

# QASR Hot Topics

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

Ana Lazo, B.S., RQAP-GLP

DeLisa Davis, B.S.

Jordan Desilva, B.S.

Emily Smith, DVM

Leslie Rhodes, DVM

Elizabeth Cottrell, DVM

# Topics

- **Quality Assurance Study Reviewer (QASR) Program**
  - A. Top 10 findings in paper-based studies (Good Laboratory Practices (GLP) and Good Clinical Practices (GCP))
  - B. Top 10 findings in EDC studies (GLP and GCP)
  - C. Helpful hints for improving our submissions
- **ONADE EDC Remote Access Pilot Program – Updates**
  - A. Participation and feedback
- **Revised Question & Answer Document for the Data Quality Webinar**
  - A. Highlights to the revision updated 2021 (i.e., TA characterization)
- **Useful Resources**



# Quality Assurance Study Reviewer (QASR) Program

# A. Top findings in studies (GLP Part 58 and/or GCP GFI 85)

1. The final study report (FSR) does not fully and accurately reflect the raw data
2. Notes to file (NTF) written weeks to months after the relevant study phase ended to document protocol compliance without supporting contemporaneous documentation
3. Study personnel not fully understanding or executing their responsibilities
4. Apparent lack of training (e.g., GLP, GCP, protocol, etc.)
5. Documentation, notification, and investigation of adverse events (AEs)
6. Clinical observations not performed in compliance with the protocol

# A. Top findings in studies (GLP Part 58 and/or GCP GFI 85)- cont'd

7. The amended FSR or amended contributing scientist reports do not clearly identify which part(s) of the FSR were changed and why
8. The quality assurance unit (QAU) inspection of the FSR not present on the QA statement.
9. The QAU not conducting protocol required inspections
10. QA inspection reports not reported to the SD and Test Facility Management (TFM) in a timely manner
11. Monitors participating in the study conduct of GCP studies.

## B. Top 10 findings in Electronic Data Capture (EDC) studies (GLP Part 58 and/or GCP GFI 85)

1. Unexplained time discrepancies observed when comparing the audit trail date and time stamps to the protocol and other study documentation.
2. EDC system limitations are not described in the submission.
3. Lack of a description of quality control procedures used if data was transcribed into the EDC system.
4. The ReadMe file does not include a description of the contents of the audit trail file including the variable names, label, or description, and any other information necessary for review.
5. Entry errors and discrepancies indicating a lack of training on use of the EDC system.

## B. Top 10 findings in Electronic Data Capture (EDC) studies (GLP Part 58 and/or GCP GFI 85)- cont'd

6. No statement that the EDC system is validated.
7. The validation statement for the EDC system does not address if the EDC system was validated by the sponsor for their use of the system for the relevant study.
8. User roles do not include descriptions of what information each role can access to maintain masking.
9. Electronic Case Report Forms do not document if a recorder was used separate from the observer.
10. Study personnel using other study personnel accounts.

## C. Helpful hints for improving your submissions

1. Ensure the final study report fully summarizes and explains the conduct of the study and accurately reflects the raw data.
2. Provide clear and concise reviewer roadmaps/ notes
3. Provide a table of contents for the submission that includes a description of the content of each file so that information is easy to identify and locate .
4. Provide a complete audit trail Read-me file
5. Data Management Plans
6. Provide copies of raw data collected manually and/or transcribed into an EDC system in scanned, OCR'd (optical character recognition) PDF format.

# ONADE EDC Remote Access Pilot Program - Updates

# Objectives

- Background
- Current Process
- Current Thoughts
  - QASR Perspective
  - Primary Scientific Reviewer Perspective
  - Common Concerns
- Final Thoughts



# ONADE EDC Remote Access Pilot Program - Background

- The CVM/ONADE Electronic Data Capture (EDC) Remote Access Pilot Program was created in response to industry feedback regarding the challenges of submitting copies of raw data to CVM.
- Until recently the procedure to participate in the pilot program involved sponsors answering multiple sets of questions and a minimum of two meetings between the sponsor and CVM to determine if a study could be accepted to participate in the pilot.
- The process has been evaluated and modified after each participating study has been reviewed by CVM. Feedback is regularly collected as part of the pilot.



