Question and Answer Document
for the
Data Quality Webinar
held June 4 and 6, 2013
(UPDATED April 2021)

The questions in this document represent all questions that were asked of Center for Veterinary Medicine (CVM) during the June 2013 Data Quality Webinar or submitted to CVM after the webinar. The wording of the questions was revised for clarity in some instances. Other questions may represent the substance of multiple related questions that we determined were best addressed with a single question and answer. The questions have been grouped by topic without regard to when the question was asked.

Answers to these questions were originally made available to the public by the posting of this document in the docket with the presentations and transcript of the data quality webinar in 2014. Later the documents were moved to a publicly available archive. In the original version, where necessary, we corrected any verbal answers that were provided during the webinar.

Clear and accurate communication to stakeholders is critical for CVM to achieve its mission. CVM updated this document so that it continues to be a useful and relevant resource, providing general information on several topics related to data quality. To be clear, CVM did not make revisions to any of the questions and only revised some answers.

Unless stated otherwise, all regulatory citations are from chapter I of Title 21 of the Code of Federal Regulations (CFR).

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Abbreviations Used in this Document

ADUFA – Animal Drug User Fee Act
AE – adverse event
AGDUFA – Animal Generic Drug User Fee Act
ALCOA- Attributable, Legible, Contemporaneous, Original, Accurate
ANADA – Abbreviated New Animal Drug Application
CDER – FDA's Center for Drug Evaluation and Research
CFR – Code of Federal Regulations
cGMP – current Good Manufacturing Practices
CMC – Chemistry, Manufacturing, and Controls
Codec – coder-decoder
CSF – cerebrospinal fluid
CSV – comma-separated values [file format]
CVM – Center for Veterinary Medicine
DCF – data capture form
EDC – electronic data capture
EFF – effectiveness
EI – early information
EIR – establishment inspection report
ERA – End Review Amendment
ESS – CVM's Electronic Submission System
FDA – Food and Drug Administration
FFDCA – Federal Food, Drug, and Cosmetic Act
FOI – Freedom of Information
FSR – Final Study Report
GC – General Correspondence file
GCP – Good Clinical Practice
GFI – Guidance for Industry
GLP – Good Laboratory Practice
GMP – Good Manufacturing Practice
INAD – Investigational New Animal Drug
IVPP – investigational veterinary pharmaceutical product
JINAD – Generic Investigational New Animal Drug
LS – least squares
MPEG – standard for encoding and compressing video images
MP3 – MPEG-2 Audio Layer III digital audio file format
MP4 – Also known as MPEG-4, is a video file format that defines the compression of audio and visual (AV) digital data
MRI – magnetic resonance imaging
NADA – New Animal Drug Application
NCIE – notice of claimed investigational exemption
OCR – Optical Character Recognition
OECD – Organisation for Economic Co-operation and Development
P&P – Policy and Procedures document
PDF – Adobe's portable document format [file format]
PSC – Presubmission conference
QA – quality assurance
QAU – quality assurance unit
RWD – Real world data
SAE – serious adverse event
SAS – Statistical Analysis System

SEND – Standard for Exchange of Nonclinical Data
SI units – International System of Units (Le Système international d'unités)
SOP – standard operating procedure
SRT – shortened review time
TAC – test article characterization
TAS – target animal safety
TXT – text file [file format]
URL – Uniform Resource Locator
USA – United States of America
VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMF – Veterinary Master File
XLS(X) – Microsoft's Excel™ [file formats]
XPT – SAS transport [file format]
XML – eXtensible Markup Language [file format]

General Information

1. Could you please reference all guidance documents applicable to each presentation?

The high-level guidance documents are listed below. For the full list of available guidance documents, please visit our webpage at https://www.fda.gov/animal-veterinary/guidance-regulations.

After you have read through and identified the guidance documents which you think apply to your study, we strongly encourage you to contact CVM and request a meeting with the appropriate division(s) before initiating the study. We encourage you to engage in an open dialogue with CVM throughout the development of your study protocol, and to request CVM's current thinking on your study questions.

Overall Guidance Documents:
Good Clinical Practice, Guidance for Industry (GFI) #85
Computerized Systems used in Clinical Investigations, GFI #105
Target Animal Safety for Veterinary Pharmaceutical Products, GFI #185
Target Animal Safety Data Presentation and Statistical Analysis, GFI #226
Bioequivalence Guidance, GFI #35

Protocol development:
Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials, GFI #56
Target Animal Safety and Effectiveness Protocol Development and Submission, GFI #215
Bioequivalence: Blood Level Bioequivalence Study, GFI #224

Report and Submit:
How CVM Intends to Handle Deficient Submissions Filed during the Investigation of a New Animal Drug, GFI #119

Documenting Electronic Data Files and Statistical Analysis Programs, GFI #197
Providing Regulatory Submissions in Electronic Format - General Considerations, GFI

2. Are communications with CVM within the context of a GC or VMF file protected from FOI requests in the same manner that communications to an INAD file are protected?

Under 21 CFR § 514.12(a), the existence of an INAD file will not be disclosed unless it has previously been publicly disclosed. And under 21 CFR §§ 514.12(b) and 514.11(c), if the existence of the INAD file has not been publicly disclosed, then no data or information in the file are available for public disclosure. This protection against disclosure of the existence of the file is not afforded to a GC or VMF file. However, a sponsor's trade secret, confidential commercial, or financial information is protected from disclosure to the same extent whether it's in an INAD, GC, or VMF file.

Under 21 CFR § 20.61(c), "Data and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial or financial information are not available for public disclosure.". This regulation protects any trade secret/confidential commercial/financial information that we receive from sponsors from disclosure to the public.

3. What is an FDA Form 483 and what are the implications if one is issued to an establishment (GLP study) or clinical investigator (GCP study)?

A Food and Drug Administration (FDA) Form 483 is a document issued to firm management at the conclusion of an inspection when an FDA investigator(s) has observed any conditions that in their judgment may constitute violations of the Federal Food, Drug, and Cosmetic Act (FFDCA) and related Acts and implementing regulations. An FDA Form 483 is not issued for every inspection conducted by the agency. As discussed during the webinar, not all findings of noncompliance are significant enough to be listed on an FDA Form 483. As described in the Compliance Program Guide 7348.808 and 7348.811, issues are not listed on an FDA Form 483 if the findings or problems: 1) have been observed and corrected by the firm through its internal procedures, or 2) if the findings are minor and are one-time occurrences that are thought to have no impact on the firm's operations, study conduct, or data integrity.

The issuance of an FDA Form 483 does not constitute a final agency determination of whether any condition is in violation of the FFDCA or any of its relevant regulations. A written report called an establishment inspection report (EIR) is written for all inspections and includes the FDA Form 483 (if issued), all evidence or documentation collected on-site, and any responses made by the firm during or following the inspection. The agency considers all of this information and then determines what further action, if any, is appropriate to protect public health.

4. Please explain the purpose of establishing an organizational chart for a GLP facility. This chart is one of the first things that FDA Inspectors often ask for after they show the site their credentials.

FDA inspectors evaluate whether the organizational structure is appropriate to ensure that studies are conducted in compliance with good laboratory practice (GLP) regulations (21 CFR part 58), and to determine whether testing facility management, quality assurance unit, study directors, and laboratory personnel are fulfilling their responsibilities under the GLPs. As part of the inspection, they will need to identify the various organizational units, their role in the GLP studies, and the management responsible for the organizational units. An organizational chart, while not the only way to document this information, is one useful way to demonstrate organizational compliance with the GLP regulations during the FDA inspection.

5. What is CVM's preference for what information is submitted with or as part of a request to establish an INAD, an H submission, or a request for a pre-submission conference?

CVM's preference for what information is submitted depends on the purpose of the information a sponsor plans to submit. There are many different variables and issues specific to a project that may influence the type and timing of information submitted to CVM. Three types of submissions: the first submission to establish an INAD (A-0000), an H submission (submission of supportive information), or a Z submission (request for a meeting, including a presubmission conference (PSC)) can be used early in the development process to provide the information needed to enable CVM to make binding agreements in a PSC and/or later concur with a protocol. Regardless of the submission type, sponsors should clearly state the purpose of the submission, include specific questions or issues for CVM to address, and organize their submission in a manner that allows CVM to efficiently review the provided information. CVM encourages sponsors to have early conversations with CVM to discuss the different types of information that might be needed to make a decision regarding a particular issue and the optimal timing of submitting that information. Sponsors are encouraged to discuss the most appropriate submission type with their project manager before submission. New sponsors who do not yet have an assigned project manager may contact CVM.ONADE.PM@fda.hhs.gov for assistance.

As part of the negotiations for the reauthorization of the Animal Drug User Fee Act (ADUFA) III, CVM introduced early information (EI) submissions to provide new avenues for an earlier dialogue and exchange of information between drug sponsors and CVM in order to enable the parties to reach agreement regarding some or all of the investigational requirements for approval at a PSC and to move into protocol review and concurrence more efficiently. ADUFA IV maintains this provision for EI (https://www.fda.gov/media/116001/download). Both the ADUFA III and ADUFA IV performance goals letters define EI as data or information which uniquely describes the general attributes of the new animal drug (e.g., the known characteristics of the drug that can impact safety, effectiveness, or quality). CVM's P&P 1243.2200, about submission and review of EI prior to presubmission conferences and protocol review is publicly available at: https://www.fda.gov/media/92524/download.

The specifics of the development plan for a particular drug, including the types and numbers of studies a sponsor intends to conduct, will dictate how early an exchange of information should occur before agreements can be reached at a PSC. The timing should reflect the availability of the information and the general timeline for the drug development. Generally, the earlier the information is shared, the more likely CVM is able to provide earlier decisions that reflect more targeted requirements.

