADE.
- Improvement in submission and study quality, which has consistently been a concern of CVM.

Electronic Data Capture

Electronic Data Capture

- To recap on 2017 SQA presentation, there are two different types of raw data 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 that have been subjected to an optical character recognition (OCR) process.
 - Electronic Data Capture (EDC)
 - Collected via entry into an electronic system in electronic form.

Overview

Common EDC Questions

- Since participating in the 2017 Society of Quality Assurance Annual Meeting & Quality College, sponsors have requested meetings with CVM to discuss their Electronic Data Capture (EDC) systems.
 - Based on the questions that are commonly asked of us, we have identified common EDC related questions.
 - We will outline common EDC related questions and provide points to consider.

Copies of Raw Data Submitted to CVM

- Electronic Data Capture (EDC)
 - Require the electronic data be in eXtensible Markup Language (XML), SAS xPORT (XPT) format, or PDF* in order to secure longevity of the data in a format with audit trails.
 - Refer to the CVM Recommended File Specifications for eSubmitter document.
 - Static data: Data that cannot be altered or changed once recorded.
 - Dynamic data: E-data that allows interaction between the user and the record content.

* that have been subjected to an OCR process



Common EDC Related Questions

- What are CVM's expectations for submission of copies of raw data collected using an EDC system?
- Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?
- Does CVM have preference for file naming for a submission of Table of Contents?
- If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?
- Is there an EDC system that CVM prefers? What are the typical areas of concerns?

Common EDC Related Questions

- **What are CVM's expectations for submission of copies of raw data collected using an EDC system?**
- Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?
- Does CVM have preference for file naming for a submission of Table of Contents?
- If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?
- Is there an EDC system that CVM prefers? What are the typical areas of concerns?

Submission of Copies of Raw Data Collected Using EDC Systems – *Points to Consider*

- The Data and Key Associated Metadata
 - Exported directly from the source EDC system and provided in XML file(s).
 - If any XML files cannot be directly exported from the original EDC system
 - Describe the process and the controls in place for the transformation or manipulation of data to the final XML format.

Submission of Copies of Raw Data Collected Using EDC Systems – *Points to Consider*

- Electronic Audit Trails
 - Should be linked to the original data points and identify the data modified, operator ID, time/date stamp, and reason for change.
 - Provided in XML format.
 - If this information cannot be provided
 - Describe how the attributes of ALCOA are maintained within the EDC system.

Submission of Copies of Raw Data Collected Using EDC Systems – *Points to Consider*

- XML Specifications
 - The files should be in a plain text format, structured within a simple (flat) tabular form, where each file represents a singular data set structure.
 - What we don't want:
 - Combined/Appended data sets of varying structures within a single file.
 - Hierarchical “tree” structured data that requires an underlying knowledge of the source system to map/import.

Submission of Copies of Raw Data Collected Using EDC Systems – *Points to Consider*

- Describe how the attributes of ALCOA are maintained for the collected data throughout the internal handling of the data files through the submission of the data files to CVM for evaluation.
- Describe what data are collected electronically, directly into the various EDC systems uses.
 - Describe what data are collected and recorded manually and what data are collected manually and transcribed into an EDC system.
- Describe the quality control procedures and methodology used when transferring values for processing or evaluation.



Submission of Copies of Raw Data Collected Using EDC Systems – *Points to Consider*

- Additional XML Constraints*
 - Length of element names
 - No more than 32 characters
 - Character set for element names
 - Alphanumeric and underscores
 - No special characters
 - Number of element levels
 - No more than three: Table/data descriptor, row identifier, column/variable name

* CVM is updating these constraints in the eSubmitter File Specifications document.

Common EDC related Questions

- What are CVM's expectations for submission of copies of raw data collected using an EDC system?
- **Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?**
- Does CVM have preference for file naming for a submission of Table of Contents?
- If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?
- Is there an EDC system that CVM prefers? What are the typical areas of concerns?