# ONADE EDC Remote Access Pilot Program – Current Procedure

- Currently, sponsors are asked to answer one set of questions (on the following slides) and meet with CVM once prior to testing access.
- Sponsors submit answers to the questions in a formal (Z) meeting request.
- CVM reviews the sponsor's answers. During the meeting, the answers and any follow-up questions or clarifications from CVM are discussed. The sponsor can also ask additional questions regarding the pilot.
- CVM notifies the sponsor of the acceptance of the study into the pilot either during the meeting or in the acknowledgement letter accompanying the memorandum of conference for the meeting.



# ONADE EDC Remote Access Pilot Program – Current Procedure

- Prior to the sponsor submitting the study
  - CVM provide any information necessary for CVM reviewers to access the EDC system(s).
  - Once CVM reviewer access has been established, CVM reviewers test access and confirm access with the sponsor.
  - Within 2 weeks before or after the study is submitted to CVM, the sponsor and CVM coordinate an informal orientation meeting for the sponsor to provide a brief overview of the EDC system(s) and locations of relevant raw data. Although CVM reviewers are familiar with a variety of EDC systems, studies vary in how data is captured and viewed.



# ONADE EDC Remote Access Pilot Program – Current Questions

1. State the INAD or JINAD file number for which you are considering for the EDC Remote Access Pilot Program. Please include the type of study and the study number you wish to be part of the pilot.
2. Describe the EDC system(s) used for your study. For each EDC system:
  - A. Identify each EDC system by name, server location, and study phase.
  - B. Confirm the EDC system has been appropriately validated by you as the sponsor.
  - C. Confirm that the EDC system can be accessed using a computer running Microsoft Windows 10 Operating System. Identify any minimal requirements needed for Microsoft Windows 10 to access and navigate the EDC system.
  - D. Identify whether any software, cookies, etc. are needed on CVM's end to navigate within the system.



# ONADE EDC Remote Access Pilot Program – Current Questions

2. (cont.) Describe the EDC system(s) used for your study. For each EDC system:
  - E. If your EDC system can be accessed by a web browser, confirm that either Microsoft Edge Version 106.0.1370.52 or Google Chrome Version 106.0.5249.119 can access and be used to navigate the EDC System
  - F. If your EDC System Is compatible with Microsoft Office Software, confirm that Microsoft Office 365 Version 2108 is compatible with your EDC system.
  - G. Identify and list, if any, IP addresses that must be whitelisted to permit access to the EDC system.
3. Provide a brief description of how the raw data are captured within the system and what controls are in place that ensure the raw data captured meet the principles of ALCOA: Attributable, Legible, Contemporaneous, Original and Accurate. Include a description of when (and if) the audit trails begin relative to initial data entry.



# ONADE EDC Remote Access Pilot Program – Current Questions

4. Describe how data may be exported from the EDC system and what file format(s) are available in that export that can be used for review purposes. Please also describe how the audit trail information is exported from the EDC system, the INAD or pilot.
5. Explain if the exported data files are human readable once exported using readily available software (Web browser, MS Excel, etc.) or if they must be manipulated prior to viewing or viewed using special software.
6. Describe any perceived “gaps” in the system (mainly gaps in data integrity) and what you plan to do or have done to mitigate those gaps. For example, if your EDC system relies on a secure internet connection and the internet connection becomes unavailable, what procedures are in place to ensure the raw data collected meets ALCOA.



# ONADE EDC Remote Access Pilot Program – Current Questions

7. Identify which EDC systems used CVM will be able to access for the study. For the EDC systems CVM won't have remote read only access to, describe how you plan to provide copies of electronic raw data to CVM for review.
8. Describe the process by which CVM personnel would access the EDC system.
  - A. Will individual user identifications and passwords be provided for each CVM review team member, and can multiple individuals review data simultaneously?
  - B. Can you confirm that the data are “read only” and locked so that it is only viewable by CVM reviewers and no inadvertent changes can be made.
  - C. How much time is needed to create an account(s)? CVM will work the sponsor to create the accounts for the CVM review team members.