Regarding information to be submitted in a request to establish an INAD, an H submission, or a request for a PSC:

- The A-0000 submission and/or the H-submission may include EI as described in P&P 1243.2200.

- A request to establish an (J)INAD (A-0000) file, should, at a minimum, include sponsor information, drug identification information, and any additional general information the sponsor has on the investigational new animal drug, such as proposed target species (and class if applicable), dosage regimen, and indication. A request to establish a JINAD file should also include the reference listed new animal drug information and any relevant patent or marketing exclusivity information. Various other types of information, including EI, may also be provided in the A-0000, depending on the project.

- Sponsors may submit supporting information in an H submission either before or after a PSC. In addition to information identified as EI, H submissions typically contain data or information intended to support the design of a study protocol, information on the pharmacological/toxicological characteristics of a compound, or background information for product development prior to a meeting.

- PSC meetings may be held to establish agreement between FDA and a potential applicant regarding the number and types of studies or information required for approval. PSC meeting requests should meet the requirements of 21 CFR § 514.5(b). Robust discussions at the PSC, particularly in situations where novel concepts are presented (e.g., relative to the disease, indications, study design, delivery devices, etc.) are facilitated by the sponsor providing a clear and complete agenda, objectives for the meeting, and specific questions with robust justification and information to enable CVM to address those questions. Although the request for a PSC meeting should not include EI, sponsors may request a PSC meeting (to be held no sooner than 100 days after submission of an A-0000 or H submission containing EI, to discuss aspects of the development plan that rely on the EI.

6. Is CVM phasing out the end-review-amendment process?

Yes. On October 1, 2014, CVM discontinued the end review amendment (ERA) process and replaced it with shortened review time (SRT) processes for reactivations of NADA and ANADA files and for resubmission of certain INAD and (J)INAD submission types that are submitted through the CVM Electronic Submission System (ESS) using the eSubmitter tool. These shortened review processes originally were outlined in the ADUFA III/AGDUFA II Goals Letters. The current processes are described in the ADUFA IV/AGDUFA III Goals Letters. Submissions are eligible for the shortened review processes if certain criteria, as outlined in the respective Goals Letter, are met.

The ADUFA IV Goals Letter can be accessed at https://www.fda.gov/media/116001/download.

The AGDUFA III Goals Letter can be accessed at https://www.fda.gov/media/116328/download.

The tables below outline the eligible submission types and their associated review times.

Table 1: Eligible Submission Types and Review Times for the Shortened Review Time Processes

Submission Type	Initial Submission: Standard Review Time	Reactivation or Resubmission: Shortened Review Time
Non-Administrative Original New Animal Drug Applications	180 days	135 days
Non-Administrative Abbreviated New Animal Drug Applications	240 days	120 days
Non-administrative, Non-manufacturing supplemental New Animal Drug Applications	180 days	135 days

Table 2: Eligible Submission Types and Review Times for the Shortened Review Time Processes

Submission Type	Initial Submission: Standard Review Time	Reactivation or Resubmission: Shortened Review Time
Investigational New Animal Drug Study Submissions (INAD technical section submission, with exception of stand-alone Human Food Safety- Microbial Food Safety Hazard Characterization)	180 days	60 days
Generic Investigational New Animal Drug Study Submission (JINAD technical section submission)	180 days	60 days
Investigational New Animal Drug Protocols without Data Submissions	50 days	20 days

7. Does CVM prefer the terminology used in the TAS guidance (GFI #185) or

in the GLP regulations to describe the drug being tested and a placebo?

We prefer the terminology (test article and control article) of the GLP regulations, but either is acceptable. The terms used in the target animal safety (TAS) guidance (investigational veterinary pharmaceutical product and negative control) reflect the internationally-agreed upon language of the VICH process and are therefore acceptable as well.

eSubmitter

Various questions below refer to a spreadsheet, Excel, or Microsoft's Excel's file format (XLS(X)). A spreadsheet is a computer application for organizing and analyzing tabular data. Excel is a popular spreadsheet application by Microsoft. XLS(X) is the file extension used by Excel. All references to these terms below will be viewed in the most common form of spreadsheet.

8. Can you please explain what you mean by "paper" submissions, especially with respect to electronic file types?

A "paper" submission is any submission that was not prepared and packaged using the eSubmitter tool and submitted through the FDA Electronic Submission Gateway (ESG).

9. When submitting data in electronic format, what software formats are acceptable (e.g., Excel, SAS, SYSTAT, SigmaPlot)?

Extensible markup language (XML) file format, SAS transport (XPT) file format, and Adobe's portable document format (PDF) are the only data file formats acceptable for use in an eSubmitter submission at this time; however, updates will include other file formats. Sponsors should contact CVM regarding the acceptability and utility of 'non-eSubmitter' file formats before their use when submitting electronic information. Refer to CVM eSubmitter File Specification Guide (https://www.fda.gov/media/120368/download) and Guidance GFI #197 Documenting Electronic Data Files and Statistical Analysis Programs (https://www.fda.gov/media/75077/download) for further information on electronic submissions.

10. Are files with TXT extensions acceptable in eSubmitter?

No. PDF, XML, and XPT are the only currently acceptable file formats for use in eSubmitter. TXT files may be converted into PDF files for inclusion within an eSubmitter submission. In the future, updates to eSubmitter will support TXT files, as well as comma-separated values (CSV) file format files.

11. For spreadsheets, do you want those submitted as XML, PDF or XLS(X) files?

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.

12. Are graphs done in Excel acceptable? If so, should the Excel sheet be submitted in eSubmitter and in what format?

Yes, graphs created in Excel, or any other graph generating software, are acceptable as long as those graphs are submitted as static images in PDF format (this is the only format that graphs are accepted). Therefore, graphs should not be submitted as Excel files.

Additional information is available in public resources such as GFI #197, "Documenting Electronic Data Files and Statistical Analysis Programs" and GFI #226, "Target Animal Safety Data Presentation and Statistical Analysis".

13. Assuming the sponsor chooses to submit electronic datasets in XPT format rather than XML format, is it also necessary to provide a PDF "print-out" of those datasets?

No. PDF printouts that are an exact copy of the data submitted in XML or XPT formats should not be submitted. For example, printing an XPT file in PDF format and submitting the PDF printout along with the XPT file is not required or recommended.

14. Should an XML map be provided for all XML files as well? Is there a preferred XML schema for data files, or is the 'general' unformatted schema preferred?

An XML map should be provided for all XML files attached to eSubmitter submissions. An unformatted, or general, schema is preferred for XML files. For more information refer to the eSubmitter File Specification Guide (https://www.fda.gov/media/120368/download) or email the eSubmitter help desk at CVMESUBMITTER@fda.hhs.gov.

15. How are sponsors handling data files within the eSubmitter submissions? Is it common practice to submit an index or ReadMe file with the data sets to explain them? Where does this file go?

eSubmitter requires README files (as PDF files separate from the final study report (FSR)) 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 analyses. Although README files are optional in the eSubmitter technical section templates for Human Food Safety, Environmental, and Bioequivalence studies, all data submissions should be accompanied by a README file. Many sponsors already do this, and it is appreciated. The README file should be attached in eSubmitter along with the data files. The structure and content requirement of a README file is described in the GFI #197.

16. Could you provide an example of inclusion of the same variable in multiple files (other than sex, ID, etc.)?

Body weight is one example of a non-demographic variable (not identification (ID), sex, etc.) that might be included in multiple data files. Depending on the purpose of the submission, body weight might be included in data files dedicated to organ weight, feed efficiency, or dose determination. However, body weight may also be included in only one data file and that file can be merged with other files to make calculations such as organ weight as a percent of final body weight.

17. Can a link to the external raw data (database) from an EDC system be submitted in eSubmitter or a URL be submitted rather than the actual raw data?

Although we cannot accept a direct link or uniform resource locator (URL) in eSubmitter, CVM encourages sponsors to consider providing remote access to their raw data *in lieu* of providing copies of raw data in a submission. If this option is chosen by a sponsor, CVM should have direct read-only access to the data and be able to navigate the appropriate electronica data capture system(s) and fully access all relevant information. Sponsors interested in exploring this option should contact the Division of Business Information Science and Management in the Office of New Animal Drug Evaluation.

18. How should video information be submitted?

CVM does not currently recommend submitting video files. Updates to the eSubmitter program will include the acceptance of MP4 file format. If you need to submit video, we encourage you to contact CVM. The file formats that we currently support (XML, XPT, and PDF) only provide for data and text. These formats were chosen because they are robust and well-supported open formats. We think these formats will best preserve and maximize our ability to use this information for many years. We also anticipate that these format restrictions will minimize our future efforts to migrate this information to new formats should it be necessary. Additionally, updates to the eSubmitter program will include the acceptance of MP4 file format. If you need to submit video, we encourage you to contact CVM.

Study Protocol

19. Must the study protocol be written following the order and organization suggested by the GCP guidance (GFI #85)?

No. The good clinical practice (GCP) guidance provides an outline of all topics that a study protocol should address for effectiveness studies. The order of topics described in the guidance is one logical ordering of the topics, but others are acceptable.

20. What is the difference between a protocol amendment and a protocol deviation?

An amendment to a study protocol is a change or modification to the signed study

protocol that is put into place before the execution of the protocol or the execution of the task that has been modified. A protocol deviation is a departure from the procedures as stated in the study protocol.

21. Is there a requirement for animals used in a study to not have participated in another study in the previous 30 days?