Data Recorded on Paper and Transcribed into an EDC System – *Points to Consider*

- Copies of raw data collected manually and then transcribed into an EDC system should be provided in scanned, OCR'd (optical character recognition) PDF format.
 - Transcribed electronic data should be provided in XML or XPT file format.



Common EDC related Questions

- What are CVM's expectations for submission of copies of raw data collected using an EDC system?
- Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?
- **Does CVM have preference for file naming for a submission of Table of Contents?**
- If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?
- Is there an EDC system that CVM prefers? What are the typical areas of concerns?

Table of Contents

File Naming – *Points to Consider*

- Describe the content of each file so that it is easy to identify and locate the information provided within the files.
 - Provide a descriptive file name for each file included in the table of contents.
 - It is helpful if the table of contents are provided as a separate standalone document.
- Refer to Guidance for Industry #197 (Documenting Electronic Data Files and Statistical Analysis Programs) for additional information.



Common EDC related Questions

- What are CVM's expectations for submission of copies of raw data collected using an EDC system?
- Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?
- Does CVM have preference for file naming for a submission of Table of Contents?
- **If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?**
- Is there an EDC system that CVM prefers? What are the typical areas of concerns?

Individual File Size in eSubmitter – *Points to Consider*

- For XML, XPT, and OCR'd PDF files in eSubmitter
 - No individual file sizes over 100MB.
 - If the file size is over 100MB, break apart into logical components that meet the size limits.
 - If there are no logical separation points for the data:
 - Break apart into <100MB files.
 - Describe how the separation points are chosen and how the resulting split files piece together.



Common EDC related Questions

- What are CVM's expectations for submission of copies of raw data collected using an EDC system?
- Should both paper and electronic files be submitted if the data were captured on paper and transcribed into the EDC system?
- Does CVM have preference for file naming for a submission of Table of Contents?
- If an individual file size is larger than eSubmitter will allow, what is CVM's recommendation?
- **Is there an EDC system that CVM prefers? What are the typical areas of concerns?**

EDC Systems – *Points to Consider*

- Each sponsor should evaluate the needs for their study and select appropriate equipment and systems.
 - Any systems used in a study should provide data that meet CVM's requirement for submission.
 - The attributes of ALCOA should be maintained throughout the data lifecycle:
 - Data collection
 - Changes to the data
 - Import and export of data
 - Submission to CVM
 - Archive

EDC Meetings with ONADE

EDC Related Meetings

- ONADE has developed several points for sponsors to consider when evaluating EDC systems and their use in regulatory studies.
 - Responses to these questions submitted in the agenda for the EDC meeting request can facilitate a more successful discussion.
 - This information will help us understand the EDC system proposed to be used and will provide constructive feedback during the meetings.

EDC Related Meetings

- Points for sponsors to consider when talking to CVM about EDC systems:
 - Make sure we know what EDC system(s) you are using.
 - How are the raw data captured by the system and what controls are in place that assure the raw data meet the principals of ALCOA?
 - How are data exported from the EDC system and what file format(s) are available in that export and whether the audit trail information is exported with the data elements in the same file or separately?
 - Are the exported data files readily human readable once exported using “normal” software or it must be manipulated prior to viewing or viewed using special software?
 - Are any data collected on paper, other automated collection system(s) or instrument(s) and then transcribed into an EDC system?
 - Would it help us understand if you provided an example of the table of contents or organizational structure for the data files in the submission?
 - Would it help us understand if you provided a few example screenshots of the system data forms?
 - Are there any perceived “gaps” in the system (mainly gaps in data integrity) and the mitigation plan?

Electronic Data Submission

How can you help us?

- You can facilitate our review if you include the following information within the submission.
 - Final Study Report
 - Names of data acquisition systems used and the data collected by each system
 - A statement indicating the system(s) and/or equipment were validated and/or calibrated as appropriate
 - Clear identification of data collected manually vs. electronically
 - Identification for data collected manually and later transcribed for statistical analysis and the QC procedures used to verify the accuracy of the transcription
 - Information on retention of the electronic data

Electronic Data Submission

How can you help us?