# ONADE EDC Remote Access Pilot Program – Current Questions

9. Describe in detail what information would be available for CVM to view remotely for each EDC system.
  - A. How will you assure CVM that the data that are viewable by CVM remotely are the identical data that are viewable to the sponsor? This could be either be a statement from the sponsor or the EDC vendor.
  - B. What modules or permission structure would be viewable by CVM?
  - C. Can you provide example screenshots of the electronic data capture forms? If the electronic data capture forms have previously been submitted to CVM in another submission such as a protocol submission (E), you can refer to the submission number if the forms have not changed.
  - D. Do data have to be unarchived to be viewed? If the data don't have to be unarchived, will CVM be reviewing archived data? Would all audit trails be viewable?
  - E. How can data be filtered while viewing?



# ONADE EDC Remote Access Pilot Program – Current Questions

10. Describe the system support available to the CVM reviewers during their access (EDC system vendor resources, training manuals, sponsor personnel, etc.).
11. Include a discussion of the contents of the submission and what data will be available through the EDC system and what data will be included in the submission that won't be available through the EDC. Please provide a description of raw data that may be collected manually<sup>1</sup>, other automated collection systems(s), or instruments(s) and then transcribed into an EDC system.
12. If available, please provide an example of the table of contents (TOC) or organizational structure for the data files within the submission
13. Provide a list of questions for CVM to address at our meeting with you.



# ONADE EDC Remote Access Pilot Program – Current Procedure

- Submissions accepted as part of the Remote Access Pilot Program do not contain copies of electronic raw data. Studies submitted through eSubmitter will still contain:
  - Final value data for statistical analysis.
  - Manually collected data as optical character recognized PDFs that cannot be uploaded into an EDC system for which remote access has been provided.
- The CVM review team receiving read-only remote access to the sponsor's EDC system and the stored data for the duration of CVM's review (180 days) for the submitted study only.



# ONADE EDC Remote Access Pilot Program – Current Status

- As of March 2023:
  - Two sponsors have completed a cycle of review.
  - One sponsor currently has a study under review.
- All four of the submissions were/are to support Effectiveness Technical Sections.
- The CVM review teams for the completed submissions had an overall positive experience.



# ONADE EDC Remote Access Pilot Program – Current Thoughts

- Not all raw data reviewed in the EDC system will be captured in CVM's Administrative Record.
  - Raw data that are reviewed directly in the EDC system will not be retained in the CVM administrative record and CVM's archives.
  - CVM reviewers only have access to view information for which they have been given permission by the sponsor.
  - The CVM review team accesses only the submitted study and associated data within the EDC system for the duration of CVM's review. Once CVM's review is complete and the final action letter is sent, the sponsor should disable the CVM review team access.



# ONADE EDC Remote Access Pilot Program – Current Thoughts

- Copies of raw data not captured in the EDC system will still need to be submitted if these files are not uploaded in the EDC system.
  - If your EDC system has the capability to upload PDFs or other file formats, this can be a way to provide CVM copies of the raw data that are not directly recorded into the EDC system.



# ONADE EDC Remote Access Pilot Program – Current Thoughts

- If a study is not participating in the pilot XML or XPT data files to support a safety or effectiveness technical section are submitted by the sponsor via eSubmitter, then converted by CVM to Excel documents for review.
  - Necessitates use of README file
  - Many files, many containing large amounts of information
- Reviewers utilize multiple Excel sheets to evaluate the full clinical picture.
  - Many different Excel files are needed to develop the full clinical picture of an animal's case while on study
  - Difficult to develop a “day by day” clinical picture of the medical record of the animal this way
- Reviewing “paper” data “electronically”



# ONADE EDC Remote Access Pilot Program – QASR's Perspective

- Feedback has been consistently positive.
- The raw data in the EDC system were easily accessed for review in a human readable format.
- The audit trails were directly reviewable in the EDC system and did not have to be provided as a large, separate, complicated XML file.
- Data were easier to review in the EDC system, as individual data points and categories of data along with the audit trail were more readily accessible, and the data were well organized in a logical, easily navigable manner.