No. There is no absolute requirement for all animals to not have participated in another study within 30 days before being enrolled in another study. The eligibility of individual food or companion animals to enroll in specific studies is dependent, in part, on an evaluation of the medical or drug treatment history of the animal. Where previous exposure to particular drugs in a specific study is a concern, evidence of the cessation of such drug exposure for a predetermined number of days before enrolling in a new study is typically sufficient. Concerns of potential residual drug effects confounding safety or effectiveness evaluations are often addressed using inclusion criteria that preclude the use of animals that have been treated with drug(s) of concern or prohibit certain drug treatments within some specified number of days of enrollment for the new study.

22. What types of protocol deviations can be fatal (i.e., invalidate the results of) GCP efficacy and GLP target animal safety studies?

A deviation that could invalidate the results of a study is one that substantially affects the evaluation of the critical variable(s) or confounds the evaluation of study results. This may include one or more substantial deviations related to primary variables or study conduct issues that could significantly impact the outcome of the study. In some cases, numerous less substantial deviations could also lead to invalidation of study results.

Examples of potentially "fatal" protocol deviations could include, depending on the circumstances, using the incorrect dose or dosing interval, inability to assay the drug in medicated feed (or high variability in assay values or inordinate number of assay values outside the specification range), unmasked study personnel recording critical subjective variables, variations in drug storage conditions that cause the stability of the drug to be questioned or affected, errors in treatment allocation, or contamination of medicated feeds with non-study drugs. However, the protocol deviation is considered in the context of the objective(s) of the study, adherence to study standards of conduct, and the quality and integrity of the data as a whole. For example, underdosing animals or loss of drug potency may not invalidate an effectiveness study but is more likely to confound the interpretation of safety in a target animal safety study; and the impact of contamination of study feeds with non-study drug(s) will depend on the contaminating drug and the level of the non-study drug in the study feeds.

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

Protocols:

- Roles of study personnel are not clearly defined
- Inconsistencies and contradictions between different sections of the

protocol
- Different terminology used in different sections
- Inconsistent definition of primary variable(s)
- Incomplete or contradictory study schedule
- Unidentified number of study animals
- Data capture forms accessible to masked personnel that unmask treatment
- Selection criteria for study animals not defined/described
- Absent or insufficient description of randomization; just a statement that "allotment to treatment will be randomized"
- No description if randomization will be generated centrally or at each site
- Insufficient description of masking, just a statement that "Personnel will be masked to treatment"
- No specific description of which personnel will be masked
- No separation of function to preserve masking
- Descriptions of procedures which lack clarity or don't provide enough detail, such as "Animals will be observed once daily" without any reference to what observations and which forms should be used for documenting observations
- Details for one or more critical study procedures are missing (neither the standard operating procedure (SOP) nor sufficient description provided)
- Descriptions of procedures that are confusing because they do not provide enough detail
- No description of how removed animals will be included in the analysis
- No description of a rescue clause for study animals, where appropriate
- Incomplete or missing data capture forms (DCFs)
- DCFs direct the documentation of information that is not described in the protocol
- Incomplete or missing basis for determining study conclusions
- 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
- Protocol deviations not noted and/or their impact not assessed
- Collecting observations on animals previously identified as dead or otherwise removed from the study
- Insufficient time taken to make observations on pens of animals (e.g., start/end times for observations of less than 5 minutes)
- Miscalculation of primary or secondary variables
- No description or identification of the drug formulation
- Transcription and transposition errors noted in comparing raw and electronic data files
- Data files for statistical analysis don't match the copies of raw data
- Copies of raw data missing that are necessary for the reconstruction of the study and that support information described in the FSR
- Missing pages
- Missing or incomplete randomization of animals and randomization scheme
- Incomplete discussion of results, particularly those that may be unexpected

- 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 collected in raw data
- Inconsistencies between the FSR and the raw data
- Unmasked personnel making clinical observations

Investigational drug / test article

24. Must a sponsor submit an NCIE when testing an approved drug for an unapproved indication in a clinical study?

Yes. For a new animal drug intended for investigational use to be exempt from the requirements in Section 512(a) and (m) of the FFDCA, the conditions in 21 CFR § 511.1 must be met. Where the investigational use is in clinical studies, the requirements are found in 21 CFR § 511.1(b). The previously approved drug is considered an investigational drug because it is not approved for the indications for which it is being investigated. Among these requirements are the requirements for the sponsor to submit to CVM a "Notice of Claimed Investigational Exemption for a New Animal Drug" (21 CFR § 511.1(b)(4)) and for the investigational drug to bear the 'caution label statement' found in 21 CFR § 511.1(b)(1).

The regulatory requirements found in 21 CFR § 511.1(b) may also apply to some situations involving the collection of real world data (RWD) for approved drugs. When information is collected on the use of an approved drug in the normal course of veterinary practice, the requirements in 21 CFR § 511.1(b) are not applicable. However, if RWD are being collected to determine the safety or effectiveness of the approved drug, and the process for gathering that data would influence treatment decisions, the requirements in 21 CFR § 511.1(b), including the need to submit a notice of claimed investigational exemption (NCIE), would likely apply. For example, simply observing how a veterinarian uses the approved drug for both on label or off label uses would not be considered an investigational use. Retrospective analyses of existing RWD involving the extra label use of an approved drug would also generally not be considered an investigational use. By contrast, the prospective collection of RWD for a registry designed to determine the effectiveness of an approved drug for a new intended use where investigators are instructed to treat specific patients or otherwise administer the drug in a specific way or follow up activities are performed for the purpose of research would likely be subject to the requirements in 21 CFR § 511.1(b). Because the gathering of RWD is different from traditional investigations, we recommend that you contact CVM if you have questions about whether an NCIE is required.

25. What are the labeling requirements for the use of approved drugs in a clinical study where such drugs are not under investigation?

If the approved drug is not the investigational drug (e.g., it serves as a positive control, or it is used to medically treat the investigational animals), then we do not need prior notification of its shipment for use in a clinical study, nor must such a

drug be labeled as an investigational drug. However, other documentation of their use may be required for compliance with the study protocol.

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?

Background

21 CFR § 58.105 (test and control article characterization) states the following:

"(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch."

In most cases (except for certain studies using Type C medicated feed), CVM will only consider analytical tests to characterize or demonstrate the stability of an IVPP performed by, or on behalf of, the sponsor to be valid because the sponsor possesses the analytical methods and specifications.

For the subset of GLP studies discussed during the webinar (TAS studies), CVM expects that 1) the sponsor will use the intended final formulation of the new animal drug, and 2) good manufacturing practice (cGMP) manufacturing practices, or similar conditions, will be applied to the test article. This is consistent with Section 2.1 of CVM Guidance #185, Target Animal Safety for Veterinary Pharmaceutical Products VICH GL 43, which states "Margin of safety and other laboratory safety studies must be performed in conformity with the principles of Good Laboratory Practices (GLP). The concepts of current Good Manufacturing Practices (cGMP) must be applied to the IVPP as appropriate for new animal products intended for investigational use."

Full cGMP compliance means that a facility satisfactorily complies with 21 CFR § 211, 225, or 226, as appropriate. Unapproved new animal drugs used for the clinical (EFF; GCP) and nonclinical (TAS; GLP) studies should be manufactured under cGMP-similar conditions; they may be manufactured in a pilot or smaller facility unless we determine that manufacturing at a full-scale production facility is necessary to ensure the safety or effectiveness of the drug (section 512(c)(4) of the FFDCA). FDA-approved drugs used in clinical or nonclinical studies should be manufactured with full cGMP compliance.

Although the lots of investigational drug product (unapproved drug) are expected to be manufactured and tested using practices as close to cGMPs as possible, there are some characteristics of full cGMP compliance that might not be complete before

approval. These conditions are referred to as cGMP-similar conditions. This approach is consistent with FDA's Center for Drug Evaluation and Research (CDER)'s "CGMP Guidance for Phase I Investigational Drugs." The potential missing elements of full cGMP compliance include:

- Full production scale: usually 10% or more of production scale is acceptable for investigational products;
- Final production facility: the lots of investigational drug product might not be made in the same facility as will be used for production post-approval;
- The lots of investigational drug product might not be tested and manufactured using fully validated methods. Often the technical section with the validations doesn't come until years after the relevant studies are done; and
- The lots might not have all the relevant analytical tests done for the certificate of analysis. We can and do request additional tests after reviewing Chemistry, Manufacturing, and Controls (CMC) data.

Often the EFF and TAS technical sections are submitted and reviewed before the CMC technical section is submitted. The EFF and TAS technical sections are considered complete under the presumption that the CMC of an unapproved drug will be satisfactory. The review of the CMC technical section, in conjunction with the results of any manufacturing facility inspection, determines whether the CMC of the unapproved drug is satisfactory. Therefore, situations where a TAS study is reviewed before a determination of whether the CMC of the unapproved drug is satisfactory, and/or is manufactured under cGMP similar conditions, requires flexibility in the interpretation of the GLP regulations pertaining to test article characterization.

Responsibilities for GLP studies

Although CVM agrees that either full compliance with cGMPs (for FDA-approved products) or cGMP-similar conditions (for unapproved final formulation products) is scientifically justified in GLP studies in which the intended final formulation is used (e.g., TAS studies); documentation is necessary to demonstrate to CVM and to FDA inspectors that while following cGMP standards, the study director has reviewed and is appropriately documenting results of test article characterization and stability for each batch of test or control article used in the study in a manner that allows the study director to interpret, analyze, and draw meaningful conclusions about the results of the study, and assure the quality and integrity of the safety data.