- README File

- Refer to the draft Guidance for Industry (GFI) #197 and the current eSubmitter template.
 - A listing and description/purpose of each data file and program files.
 - List of all variable, abbreviations used, columns in the data file, and units of measure.
 - Audit trail file listing and audit trail file content if the electronic audit trail will be submitted separately from the data files.

- Standalone Document

- Description of the systems used to generate XML files for submission
 - Validation status / How did you maintain the integrity of the data from collection to submission.
 - Description how data integrity is maintained when information is converted to a format different from that used for original capture.
- Description of the controls in place after export of data from controlled environment in preparation for submission to CVM.



Electronic Raw Data Pilot Program: Read Only Access

- CVM initiated a pilot program to test the read only access to electronic raw data *in lieu* of submitting copies of electronic raw data.
 - If a sponsor is considering providing CVM with the read only access to the raw data, the sponsor should confirm that one or more electronic data capture (EDC) systems were used during the conduct of the study and if so, during what phase(s) of the study were they used.
 - The sponsor should confirm that the electronic data are read only and locked so that it is only viewable by CVM and no inadvertent changes can be made.
 - Some questions for sponsors to consider if interested in this pilot program are provided on the next several slides.
 - Further discussion with CVM will be necessary to discuss the details of the read only access review prior to submission.
 - Additional information may be requested.



Electronic Raw Data Pilot Program: Read Only Access

- A series of questions to consider for read only access:
 - For each EDC system, can you
 - Identify the EDC system by name and location?
 - Confirm the system has been appropriately validated?
 - State the purpose of the EDC system and the phase of the study where the EDC system is used?
 - Identify whether any software, cookies, etc. are needed to access and use the system?

Electronic Raw Data Pilot Program: Read Only Access

- A series of questions to consider for read only access (continued):
 - Will you be giving CVM access to all the EDC systems used during the study or do you propose to give CVM access to certain EDC systems used during the study?
 - For the EDC systems CVM won't have access to, how do you plan to provide copies of raw data to CVM for review?
 - How would CVM personnel access the system:
 - Are individual user identifications and passwords to be provided?
 - Will multiple CVM personnel be able to access data at the same time?
 - What would be the length of time CVM would have access to the data?

Electronic Raw Data Pilot Program: Read Only Access

- A series of questions to consider for read only access (continued):
 - What information would be available for CVM to view for each EDC system:
 - Would you be able to provide a certification that the data that are viewable by CVM is the identical data that are viewable to sponsor employees?
 - What modules would be viewable? Would all audit trails be viewable?
 - Do data have to be unarchived to be viewed?
 - Can data be filtered while viewing?
 - Can reports or copies of the raw data be exported if needed for documentation in a CVM review?
 - If your study included manually collected data, explain how the raw data would be viewed.

Electronic Raw Data Pilot Program: Read Only Access

- A series of questions to consider for read only access (continued)
 - Would you (the sponsor) or a representative be able to provide support to CVM if there are any problems or questions accessing the data or navigating the system?
 - Are there manuals, training guides, or SOPs available for the EDC system(s)?
 - Are there abbreviations, modifiers, flags, or codes used within the system that need to be referenced by other documents?
 - Are you (or your QAU) willing to provide EDC access and generating report training?



Electronic Raw Data Pilot Program: Read Only Access

- All statistical files will still need to be provided to CVM in XML or XPT format.
- Manual data will be need to be submitted as scanned copies in OCR'd PDF format.
 - If any data recorded on paper forms are transcribed into the EDC system, please provide the original data in PDF format.
 - Identify which data collected manually and electronically in your submission. Also, clearly identify data collected manually and later transcribed into the EDC system in your submission.