# ONADE EDC Remote Access Pilot Program – Primary Scientific Reviewer’s Perspective

- Overall, the EDC Remote Access Pilot Program is a success due to ease of review and ability to see clinical picture of each animal
- Medical records, daily monitoring, physical exams, concomitant medications, and any adverse events were easily viewed for individual patients
- Easy to navigate; “one stop shop” vs data spread over numerous spreadsheets
- EDC access similar to typical electronic medical records seen in practice
  - From the review team’s perspective, data were easier to review in the EDC system, as individual data points and categories of data were more readily accessible, and the data were well organized in a logical, easily navigable manner.



# ONADE EDC Remote Access Pilot Program – Common Concerns

- Will CVM look at data they would not have had access to otherwise?
  - No: CVM only reviews the relevant study data submitted under an associated data (P) submission. Additionally, sponsors control the permissions that are provided to CVM to view data.
- Will CVM review data in the EDC system differently than data submitted in XML files?
  - No: CVM's review process does not change for submissions participating in the pilot. The only difference is the presentation of the raw data.

# ONADE EDC Remote Access Pilot Program

- Final Thoughts:
  - Overall, the CVM review teams had a positive experience with the completed submissions.
  - Sponsors' feedback from the completed remote access pilot program submissions were positive.
  - EDC access facilitated the ease of viewing these forms in a coherent, stepwise manner, and allowed ONADE reviewers to view files for each study animal as the investigator would have entered in data and viewed the file.
  - The EDC was easy to use, intuitive to navigate and access data collected for individual animals, and readily accessible.
  - Because ONADE reviewers were granted read-only access, there was no concern for any accidental editing of values.
  - CVM will continue developing the EDC Remote Access Pilot Program.



# ONADE EDC Remote Access Pilot Program

- If you have questions about CVM/ONADE's data quality program or would like to participate in the EDC remote access pilot program, please contact the Quality Assurance Team Leader:  
[Michelle.Kornele@fda.hhs.gov](mailto:Michelle.Kornele@fda.hhs.gov)

We encourage you to participate in the pilot program!

# Revised Question & Answer Document for the Data Quality Webinar

# Highlights to the Revised Questions and Answer Document for the Data Quality Webinar held June 4<sup>th</sup> and 6<sup>th</sup>, 2013 (revised 2021)

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

Ana Lazo, B.S., RQAP-GLP

Elizabeth Cottrell, DVM

Emily R. Smith, DVM

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# Background

- Previous version of this document was published in October 2014
  - Document was developed as a result of a data quality webinar held on June 4 and 6, 2013
  - Target audience were sponsors, contract research organizations, study directors, and clinical investigators designing, conducting, and submitting data from clinical and non-clinical laboratory studies to the Office of New Animal Drug Evaluation (ONADE)
- A new revised version of the Data Quality Webinar Q&A document was published early April 2021
  - Includes updated answers to the original webinar questions; original questions were not changed, and the answers stayed within the original scope of the question



# Objective

Today's objective will be to highlight important revisions to the document and address questions resulting from previous SQA Webinars on this document

# Important to keep in mind...

- This document is intended to give sponsors some direction; none of the updates are absolute
- Sponsors work across multiple divisions within ONADE, and this document will provide predictability and consistency
- The responses were written at a high-level and sponsors should determine (or work with ONADE) how these would apply to their specific situation

# Questions and Answers

The document includes Q&As relating to the following topics:

- General information
- eSubmitter
- NCIE (notice of claimed investigational exemption)
- Study protocol
- Investigational drug/test article
- Raw data
- EDC systems
- Data capture forms
- Adverse events
- Masking
- Statistics
- Sponsor GLP compliance statement
- Study conduct
- Final study report

# Submission of Spreadsheets (Q 11)

**QUESTION #11: For spreadsheets, do you want those submitted as XML, PDF or XLS(X) files?**

**Updated response:**

- Data organized in a spreadsheet should be converted (preferably) to XML or XPT formats. If this is not possible, an optical character recognition (OCR) PDF may be acceptable for the submission; however, if CVM needs to process the data as part of our review, spreadsheets may be submitted in XML or XPT file formats only (not PDF).
- If a spreadsheet is created as an intermediate tool for data transfer, quality control procedures should be in place to ensure the integrity of the data from the point of collection through to the submission to CVM. If the raw data are directly captured into a spreadsheet file, attributes of ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate) should be maintained within the spreadsheet.