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. Study directors and sponsors may cite Section 2.1 of VICH 43 as an acceptable reason for the use of full cGMP compliance or cGMP-similar conditions instead of 21 CFR § 58.105(a) in the protocol, final study report, and sponsor GLP compliance statement for TAS studies.

a. Unapproved final formulation drug products used as test articles (IVPP)

   Typically, for TAS studies using the final formulation of the test article (IVPP), the study sponsor (rather than the testing facility) should perform the test article

characterization and stability testing following cGMP or cGMP-similar conditions. Per 21 CFR § 58.105(b), the sponsor should also determine the stability of the specific lot/batch used in the study either before or preferably, concomitant with the study. If stability testing is performed before the study, the data should be generated using IVPP manufactured identically to the lot/batch used in the TAS study (same formulation; same suppliers of raw materials; same manufacturing site, process, equipment, and scale; same container-closure system).

If the TAS study is conducted before submitting the CMC technical section, sponsors should use batches of test article in the TAS study that they plan to include for evaluation in the CMC technical section. The Division of Manufacturing Technologies confirms that batches evaluated in the CMC technical section were used in EFF and/or TAS (GLP) studies. If the TAS study is conducted after completing the CMC technical section, sponsors should characterize the test article using the methods and specifications reviewed and accepted by CVM in the CMC technical section. In all cases CVM reviews and confirms the acceptability of batches/lots of final formulation product used in TAS studies before drug approval.

When cGMP-similar conditions are used for test article characterization in a TAS study, the protocol should state the following:

1) The use of cGMP 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.

2) The sponsor will provide the study director with a statement describing what tests were conducted, information (such as a Certificate of Analysis) which documents the identity, strength, purity, and composition of the test article, and the results of stability testing on the lot/batch used in the study, which was performed before study initiation or concomitant with the study (performing stability testing concomitant with the study is preferred).

3) The sponsor will provide a statement to the study director which describes how the batch was manufactured, where the raw data supporting the test article characterization and stability results are archived, and that either appropriate information on the batch used in the study will be submitted to the CMC technical section (if the study is conducted before submitting the CMC technical section); or if the CMC technical section is complete, that the characterization and stability testing of the test article will be conducted using the methods and specifications reviewed and accepted by CVM in the CMC technical section. If a different approach is needed, the sponsor should propose and justify their plan in the protocol.

   The information described above should also be described in the final study report and in the sponsor GLP compliance statement.

   Alternatively, if the test article characterization (TAC) and/or stability testing is performed by testing facility or contributing scientist, the results and raw data should be archived with the rest of the study data and available for review during an inspection.

b. Marketed products used as test or control articles

21 CFR § 58.105(a) allows for testing facilities to rely on the labeling of "marketed" products used as control articles for the purposes of characterizing the identity, strength, purity, and composition of these products. 21 CFR § 58.105(b) does not allow testing facilities to rely on the labeling to determine the stability of "marketed" products. In the context of TAS GLP studies submitted to CVM that use marketed final formulation products, CVM interprets "marketed" to mean FDA-approved. Some exceptions exist (e.g., sterile saline used as a control article that is not FDA-approved would be considered a marketed product in this situation).

When FDA-approved products manufactured in full compliance with cGMPs are used as test OR control articles in TAS studies, the testing facility may rely on the labeling and certificate of analysis for the purposes of characterizing the identity, strength, purity, and composition of these products. In most cases, generation of additional stability data for FDA-approved test or control articles is not required as long as the test or control articles are stored and handled in accordance with their approved labeling and used within their labeled expiration date (in accordance with the stability data reviewed and accepted by FDA for approval of the drug product). During the review of the TAS study and before approval of new indications for an approved product, CVM will review and confirm the acceptability of batches/lots of final formulation test article used in TAS studies.

When FDA-approved products manufactured in full compliance with cGMPs are used as test or control articles in a TAS study, the protocol should include the following:

1) The use of full compliance with cGMPs 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. Sponsors may cite Section 2.1 of VICH 43 as an acceptable reason for the use of full cGMP compliance instead of 21 CFR § 58.105(a) and (b).

2) The sponsor will provide the study director with the certificate of analysis for the batch(es) of test article provided to the testing facility. The test article will be handled and stored in accordance with the approved labeling and used within the labeled expiration date.

The information described above should also be referenced in the final study report and in the sponsor GLP compliance statement.

Studies in which unapproved final formulation drug products or marketed FDA-approved products are used as the test or control article in a nonclinical laboratory study are a small subset of studies inspected by FDA inspectors. Therefore, it is critical to document the planned use of full cGMP or "cGMP-similar" compliance to fulfill the requirements for TAC in 21 CFR § 58.105(a) and (b) as part of the protocol, final study report, and sponsor GLP compliance statement. Any communication with CVM regarding this issue should also be

included in the study documentation. CVM will inform FDA inspectors of CVM's acceptance of pre-planned items of GLP noncompliance in field inspection requests. If you have any questions about inspections or specific questions about a Form FDA 483, Inspectional Observations, you may contact CVM's Pre-Market Compliance and Administrative Actions Team in the Office of Surveillance and Compliance.

27. Please define "secure" location for storing test and control articles. Specifically, how should drug products be stored that require refrigeration? If the study site refrigerator can only be accessed by study personnel, is this sufficient or is a separate refrigerator under lock and key required?

There is no regulatory definition of a secure location. For articles requiring refrigeration, one option is that the refrigerator could be locked or placed in a room with controlled access.

28. In a GLP study, what is considered the "test article" for medicated feeds – the Type A medicated article, or the Type B or C medicated feeds?

The test article, for which characterization and stability data should be provided, is the Type A medicated article. The Type B or C feeds fall under the regulations in 21 CFR § 58.113 as "mixtures of articles with carriers." If the test facility is receiving Type A medicated article from the sponsor and then mixing the feed (or having a contract facility mix the feed), the test facility will be responsible for possessing the documentation that they have appropriately conducted all appropriate analytical tests as described in 21 CFR § 58.113.

Raw data

29. Can you define "raw data"?

The term is used and defined within the context of both nonclinical (GLP) and clinical (GCP) studies.

Raw data is defined in 21 CFR § 58.3(k) as "any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments."

In GFI #85 (GCP Guidance), the term is defined in section 1.24 as "any original worksheets, calibration data, records, memoranda and notes of first-hand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from

automated instruments, and hand-recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data."

These definitions are very similar, but they are not identical. The main difference relates to transcribed data. The GLP definition of raw data permits exact transcripts of raw data (e.g., tapes) that have been prepared and verified as accurate to be acceptable or to be substitutable for the original source as raw data. The GCP definition excludes facsimile transmissions and transcribed data from the definition of raw data.

30. Define raw data when data are captured electronically in compliance with part 11.

The first permanent recording of an observation is considered the raw data. The types of information, and the quality and characteristics that define that information, that constitute raw data are the same regardless of the capture medium. What may differ are the methods and activities that achieve these qualities and characteristics. For example, when changes are made to raw data properly recorded in ink on paper, the change is noted on the paper by a single line of strike-through, the date of the change, the reason for the change, and the signature of individual making the change. In an electronic data capture (EDC) system, these changes are captured in an appropriately designed audit trail system that is computer-generated, time-stamped to record the date and time of operator entries and actions that create, modify, or delete electronic records (see 21 CFR § 11.10(e)). The audit trail system should maintain data integrity along with the attributes of ALCOA. As a change to a paper record is intrinsic to that record, so too is the audit trail to an electronic record. Therefore, the audit trail of electronic records must be submitted as part of the raw data for those electronic records. The sponsor should demonstrate 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 review. Please refer to GFI #197 (Documenting Electronic Data Files and Statistical Analysis Programs) for additional information. If the suggested processes cannot be met, sponsors should contact CVM for other suitable options.

31. Is it CVM's intent to adopt the SEND data format in lieu of a copy of the raw data?

No, SEND is not a format for providing copies of raw data. Sponsors should submit copies of raw data in conjunction with any final observation data files submitted in SEND format. Because SEND data files are modified data and do not contain audit trails, these files would not substitute or replace raw data or audit trail information submitted to CVM.

32. What data does CVM expect to be submitted for each supportive (non-pivotal) safety or effectiveness study?

Studies that are supportive in nature typically may be submitted in summary form (final study report, or, if not available, an abstract summary) without the raw data. In some cases, we may request a copy of all of the raw data or data from selected individual animals to address a particular issue.

33. What raw data does CVM expect to be submitted for each pivotal safety or effectiveness study?

We continue to expect, except in unusual circumstances, copies of raw data for critical information for the study to be submitted. The sponsor should discuss any potential exceptions with the review division before submitting the study in question for review.

If the data are first recorded on paper, we expect to see electronic scans of those records. If the data are first recorded in a properly validated EDC system, then a copy of that raw data as one or more XML or XPT file(s) is acceptable. In addition, copies of audit trails should be submitted (in XML or XPT). If it has not been previously submitted, the sponsor should also provide assurance of compliance with 21 CFR § 11 for any EDC system used.

We generally expect that data from all pivotal studies will be provided to CVM in electronic format. (Please contact CVM before submitting the data for potential exceptions.)

Do not confuse a "copy of all raw data" with "an electronic file of the data that is suitable for evaluation." These are not the same thing, even when the data are first recorded electronically.

34. How are transcriptions of raw data, e.g., concurrent medications for investigational animals transcribed from their clinical medical records, handled?

Transcribed data may be added to the study documentation but should be clearly marked as transcribed data. When information from medical records must be transcribed onto a DCF, an electronic scan of the medical record should be included as this is the first recording of the information and considered the raw data. If a DCF has been damaged, and is illegible, making transcription necessary, the original damaged form should be attached to the transcribed form.