QASR Current Projects

BIMO Inspections

- QASRs are now participating in BIMO Inspections:
 - QASR participation is discussed and agreed upon by the review team.
 - QASRs participated in their first BIMO inspection last year. As a reminder, inspections are led by the FDA field investigator.
 - Goal of participation: to provide additional assurance regarding the overall quality and integrity of studies conducted at the study site. As stated previously, QASRs have industry experience in QA and are able to apply that experience when participating in inspections.

BIMO Coordinators

- New roles, fulfilled by one of ONADE's QASRs (the other is in OSC)
- Objectives:
 - Goal is to work with the Office of Surveillance and Compliance (OSC) BIMO Coordinator to unify and harmonize BIMO processes throughout CVM.
 - Bridge between ONADE and OSC to enhance consistency and predictability of CVM requested inspections.

Data Quality Standards

- QASRs are also working with colleagues via a variety of internal working groups to develop, document and communicate clear data quality standards for submissions and studies used to support new animal drug approval.
- Examples include
 - Update and revise raw data requirements for submissions.
 - Update Guidance for Industry #197.
 - Update CVM's process for selecting subjects for Bioresearch Monitoring Inspections.
 - Update the 2013 Data Quality Webinar Q&A document with CVM's current thinking.
 - Enhance transparency of the animal drug approval process to industry via a new webpage.

Final Thoughts

- 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 studies, investigators, contract research organizations, and sponsors.
- Will continue to work with review teams to request and participate in BIMO inspections.
- Will continue to develop tools for outreach to maintain communication with stakeholders regarding data quality standards and expectations.

Useful Resources for Data Quality

- The Data Quality Webinar and Q & A document:
<http://wayback.archive-it.org/7993/20170111100024/http://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm348902.htm>
- Guidance for Industry – Computerized Systems Used in Clinical Investigations:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computerized-systems-used-clinical-investigations>
- CVM Recommended File Specifications for eSubmitter:
<https://www.fda.gov/media/120368/download>

Useful Resources (continued)

- Guidance for Industry #197 – Documenting Electronic Data Files and Statistical Analysis Programs:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-197-documenting-electronic-data-files-and-statistical-analysis-programs>
- FDA GLP – Good Laboratory Practice for Nonclinical Laboratory Studies: https://www.ecfr.gov/cgi-bin/text-idx?SID=278873cff30cd921039ec47f65e123d3&mc=true&tpl=/ecfrbrowse/Title21/21cfr58_main_02.tpl
- Guidance for Industry #85 – Good Clinical Practice; VICH GL9:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-85-vich-gl9-good-clinical-practice>

QASR Resources

- QASR P&P (1243.3215) is public at:
<https://www.fda.gov/media/117099/download>
- If you have question about CVM/ONADE's data quality program please contact the Quality Assurance Team Leader:

Michelle.Kornele@fda.hhs.gov



Questions?

CVM's Questions for SQA

1. CVM is exploring alternative methods for data submission to CVM. One potential alternative is granting some members of the review team, such as the primary reviewer (PR) and the quality assurance study reviewer (QASR), Read-Only remote access to the EDC systems used. What challenges do you foresee in granting these individuals from CVM to use the EDC systems to review the data remotely? What suggestions can you propose to help mitigate these challenges, if any?
2. What are the greatest challenges and pitfalls when conducting regulatory studies to support new animal drug approval? For clinical effectiveness studies (especially those conducted in the clinic or on a farm), are there additional or different challenges?

CVM's Questions for SQA

4. For GLP studies, how do you ensure all circumstances that may have affected the data quality or study integrity and their impact assessment are described in the final study reports?
5. What criteria or process do you use to identify and qualify clinical sites or testing facilities to ensure that they can conduct a regulatory study according to its standard of conduct?
6. How do you go about conducting training of clinical investigators and their staff for each study, such as on the GCPs and the protocol? What does this process look like? How long do you spend?
7. Do you have SOPs/QC procedures on how the submission package is put together? How involved is the process or any formal process in preparing a study for submission?