**Description of changes:**

- The emphasis was changed to clearly state CVM's preferences for how to submit the information.
- The revised response also includes information on maintaining data quality.

# eSubmitter, README FILES (Q 15)

**QUESTION #15: How are sponsors handling data files within the eSubmitter submissions? Is it common practice to submit an index or readme file with the datasets to explain them? Where does this file go?**

## **Updated response:**

- eSubmitter requires README files (as PDF files separate from the final study report) to be submitted for Target Animal Safety and Effectiveness studies. These README files describe the file contents (variables, variable abbreviations, units of measure) and uses in data analysis. Although README files are optional in eSubmitter technical section templates for HFS, ENV, and Bioequivalence studies, all data submissions should be accompanied by a README file.
- The structure and content requirements of a README file is described in GFI #197.

## **Previous recommendations stayed the same:**

- The README file should be attached in eSubmitter along with the data files.

# QUIZ

The XYZ EDC system was used to collect electronic raw data on Study 09876. What information would be useful to include in your submission regarding the system?

- A. A description of the data collected electronically or manually
- B. A description of the data transcribed into the EDC system
- C. A description of the costs involved to validate the EDC system
- D. All of the above
- E. A and B

# Electronic data capture systems (Q 40)

**QUESTION #40: What information would be most useful for CVM to evaluate an EDC system? Is there specific information that would be needed for a GLP or GCP study? What information would be needed to ensure an EDC system is compliant with part 11?**

**Updated response:**

A description of data collected electronically, directly into the EDC system; a description of data recorded manually and transcribed into the EDC system

**Previous recommendations stayed the same:**

- a description of the process or procedures that are used to capture the raw data,
- a description of the equipment or instrumentation that are used to capture the raw data
- representations of human readable input screens,
- the nature and location of the storage of the electronic data, and
- a statement of compliance with part 11.

# Electronic data capture systems (cont.)

**QUESTION #40: What information would be most useful for CVM to evaluate an EDC system? Is there specific information that would be needed for a GLP or GCP study? What information would be needed to ensure an EDC system is compliant with part 11?**

**Is there specific information that would be needed for a GLP or GCP study?**

**Updated response:**

The information generally necessary to “**ensure data quality and integrity**” include procedures and controls designed to ensure authenticity, integrity, confidentiality, and non-repudiation of the signed electronic record.

**What information would be needed to ensure an EDC system is compliant with part 11?**

**Updated response to include:**

The sponsor is responsible for evaluating the specific needs for conducting their study and selecting the appropriate equipment and systems that are essential. The sponsor should explain how the data maintained the attributes of ALCOA for the collected data throughout the internal handling of the data files through the submission of the data files to CVM for evaluation.



# Electronic data capture systems (Q 42 & Q 43)

**QUESTION #42: When using an EDC system does the CVM want screen shots of all forms? And if so, would this be limited to the primary forms?**

**QUESTION #43: Should the sponsor submit electronic data capture form equivalents (screen shots) with the protocol? Can a sponsor generate data capture screen after protocol concurrence?**

## **Updated response:**

If inclusion of screen shots or visual representations of the data capture form is not possible, the sponsor may provide a list of forms planned for data collection and include the relevant details about the information to be collected on each form. The description should also specify whether there will be listed options, check boxes, text fields, and how additional unstructured comments will be recorded.

## **Previous recommendations stayed the same:**

- Review of screen shots of all forms (paper and EDC) are used to ensure data are collected appropriately, to minimize bias, and ensure all data (including unstructured or unanticipated observations) are collected adequately.
- The protocol should state which forms will be used in each relevant section of the protocol.