35. What does CVM consider the raw data from a third-party facility contracted to perform an analysis?

The raw data is the first permanent recording of the data. Depending on the particular equipment, that may occur electronically or may occur when the results are documented on paper. The physical location of where the raw data are being generated has no bearing on what is considered the raw data. The transmission of the raw data (either in paper or electronically) from the third-party facility to the facility that contracted the analysis creates a copy of that raw data. The only exception would be the instance in which the raw data at the third-party facility were originally collected in an EDC system and a copy of that EDC file is provided (transmitted) to the facility that contracted the analysis.

36. Is it necessary to include a copy of the raw data in a GLP study when the data were collected electronically, and individual and summary animal data are included in the final study report?

For this document, CVM considers the following terms to be synonymous with one another: "individual animal data," "study animal data listings," "line listings," and "final values." These terms refer to the final data entries or observations included in the analyses of the study results. The data encompassed by these terms are typically presented as a table, or catalog, of the "individual animal data" (e.g., pivotal variables, clinical observations, etc.). The difference between raw data (or even a copy of the raw data) and "individual animal data" is that "individual animal data" may have been manipulated or edited for presentation, while raw data are the original observations within the context of the recording event.

To this end, CVM expects to have access to copies of raw data for critical information obtained during the conduct of a GLP study, even when the data were collected electronically and the "individual animal data" are summarized in the final study report. Providing copies of the raw data allows CVM to review the data observations as they were recorded originally. Sponsors should discuss with CVM what raw data are critical and should be submitted. In situations where copies of raw data can be accessed by means other than inclusion in the submission, CVM encourages sponsors to have discussions with CVM about other options.

CVM discourages the inclusion of individual animal data in the final study report because they are another version of the study data and we would need to compare them to the raw data before we could rely on them. However, CVM encourages the inclusion of tables, graphs, or other representations that present a summary of "individual animal data" in the final study report. These summary representations of the "individual animal data" can provide clarity to the final study report and aid in the comprehension of author's statements and conclusions.

37. Are 'study animal data listings' required (or helpful) in submissions of clinical or non-clinical studies when provided in addition to the raw data?

See the answer to Question #36.

38. What are the citations for the archiving requirements present in the GLP regulations?

21 CFR §§ 58.190 and 58.195.

Electronic data capture systems

39. When is the best time to discuss the development, acquisition, or use of an EDC system with CVM?

We encourage the adoption and use of a well-validated EDC system in the conduct of a study. We encourage sponsors to discuss with CVM their potential development, acquisition, or use, well before study protocols are submitted for review. Such a meeting should familiarize CVM with the system and its operation and allow for a discussion of how such a system could capture all relevant data. Meetings to discuss EDC systems are scheduled as "Other ONADE" with the Division of Business Information Science and Management, as needed. See CVM P&P 1243.3024 for

more information on scheduling meetings.[1]

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?

The information that would be most useful for CVM to evaluate an EDC system for either clinical or nonclinical studies would include items such as:

- 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 (e.g., a tablet used 'animal-side' by an individual to input data or a laboratory instrument that is securely connected to the EDC system)
- A description of data collected electronically, directly into the EDC system; a description of data recorded manually and transcribed into the EDC system,
- Representations of human readable input screens
- The nature and location of the storage of the electronic data
- A statement of compliance with 21 CFR § 11

The information generally necessary to ensure data quality and integrity include procedures and controls that are designed to ensure the authenticity, integrity, confidentiality (where appropriate), and non-repudiation of the signed electronic record. These requirements are discussed in greater depth in 21 CFR §§ 11.10 and 11.30.

The sponsor is responsible for evaluating the specific needs for conducting their study and selecting the appropriate equipment and systems that are essential. As mentioned above, 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.

41. Is there a guidance document available that addresses 21 CFR part 11 compliance?

GFI "Part 11, Electronic Records; Electronic Signatures- Scope and Application" is available on the FDA website at: https://www.fda.gov/media/75414/download

GFI "Computerized Systems Used in Clinical Investigations" supplements the GFI listed above for source data generated at clinical study sites and is available on the FDA website at: https://www.fda.gov/media/70970/download

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?

The rationale for looking at "screen shots of all forms" is to assure ourselves that steps have been taken to identify the recorder, to maintain the masking of the

[1] CVM Policy and Procedures Manual #1243.3024 "Scheduling and Holding Meetings with Outside Parties" https://www.fda.gov/animal-veterinary/policies-procedures-manual/cvmoffice-new-animal-drug-evaluation-onade-reviewers-chapter

recorder to minimize bias in the recording of the observations, to reduce the error rate of recording observations, and to ensure that there are adequate and appropriate opportunities for recording unstructured or unanticipated observations.

If the EDC system presented screens for all data input that essentially replicated paper DCFs, then yes, screen shots of all "electronic" DCFs would likely be sufficient to address our concerns. However, if the screen shots of the "electronic" DCFs are not available when the protocol is submitted for review, visual representations of the data capture forms that contain the data fields to be used in the EDC system can be included. Independent of the availability of the DCFs, the protocol should state which form(s) will be used in each relevant section of the protocol.

If inclusion of screen shots or visual representations of the data capture forms is not possible, the sponsor may provide a list of forms planned for data collection, state in the text of the protocol the form(s) to be used to record the study data in each relevant section and include details about the information to be collected on each form. The protocol should specifically detail how the electronic forms or screens will be presented to the user. This information should include a description of the fields and the data entry options that will be available during data entry, and a description or listing of all other information that will be included on the form, including animal identification, treatment code, identity of observer (and recorder, if different), etc. The description should also specify whether there will be drop-down menus (including the list of options on the menu), check boxes, text fields, etc. and how additional unstructured comments will be recorded.

If display of data input fields is dependent on responses to preceding entries or prompts that direct the recorder to one or more permissible screens based on those data entry answers or prompts, then a different approach would be more useful to CVM. For example, a flowchart diagramming the permissible routes by which the recorder can arrive at the data input fields may be helpful in addressing our concerns.

43. Should the sponsor submit the electronic data capture form equivalents (screen shots) with the protocol? Can a sponsor generate data capture screens after protocol concurrence?

We generally expect that the screen shots of DCFs be submitted for review with the study protocol. The rationale for this request and details on what the sponsor could submit if screen shots of DCFs are not available when the protocol is submitted are provided in the answer to Question #42. If the screen shots of DCFs were to be designed and built after we concurred on a study protocol it is difficult for CVM to be certain that our concerns regarding their design would be met.

44. At the end of a study using an EDC system, what is submitted as raw data, e.g., PDF versions of the DCFs containing the data that were entered, PDF listings, or just the SAS datasets (or some combination)?

Regarding the submission of data from an EDC system, please refer to GFI #197 which reflect CVM's current thinking on submitting electronic data files and statistical analysis programs and the GFI "Computerized Systems Used in Clinical Investigations". Additionally, if the electronic audit trails linked to the original data

points cannot be provided, a description regarding how the attributes of ALCOA were maintained within the EDC system should be provided in the submission.

Data capture forms

45. Please comment on the importance of DCF design consistency and investigator input, because they are not mutually exclusive.

Feedback from investigators on the DCF design may be helpful, because they may provide an outside perspective, distinct from the authors of the protocol, as to how to make the DCF easier to understand or to complete. A common problem that may increase the chance of errors is a DCF which captures too much information on one form, such as animal signalment, diagnostic tests results, inclusion/exclusion criteria, and physical examination observations. Care should also be given to form design to maintain masking. It is counter-productive if the sponsor creates a DCF that is confusing or doesn't provide adequate space for the information. Using the same forms at each site in multi-site GCP studies makes the data evaluation and reporting easier. Whether a site develops its own forms or whether a sponsor provides the forms to the site, it is the sponsor's responsibility to review the DCFs to assure that the content and layout of the form is consistent with the form specified in the study protocol and to ensure the data are captured appropriately for the study, bias is not introduced, and masking is preserved, as appropriate for the study. Changes made to data capture forms before implementation of the protocol or execution of the task associated with the data capture form should be documented in a protocol amendment. Other changes made to data capture forms after their initial use in the protocol should be documented as a protocol deviation.

46. Does data captured on DCFs but not included in an electronic dataset need to be identified and explained? If so, is there a preference as to how this documentation is presented? In addition, does this apply only to forms containing animal observations, or all forms / all DCFs used for the study?

It is possible that some data entered on the DCFs may not be a part of an electronic data file (i.e., data submitted to CVM in XPT or XML file format; see GFI #197). All animal-related data that are not part of an electronic data file should be identified and appropriately summarized in the final study report. These data would not be limited to the forms containing animal observations. We have no preference as to how data are presented; however, data should be presented in a way that best allows for evaluation, interpretation, and reconstruction of the study.

47. Are most sponsors sufficiently documenting informed consent, case selection, and enrollment in effectiveness study protocols (and DCFs)?

Yes, sponsors are generally doing a good job of documenting informed consent, case selection, and enrollment.

The GCP guidance (CVM GFI #85 (VICH GL9)) recommends an informed consent form for all animals participating in GCP studies whether client-owned or purpose-bought.

The informed consent form for companion animals should be written in language that is easily understood by a lay person. At a minimum, the form should state the nature

of the drug, the objective of the investigational study, provide the owner with available information on the possible risks of the drug, and the possibility that the animal may be assigned to a specific control group, such as a placebo, active control, or no treatment group. The consent form should describe the most common adverse reactions (based on safety data or scientific literature) for both the investigational product and active control product and any user safety information, in terms of appropriate handling and disposal of the drug, human risks, and information to bring to the physician in case of accidental exposure. It may be helpful to also describe any of the owner's responsibilities on the form, such as completing an owner's diary. The informed consent form should not include statements that the investigational product is safe to use for the proposed indication. However, if CVM has provided a TAS technical section complete letter, the consent form may include safety information from studies submitted to support the TAS technical section. Statements regarding the effectiveness of the product should not be included unless CVM has reviewed data to support such claims. If summaries of pilot data were submitted with a meeting request or "H" submission, then a truthful statement about effectiveness may be included.