# Protocols and Data Submissions (Q 23)

**QUESTION #23: Please provide some recent examples of common problems that CVM has seen in the review of study protocols and data submissions.**

Updated response now includes the following examples:

## Protocols

- Data capture forms accessible to masked personnel that unmask treatment
- Selection criteria for study animals not defined/described
- Details for one or more critical study procedures are missing (neither the standard operating procedure (SOP) nor sufficient description provided)
- Data capture forms (DCFs) direct the documentation of information that is not described in the protocol
- Insufficient Owner consent forms such as those that are overly promotional, do not accurately reflect the investigational nature of the drug, contain information that is not written in laymen's terms, contain information that the owner is meant to interpret (e.g., pilot study results), or that contain insufficient user and animal safety information

## Final study reports and raw data

- Final study reports that do not address deviations from the protocol or SOPs that are documented in the raw data
- Copies of raw data for critical information missing that are necessary for the reconstruction of the study and that support information described in the FSR
- Discrepancies between the intended dose and actual dose administered to a study animal(s)
- Discrepancies in drug or animal accountability data
- Missing contributing scientist report(s)
- Adverse drug events (ADEs) that were not discussed/assessed by the sponsor in the final study report or documented in the raw data
- Unmasked personnel making clinical observations

# Data capture forms (Q 47)

**QUESTION #47: Are most sponsors sufficiently documenting informed consent, case selection, and enrollment in effectiveness study protocols (and dcfs)?**

**Updated response:**

- Added that the consent form should include user safety information
  - Appropriate handling and disposal of drug
  - Human risks
  - Information to bring to the physician in case of accidental exposure
- Clarified that the consent form should not include statements that the investigational product is safe to use for the proposed indication
- Explained that effectiveness statements should not be included on the consent form unless CVM has reviewed data to support such claims

# Data capture forms (cont.)

## Owner Consent Form Examples

### Acceptable

- I have been informed and understand that this is an investigational treatment and there may be risks associated with its use.
- This investigational veterinary product has not been proven to be effective or safe for this use in the USA by an applicable US regulatory authority.

### Unacceptable

- [Drug A] has been determined to be safe in laboratory studies using dogs at a dose more than ten times higher than the highest dose used for this study.
- The safety and efficacy against heartworm disease, of the investigational product, have been assessed in pilot laboratory studies.
- The toxicity profile (the harmful nature of a drug) has been greatly improved as a result of its delivery in an extended-release formulation.



# Animal Removal from GLP studies (Q 81)

## **Question #81: "Can a study veterinarian remove an animal from study without study director approval?"**

"Yes. This removal is typically performed for humane or serious health implications. While the study director or clinical investigator should be informed of the need to remove an animal (or in emergency situations, informed of the removal), the attending veterinarian is responsible for exercising appropriate humane care of the study animals. In any case, the removal of an animal from a study should be noted in the study records and follow the removal procedures present in the study protocol."

### **Items to Note:**

- During the study "removal" typically refers to taking the animal out of the live phase if it is found dead or is euthanized due to morbidity
- Animal removal criteria, as outlined in the protocol, should be followed
- All data collected on the animal remain in the study file (including any follow-up diagnostic tests)
- Decisions regarding whether animals remain in statistical analyses depends on the objectives of the study
- For target animal safety, all data collected is considered in the safety assessment

# QUIZ

A Notice of Claimed Investigational Exemption (NCIE) is generally NOT required for...

- A. Clinical studies on effectiveness of a previously approved drug for a new indication
- B. Studies conducted to support the Effectiveness technical section under an INAD or in an NADA
- C. Laboratory studies in early product development and study not intended to support approval of specific product
- D. All studies in food animals when the products are intended for human food use



# Notice of Claimed Investigational Exemption (NCIE) (Q 24)\*

## **QUESTION #24: Must a sponsor submit an NCIE when testing an approved drug for an unapproved indication in a clinical study?**

### **Updated response:**

- Includes discussion of application of requirements in 21 CFR 511.1 to collection of real-world data (RWD).

### **Examples of situations where an NCIE may be needed:**

- Studies conducted to support the Effectiveness technical section under an INAD or in an NADA
- Other studies in client-owned companion animals
- All studies in food animals when the products are intended for human food use (includes some GLP studies)
- Clinical studies on effectiveness of a previously approved drug for a new indication

### **Examples where NCIE not generally required:**

- Approved drug used as control product
- Laboratory studies in early product development and study not intended to support approval of specific product (21 CFR 511.1(a) applies)
- Most GLP studies, including bioequivalence studies (except when investigational food use authorization needed)

\*See Also CVM ONADE Policy and Procedures Manual 1243.4066 (<https://www.fda.gov/media/75464/download>)

**QUIZ:** Which statements are **generally** true for test article characterization of an unapproved, final formulation new animal drug product used in a target animal safety (GLP) study?

- The sponsor should perform test article characterization
- The test facility should perform test article characterization
- The sponsor should determine the stability of the batch used in the study before or concomitant with the study
- The test facility should determine the stability of the batch used in the study before or concomitant with the study
  
- The test facility may rely on the labeling and certificate of analysis for characterization of the identity, strength, purity, and composition of the product supplied by the sponsor
- Test article characterization and stability testing may be performed following cGMP-similar conditions
- When test article characterization and stability is performed following cGMP or cGMP-similar conditions, this should be described as a planned exception to the GLP regulations in the protocol, final study report, AND the sponsor GLP compliance statement
  
- The test facility should have all the raw data supporting test article characterization from the sponsor to archive with the study data
- If the sponsor performs test article characterization, they should provide the study director with statements describing what tests were conducted, all results, how batches were manufactured, and the location where raw data are archived, and when the data will be submitted to CVM.



# Test article characterization for TAS studies (Q 26)

**QUESTION #26: Is compliance with cGMPs sufficient to meet the regulatory requirements for test article characterization (§ 58.105) in a target animal study? What information is required in such a study to characterize a test or control article that is already FDA-approved?**

## **Updated response:**

- Joint effort between TAD, DMT, QASRs, BIMO and cGMP team, and ORA
- No longer cites notice of proposed rulemaking for GLP regulations
- Now includes reference to Section 2.1 of GFI #185 (VICH GL 43): “The concepts of current Good Manufacturing Practices (cGMP) must be applied to the IVPP as appropriate for new animal products intended for investigational use”
- Clarification regarding stability testing
- Added detail regarding appropriate documentation
  - Protocols, final study reports (21 CFR § 58.185(a)(9)), and sponsor GLP compliance statements should all identify the use of cGMP or cGMP-similar standards as a planned exception to the GLP regulations along with the reason and discussion of the steps taken to ensure the quality and integrity of the data, as appropriate
- Additional discussion about TAD coordination with CMC technical section review

# Test article characterization for TAS studies (cont.)

## **Previous recommendations remain:**

- Use of cGMP is scientifically justified but is technically not compliant with test article characterization requirements in FDA GLPs (21 CFR 58.105) and documentation starting at protocol stage and through final study report is critical
- Recommendations differ based on type of product evaluated:
  - Unapproved final formulation product used as test article
  - Marketed product used as test or control article

# QUIZ



Which of the following are necessary elements of a sponsor's GLP compliance statement?

- A. Items of noncompliance with the GLP regulations and the reason for noncompliance with the GLP regulations
- B. An assessment and impact statement of each item of noncompliance to the GLPs
- C. A chart describing the differences between the OECD GLPs and FDA GLPs
- D. The study director's signature and date
- E. ONADE Policy Team's approval of the statement
- F. All of the above
- G. A and B

# Sponsor's GLP compliance statement (Q 74)

## **QUESTION #74: What form should the sponsor's GLP compliance statement take?**

- Removed CVMs expectation to use exact wording of statements previously listed.
- Sponsor no longer must contact ONADE's Policy Team before preparing the statement if it deviates from the language of the statements that were previously listed.
- Added references for requirements (21 CFR §§ 511.1(b)(4)(ii), 514.1(b)(12)(iii), 514.8(f), 514.15(c), and 514.110 (b)(8)).
- Provided examples of acceptable wording for the GLP compliance statement.