The informed consent form for purpose-bought animals is not required to contain any information on the safety and allotment to treatment but should include a list of the IDs of the animals bought for the study.

We discourage the enrollment of companion animals owned by the investigator or study personnel to avoid bias, but it is acceptable for the investigator to own food animals in a study.

With regard to case selection (eligibility for the study), the inclusion and exclusion criteria should be appropriate for the indication(s) and clearly detailed in the protocol. It is important to identify any medications that, if used, could warrant exclusion of the treated animal from the study evaluation.

One common problem related to enrollment (assignment to treatment) is that often the DCF does not indicate clearly that an animal has been screened and is considered by the investigator to be eligible for enrollment. This is often seen in companion animal effectiveness studies, where eligibility is dependent on clinical pathology, which may take a few days to obtain.

Adverse Events

48. Who may record and report AEs?

An adverse event (AE) for a clinical or nonclinical study is any untoward (e.g., unfavorable or unintended) observation in a study animal following the use of an article (whether the article is a new animal drug, or an article administered for the purpose of establishing a basis for comparison with the new animal drug or control product). An AE should be recorded whether or not it is considered to be drug related.

We view the recording of an AE as the act of properly documenting the occurrence of an AE in the study record, while we view the reporting of an AE by the sponsor as the act of transmitting the existence and nature of such an event to CVM. We expect all AEs to be reported in the FSR of a clinical or nonclinical study.

All study personnel are expected to record an AE when such an event is observed, and investigators should promptly notify sponsors of AEs. Training of study personnel is critical to assure complete documentation of the AE which will assist in the causality assessment. Regarding Serious Adverse Events (SAEs), see Question #51.

49. Are there differences in the way AEs should be reported for clinical effectiveness or target animal safety studies?

Unlike an effectiveness study, the primary focus of a TAS study is to identify animal health-related events that may occur in the target animal as the result of administering the investigational drug under exaggerated (usually) use conditions. In contrast to an effectiveness study, these observations (the AEs) are likely some of the primary observations of interest. Collection of these observations is fundamental to the design of the TAS study (and associated DCFs). Whether AEs are the principal focus of a study (TAS) or simply monitored for as presumably rare events (effectiveness studies), all AEs should be collected when observed. We would expect that all AEs are discussed in the FSR for each study, but we also recognize that the emphasis and manner of their discussion would reflect the type (clinical vs. nonclinical) of the study in which they were collected. Our assessment of the causality of an AE and its impact will take into account the type of study.

50. Does CVM have a recommended terminology that sponsors can provide to the investigator for AE reporting?

We are not currently volunteering a single recommended system for AE reporting for pre-approval studies. Most importantly, terminology should be consistent throughout the study so that data may be easily evaluated and summarized. The sponsor can provide clarity by training study personnel to use the same common medical terms (e.g., vomiting, dyspnea, diarrhea, and melena) and qualifiers such as mild, moderate, and severe when describing adverse events.

51. What are the requirements for reporting serious adverse events (SAE), such as a death that was untreated?

In clinical studies, the sponsor is required to promptly report any findings associated with use of the new animal drug that may suggest significant hazards pertinent to the safety of the new animal drug to CVM and all clinical investigators (21 CFR § 511.1(b)(8)(ii)). Although there is no analogous requirement for nonclinical studies, we encourage the sponsor to discuss how they plan to respond to these potential events during the development of the protocols for these studies.

When submitting an SAE, sponsors should make a causality assessment about the potential relationship of the adverse event to the drug, explain the rationale for their assessment and propose any mitigation steps, as appropriate.

52. Who does CVM expect to assess the causality of AEs? When should this assessment be made? How should this assessment be made?

Generally, the authors of the FSR have the greatest knowledge of the potential

adverse effects of the investigational drug. They are expected to make a final causality assessment in the FSR using all available information. Their causality assessment should be based on the known toxicological profile of the investigational drug, the details of the observation of the AE documented during the study, and other available study documentation (e.g., clinical pathology, gross pathology, and/or histopathology results). There may be some situations where the study veterinarian or the clinical investigators are more qualified by training to make this recommendation.

During the study, the focus should be complete documentation of the AE which will assist in any final causality assessment described in the FSR. Original observations related to adverse events should, when possible, be made by masked personnel. However, AEs should be documented by the study personnel making the observation. In other words, if an AE is observed by unmasked study personnel (such as by an unmasked treatment administrator during treatment), the person making the observation should document the AE. In general, the masked individual should not have access to the observations recorded by the unmasked individual. In most effectiveness studies and many target animal safety studies, clinical investigators and study directors, respectively, are masked due to their study responsibilities. While masked during the study, they will only be able to provide a preliminary recommendation as to causality. If study directors are not masked, responsibilities should be delegated when handling AEs in a manner that minimizes the introduction of bias.

We do not have a particular preference for how causality is assessed, other than to request that the chosen method be applied consistently across the study. We will make the final assessment of causality based on all available information during the review of the submitted study.

53. During the presentation you mentioned that in the final report, the AE causality should "reflect the authors' assessment of causality." For a multi-site study, who is considered the "author"?

For studies conducted in compliance with the GCP guidance [CVM GFI #85 (VICH GL9)], the guidance permits the investigator, the sponsor, or both together to be the author of the FSR. Additionally, the sponsor should specify if they have delegated a portion of the FSR to be authored by another person. The FSR should describe the individuals that have contributed to the authorship of the FSR. The FSR should reflect the assessment of causality from all individual(s) who author the FSR.

Masking

54. How can you determine if an adverse event is test article related without revealing treatment assignment or otherwise influencing data collection?

Study personnel observing adverse events cannot make an accurate determination of the relationship of an adverse event to the test article without being unmasked and having access to all relevant study information. As AEs are observed during the course of the study, knowledge of the anticipated adverse effects of the test article or the class of drug in general may allow the individual recording the AE to speculate as to the relationship of the AE and the investigational drug when the AE is observed.

While preliminary causality assessments may be made by masked personnel during the in-life phase, the documentation of the final determination of causality should not be part of the DCF that is used by masked personnel, unless this information is documented after data lock.

Therefore, the final assessment of event relationship to treatment assignment should be made after the dataset of the study is locked, treatment masking is revealed, and all relevant study information is available to the person making the AE causality assessment.

55. Does the investigator need to be unmasked after the occurrence of an SAE if the investigational drug does not require a specific treatment different from the control product?

The investigator of a GCP study can remain masked if the investigator can treat the SAE with a therapy (e.g., fluids) that would not be contra-indicated if the animal was treated with the investigational drug. The causality of the SAE can be evaluated after the dataset is locked and treatment assignment has been unmasked. Where client-owned animals participate in a study, the investigator has a responsibility to address the owner's concerns and, therefore, it may be necessary to identify what treatment the animal is receiving so that the SAE may be appropriately addressed. This may be handled by using another pre-determined veterinarian who is unmasked to treatment and whose sole study role is to provide medical treatment to investigational animals. Alternatively, the investigator (or other study personnel) may need to unmask in order to treat the SAE appropriately. Regardless of which individual treats the investigational animal, that individual should follow study protocol specified procedures that protect the masking of the remaining study animals and ensure future observations are made by masked personnel. Additionally, the investigator should promptly notify a sponsor representative of the SAE, because they can help determine the severity of the event and assist in the decision making of whether to unmask the investigator for that particular study animal/event. To be compliant with GCPs, the protocol should describe procedures for taking appropriate actions in response to AEs, including SAEs, and reporting AEs to the sponsor.

56. How does CVM reconcile the responsibilities of the study director (namely, being the single point of study control) with the desire to have them masked to treatment?

To reiterate 21 CFR § 58.33, the study director does have the overall responsibility for the technical conduct of the study as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director must assure that the study protocol is approved and followed, all experimental data (including unanticipated observations) are accurately recorded and verified, unforeseen circumstances that may affect the quality and integrity of the study are noted and corrective action taken and documented, and all GLP regulations are followed.

However, the study should aim to maintain balance between the study director's overall responsibility for the study and the need to minimize bias. The protocol must describe how the study will control for the potential introduction of bias (21 CFR §

58.120). If the study director is masked, one option would be for the study director to designate another qualified individual, who is unmasked, to directly oversee activities that would require unmasking.

If the study director is unmasked, the following are considerations for the tasks of an unmasked study director in GLP bioequivalence bioavailability studies or in target animal safety studies:

- The study director should not be involved in making original observations or collecting data during the conduct of the study. Unmasked study personnel, including the study director, could record observations dictated to them by masked personnel in situations where the observer cannot record the data themselves. Data verification or corrections should be made or directed by the masked personnel making the original observations.

- The study director should not make decisions regarding animal care based on observations during the conduct of the study, such as modifying treatment regimens, administration of concomitant medications, and removal of animals. Other masked individuals involved in the study, such as the study veterinarian, should make these decisions during the conduct of the study. The study director should be informed of decisions that impact the conduct of the study.

- The study director should be informed if the study veterinarian, or other staff, need to make a specific treatment-related decision about a specific animal (for example, an animal with a serious adverse event). In those circumstances that single animal's treatment can be revealed to the masked veterinarian, or other staff as necessary, for decisions regarding that specific animal. These cases should be fully documented in the final study report.

It should be noted, however, that there may be situation-specific circumstances that warrant study director involvement in these tasks. It would be acceptable for the protocol to state this possibility, describe planned procedures to preserve masking and minimize bias, and say that any deviations and their impact on the study will be documented in the Final Study Report.

57. What are CVM's thoughts on the masking status of people who are assessing compliance with the protocol (monitors, QA staff)?

Monitors and quality assurance (QA) personnel do not need to be masked as they fulfill their responsibilities and duties during the study. These responsibilities should be clearly defined in the protocol and also align with the standard of conduct for QA (21 CFR § 58.35) and monitors (GFI 85 VICH GL9 Good Clinical Practice, Section 5.2). Unmasked monitors and QA personnel should be separate from and independent from study conduct or decision making and need to be mindful of the need to maintain the masking status of study personnel during their interactions with them.

Statistics

58. Why is it necessary to convert units from SI units to US units?

We are open to accepting submission of data reported using International System of Units (SI units). However, note that in a multi-site study where multiple systems of measurement are used (e.g., two sites collected data in US units and one site collected data in SI units), all data should be converted to the same units of measurement for evaluation. Regardless of the system of measurement used in the submission, labels and Freedom of Information (FOI) summaries for US consumers should be prepared using US units. You should discuss any potential conversions with CVM before compiling your report and submission, if possible.

59. What types of data are desired in an electronic dataset format? For example, physical exam data may not be statistically analyzed or summarized in a field trial, but is collected. These data may be presented in a report table; do they also need to be submitted in a dataset?

If the sponsor uses the information to support or draw a conclusion, we expect these data to be provided as an electronic data file. A general rule would be that if the sponsor counted, calculated, or summarized the data, the sponsor should provide those data in an electronic data file. For additional information refer to GFI #197.

60. Please clarify the acceptability of using documented programming to change data for analysis. Does this refer only to inclusion/exclusion of data for analysis per protocol, or to the actual changing of values (such as correcting an error identified after database lock)? Further, what documentation is required when changing data with a program?

Recall that all data collected should be provided in an electronic datafile. If data are excluded or changed for analysis, whether all of an animal's data or select values, these changes should be made in the programming, annotated in the analysis program and clearly documented in the FSR. Reasons for exclusion or change should be briefly described and documented in the FSR and analysis programs, including previous agreement with CVM if applicable. Documentation in the FSR should include a date (indicate whether the data were changed before or after database lock), the reason the data are being changed, and the individual responsible for the change.

61. For electronic data, can the data files archived by the test facility be saved/converted/formatted into a different format, like XML, for archiving or do they need to be in the original electronic file type?

Where the choice exists within a particular system (software), sponsors should select XML or XPT as the format choice for the original recording of the raw data. Where XML or XPT is not an option, the data should be recorded in one of the formats permitted by the system. In either case, save this file as it is part of the study's raw data.

Where the data were not recorded in XML or XPT format, it will be necessary to transcribe/convert the captured data to XML or XPT format before submission to CVM. This file should also contain details regarding the conversion process or software used to make the conversion to permit assessment of the conversion as needed. This converted file should also be saved with the raw data as a transcribed version of the raw data.

62. Could you please comment with regard to the statement about utilizing XML data files for performing the statistical analysis?

To avoid any problems resulting from converting, merging, or concatenating files, the sponsor should analyze data in the same format that it provides to CVM, i.e., XML or XPT. If the software used to analyze the data cannot import data from an XML data file, provide a description of how data integrity was maintained between file types.

63. When an analysis has been conducted, do you want least squares or arithmetic means discussed in the final report?

When parametric inferential statistical analysis using a statistical model is performed, the least square (LS) means are the best estimates of the mean values of any groups that are analyzed. The LS means are adjusted for covariates and fixed and random effects included in the model and should be used when comparing groups. P-values used for comparison and inferences are associated with these LS means and should not be reported in association with arithmetic means. If baseline means are useful for interpreting results, these can be reported as arithmetic means.

When only descriptive statistics are provided, the arithmetic means should be reported and discussed.

64. For clinical pathology variables, how does one talk about "within normal values" when using LS means because normal values are not expressed using LS means?

The upper and lower values of the normal range or reference range are individual point values based on the distribution of each pertinent pathology variable. These bounds are used to evaluate individual observations, not measures of central tendency such as means. Therefore, it is not appropriate to compare LS means to reference ranges.

65. Could you please further explain 'define unexpected issue', e.g. non-convergence and missing data in the protocol?

An analysis described in the protocol may not be executable or appropriate for the data collected. For example, an analysis may not be executable because data distribution or sparseness causes non-convergence of the analysis program where the computer cannot solve the analysis problem and estimates, or tests are not achievable or are unreliable. If most of the data have the same value, e.g., 95% of the differentiated eosinophil values are 4%, it may be more informative to simply provide frequencies of observed values either in a table or text.

66. Could you also comment on interim analyses in exploratory/pilot studies vs. pivotal studies?

In general, we do not comment on the conduct and analysis (interim or otherwise) of exploratory or pilot studies. These studies are conducted at the complete

discretion of the sponsor.

If *a priori* interim analyses are planned for pivotal studies, the sponsor should submit the study protocol for evaluation and concurrence. For pivotal studies, all details of the interim analysis plan should be included, (e.g., alpha adjustments and maintaining study integrity). We are willing to discuss proposed interim analyses with sponsors before the submission of the protocol. Please refer to GFI #268 (Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs) for more information. CVM encourages sponsors to proactively discuss their innovative study design and analysis considerations with CVM.

67. Does CVM have any recommendations regarding who should review interim results and disseminate the information (e.g., a separate statistician or an independent committee)?

The key to performing any interim analysis is to obtain the target information without affecting the integrity or validity of the remainder of the study. Any interim analyses contemplated needs to be described in the protocol before the study begins. To achieve these goals, sponsors should be provided only limited information regarding the results of the interim analysis. For example, if the purpose is for sample size re-estimation, then the only information that sponsors should receive is the sample size estimation (i.e., no information regarding estimated means, differences, or variances). If the purpose of the interim analysis is to make a determination of whether to stop the study for futility or remarkable effectiveness, or to continue the study, the sponsor should only be informed whether to stop or continue the study. Therefore, any statistician performing the interim analyses should only provide decision makers with the limited information described above. One of the suggested ways to protect information is to have an independent (no association with the study) statistician perform any interim analysis. See GFI #268 for additional details regarding minimizing bias in the review of interim analyses.

68. How are study endpoints or primary variables chosen?

Study endpoints are one or more variables used to assess subjects' response to treatment. For studies to demonstrate substantial evidence of effectiveness, a primary variable(s) (also called the pivotal variable(s)) is chosen as the basis for evaluating effectiveness (21 CFR § 514.117(b)(8) and § 514.4(b)(3)). The choice of primary variable and the most appropriate assessment tool is study specific, and therefore, should be discussed with CVM on a case-by-case basis during protocol development.

It is important to select a well-defined and reliable primary variable that is relevant to the indication to provide substantial evidence of the effectiveness of the drug. The protocol should define a primary variable that is precisely and consistently measurable and describe how and when it will be measured and the personnel who will perform the assessment.

69. Discuss CVM validation and use of owner assessments.

CVM does not perform validation of owner assessments. Owner assessments are often used in companion animal studies because the owner has more opportunity to observe

the behaviors of their pets. Owner assessments may provide more information about effects of drugs, progression of disease, and quality of life. The decision to use owner assessments and/or veterinarian assessments is made on a case-by-case basis. We have no list of drugs or diseases that require one or the other assessment types. Therefore, we recommend you discuss use of either of these assessments with CVM. This is particularly true if you have a novel indication.

There are some basic criteria for owner assessments. An owner assessment should

- Be clearly defined and written in layman's terms
- Be unbiased and not lead the owner to a specific response
- Be balanced and not emphasize improvement over lack of response or emphasize certain criteria over others
- Allow for all reasonable gradations of treatment response or lack of response
- Include criteria that the owner can actually observe or quantify, and
- Be documented properly to ensure data integrity, i.e., the data must be ALCOA.

CVM prefers validated owner assessments be used in studies to support new animal drug approval, if available. If a validated owner assessment is used during a study, the assessment should be employed in the study in a manner consistent with its validation.

70. How are surrogate endpoints or biomarkers used to evaluate effectiveness?

Please refer to GFI #267 Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs.

71. What is the motivation for keeping observers from seeing previous observations?

Observations made during the course of a study should be independent and not influenced by previous observations. If an observer has easy access to previously collected data, subsequently collected data could be biased. This is called information or observational bias. While observations may have an underlying correlation because of progressive response to a drug, the observer should not be influenced by knowledge of previous observations to perpetuate a correlation or trend. Observational bias is of particular concern when the data collected are subjective.

Sponsor's GLP compliance statement

72. Does CVM expect to see a sponsor's GLP compliance statement for clinical (effectiveness, GCP) studies?

No. The regulatory requirement for the sponsor's GLP compliance statement exists only for nonclinical laboratory studies submitted as part of the application. With respect to clinical studies, one characteristic (21 CFR § 514.117(b)(2)) of an adequate and well-controlled study is that "the study is conducted in accordance with an appropriate standard of conduct that addresses, among other issues, study conduct, study personnel, study facilities, and study documentation." Further, the "protocol contains a statement acknowledging the applicability of, and intention to follow, a

standard of conduct acceptable to FDA" and the FSR "contains a statement describing adherence to the standard." We recognize the GCP guidance as a standard of conduct acceptable to FDA.

73. Is a sponsor's GLP compliance statement required for all GLP studies?

Yes. The sponsor is required to provide a statement for each nonclinical laboratory study contained in an original (21 CFR § 514.1(b)(12)(iii)) or supplemental (21 CFR § 514.8(f)) application. If the sponsor is using the phased review process for the application and these studies are submitted as part of a P submission to the investigational file, we would expect these compliance statements to accompany the studies. This statement must affirm that each such study was conducted in compliance with the FDA GLP regulations, 21 CFR § 58, or provide a brief statement of the reason for the noncompliance. This requirement is not affected by who conducted the study (i.e., a contract facility or a testing facility within the sponsor's organization), the geographic location of the study (i.e., domestic or foreign), or the standard (FDA GLP, Organisation for Economic Co-operation and Development (OECD) GLP, or other) to which the study was conducted.