# Sponsor's GLP compliance statement (cont.)

## Example of an adequate statement

- For a GLP study, the contents below are expected to be included in the 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-compliances as described below.
  - Describe all deviations and GLP exceptions – includes those noted in the study director's FSR, and others noted by the sponsor 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's GLP compliance statement (cont.)

## Examples of an inadequate statement:

- Items of noncompliance with the GLP regulations noted in the FSR were not listed on the sponsor's compliance statement, including the reason for the noncompliance and the impact assessment.
- Does not contain additional items identified by the sponsor during their assessment of the study and facilities, if applicable.
- Sponsor GLP compliance statement claims OECD GLP compliance and doesn't address exceptions to FDA GLPs.
  - The sponsor compliance statement should 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.



# OECD vs. FDA GLPs (Q 76)

**QUESTION #76: If a sponsor conducts a study in accordance with OECD GLP regulations, does CVM expect the sponsor GLP compliance statement to explain the differences between OECD GLPs and FDA GLPs?**

**Updated response:**

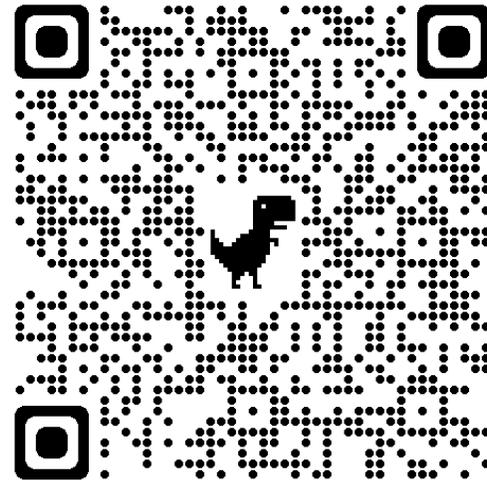
No, CVM does not expect the sponsor GLP compliance statement to contain a chart stating the differences between OECD and FDA GLP regulations if a study was conducted under OECD GLP. As stated above, the sponsor's GLP compliance statement for a study should affirm each study's compliance with 21 CFR § 58 (FDA GLP) or provide a brief statement of the reason for the noncompliance. The sponsor may provide the differences between OECD GLP and FDA GLP as part of their explanation of noncompliance, but this is not required nor is a statement (or chart) of differences alone sufficient. If an item of noncompliance is consistent with OECD GLP but not FDA GLP, the sponsor should explain the difference between the two standards of conduct and the impact of the noncompliance on the study.

**Description of changes:**

The response was revised to more directly answer the question and explain that sponsors should only state and explain those aspects of OECD GLPs that were followed and differ from FDA GLPs and not provide a comprehensive list of all differences between OECD and FDA GLPs.

# Resources

FDA Data Quality Resources page



<https://www.fda.gov/animal-veterinary/new-animal-drug-applications/data-quality-resources>

# Useful Resources for Data Quality

Data Quality Resources can be located on the webpage provided below.

Topics covered include:

- Quality Assurance Study Review Process
- Data Quality Webinar Q&A
- Submission of Electronic Captured Data
- Pilot Program: Read-only Access to Electronic Raw Data
- Bioresearch Monitoring Program

<https://www.fda.gov/animal-veterinary/new-animal-drug-applications/data-quality-resources>

# Useful Resources (cont'd)

- 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 Trials: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/guidance-industry-computerized-systems-used-clinical-trials>

# Useful Resources (cont'd)

- Guidance for Industry #197 – Documenting Electronic Data Files and Statistical Analysis Programs:  
<https://www.fda.gov/media/75077/download>
- 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](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/media/70333/download>

# QASR Resources

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

[Michelle.Kornele@fda.hhs.gov](mailto:Michelle.Kornele@fda.hhs.gov)