74. What form should the sponsor's GLP compliance statement take?

Examples for wording of the statement are provided below. Variations in the wording of the compliance statement may be acceptable if the elements required by 21 CFR §§ 511.1(b)(4)(ii), 514.1(b)(12)(iii), 514.8(f), 514.15(c), and 514.110 (b)(8) are included.

- Sponsors should affirm that each nonclinical laboratory study was conducted in compliance with the GLP regulations, or provide a brief statement explaining the reasons(s) for the noncompliance to GLP.

- Sponsors should ensure that all items of noncompliance with the GLP regulations have been listed on their compliance statement. The list should include all deviations and exceptions from GLP noted in the study director's final study report and any noted by the sponsor during their assessment of the study and facilities involved.

- Sponsors should assess and discuss the impact of each item of noncompliance to GLP described in their compliance statement. Any list of exceptions should not exclude those presumed by the sponsor to have no impact on the interpretation or outcome of the study. It is acceptable to reference information included in the submission to help describe any item of noncompliance, however; any reference should be specific. A reference alone is not sufficient to fulfill the sponsor's responsibility to identify, explain, and assess the impact of an item of noncompliance as part of the sponsors compliance statement (refer to example in section titled "Additional Consideration" below).

We provide examples for your reference. However, you may choose to use different language based on the study design as long as all the information described above are included in your compliance statement.

Studies conducted at contract facilities

Case 1

This case presumes that the contract facility is operating in conformance with the GLP regulations and has a fully functional quality assurance unit (QAU). In this case, the sponsor should take the steps necessary to assure itself that the contract facility has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly. Likewise, the sponsor should examine the procedures used by the contract facility's QAU and make a determination that such procedures are adequate to obtain GLP compliance. Finally, the sponsor should review the final study report for consistency and accuracy. Auditing of the report is not necessary as this should have already been done by the contract facility. If a sponsor has taken these actions and is prepared to make such a statement, below is an example for the sponsor's GLP compliance statement:

Statement for Case 1 (contained with the quotation marks) –

"The sponsor has:

- *assured itself that the contract facility has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly,*
- *examined the procedures used by quality assurance unit for the contract facility,*
- *made a determination that the procedures of the quality assurance unit are adequate to ensure GLP compliance, and*
- *systematically reviewed the final study report.*

On this basis, the sponsor can state that this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with the following exceptions: (if none, it is appropriate to state "On this basis, this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with no exceptions); otherwise, identify any exceptions and brief statements of the reasons for their noncompliance in a list and the impact on the integrity or outcome of the studies)."

Case 2

There may be instances where the contract facility does not have a fully functional QAU and may or may not be operating in conformance with the other provisions of the GLP regulations. In this case, the sponsor should perform all quality assurance functions and take whatever steps are required to promote the GLP compliance of the contract facility. The final report will have to be audited since this has not been adequately done by the contracting facility. In these cases, the sponsor's GLP compliance statement should take the form as written below.

Statement for Case 2 (contained with the quotation marks)

"The sponsor was not able to determine both that the contract facility was operating in compliance with the GLP regulations and has a fully functional quality assurance unit. Therefore, the sponsor has:

- *used a fully functional quality assurance unit that can fulfill such requirements as they relate to the conduct of the study at the contract facility,*
- *fulfilled other testing facility management responsibilities as necessary to assure that the contract facility has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly, and*
- *audited the final study report and supporting study documentation.*

On this basis, the sponsor can state that this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with the following exceptions: (if none, write "none"; otherwise, identify any exceptions and brief statements of the reasons for their noncompliance in a list)."

Studies conducted within the organization of the sponsor

Studies conducted within the sponsor's organization were not specifically addressed in the answer provided to question 40 of the Guidance for Industry: Good Laboratory Practice Regulations Management Briefings Post Conference Report originally issued in August 1979 (and republished in November 1998 with minor editorial and formatting changes). However, as noted in our answer to Question #73, the requirement to provide this statement is not affected by who conducted the study. It seems reasonable to CVM that the GLP compliance statement for these studies should be prepared in a manner analogous to those at contract facilities.

Case 3

This statement presumes that those elements of the sponsor's organization related to the direction and conduct of nonclinical studies are operating in conformance with the GLP regulations and that a fully functional QAU is providing oversight of the study. In this case, the sponsor should take the steps necessary to assure itself that it has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly. Likewise, the sponsor should examine the procedures used by the QAU and make a determination that such procedures are adequate to obtain GLP compliance. Finally, the sponsor should review the final study report for consistency and accuracy. Auditing of the report is not necessary as this should have already been done by the testing facility QAU. If a sponsor has taken these actions and is prepared to make such a statement, then the sponsor's GLP compliance statement should take the form as written below.

Statement for Case 3 (contained with the quotation marks)

"The sponsor has:

- *assured itself that our testing facility has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly,*
- *examined the procedures used by the quality assurance unit for our testing facility,*
- *made a determination that the procedures of the quality assurance unit are adequate to obtain GLP compliance, and*
- *systematically reviewed the final study report.*

On this basis, the sponsor can state that this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with the following exceptions: (if none, write "none"; otherwise, identify any exceptions and brief statements of the reasons for their noncompliance in a list)."

Case 4

There may be instances where the sponsor is aware that elements of their organization related to the direction and conduct of nonclinical studies does not have a fully functional QAU and may or may not be operating in conformance with the other provisions of the GLP regulations. In this case, sponsor personnel independent of those individuals related to the direction and conduct of the nonclinical study or the QAU should perform all quality assurance functions and take whatever steps are required to promote the GLP compliance of the testing facility. The final report will have to be audited since this has not been done by the testing facility. In these cases, the sponsor's GLP compliance statement should take the form as written below.

Statement for Case 4 (contained with the quotation marks)

"The sponsor was not able to determine both that the testing facility was operating in compliance with the GLP regulations and that oversight was provided by a fully functional quality assurance unit. Therefore, the sponsor has:

- *used a fully functional quality assurance unit that can fulfill such requirements as they relate to the conduct of the study at the testing facility,*
- *fulfilled other testing facility management responsibilities as necessary to assure that the testing facility has adequate personnel, facilities, equipment, and standard operating procedures to perform the study properly, and*
- *audited the final study report and supporting study documentation.*

On this basis, the sponsor can state that this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with the following exceptions: (if none, write "none"; otherwise, identify any exceptions and brief statements of the reasons for their noncompliance in a list)."

Additional Consideration

As stated above, the sponsor may reference information included in the submission to help describe any item of noncompliance, however; any references should be specific and a reference alone is not sufficient to fulfill the sponsor's responsibility to identify, explain, and assess the impact of an item of noncompliance to GLP. If the sponsor chooses this approach, the sponsor would review the study and select the appropriate case and statement described above to determine the appropriate wording for the sponsor's GLP compliance statement. For any applicable item of noncompliance, the sponsor would include clear, specific reference to documentation in the submission.

For example, the statement could read (contained with the quotation marks):

"…On this basis, the sponsor can state that this nonclinical laboratory study was conducted in compliance with the GLP regulations (21 CFR § 58) with the following exception:

A non-GLP laboratory was used for analysis of tissue samples at Site ABC. This event is described in detail in the Deviation data capture form dated January 12, 2020, included in the copies of raw data provided for Site ABC. It is also summarized as Deviation #7 in the final study report. A non-GLP laboratory was used to analyze tissue samples because the study director could not locate a GLP laboratory with the capability to conduct the required analysis. The study director has experience with the non-GLP laboratory used and has confirmed the laboratory's ability to conduct the analysis in a manner that produces reliable data. We have reviewed the study documentation for this event and determined this item of noncompliance did not impact the outcome of the study."

75. Can the sponsor draw from a study director's GLP compliance statement to create the GLP compliance statement required in 514.1?

There is no GLP compliance statement required of a study director. The study director is required to assure that "unforeseen circumstances that may affect the quality and integrity of the study are noted when they occur, and corrective action is taken and documented" (21 CFR § 58.33(c)) and to sign an FSR that includes "a description of all circumstances that may have affected the quality or integrity of the data" (21 CFR § 58.185(a)(9)).

While the burden of establishing that any noncompliance did not affect the quality of the data submitted to CVM remains with the sponsor, the sponsor is free to use whatever information is available to it to assist with such a determination. The sponsor may use information or reports provided by the testing facility as the basis for initiating (but not substituting for) the sponsor's evaluation of the study's compliance with 21 CFR §t 58. However, it should be evident from the structure of the sponsor's GLP compliance statements that, in each case, the sponsor's evaluation is independent of that provided by the personnel conducting the study (the testing facility and any third parties used, if any). The language of the statements identifies our expectations, and the commitments of a sponsor, based on the functionality and capacity of the contract facility (or testing facility of the sponsor) and the QAU used for the study. The sponsor's GLP compliance statement should be signed by an individual who has direct knowledge of the conduct of the study, an understanding of the GLPs and the ability to appropriately assess the effects that any deviations might have on the outcome of the study and interpretation of the results. As a reminder the person signing the GLP compliance statement is responsible for assessing GLP compliance, the truthfulness and accuracy of the study.

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?

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.

77. How should small establishments address appropriate separation of function between test facility management and the study director if the most qualified person to be the study director is the owner of the company?

According to the GLP regulations (21 CFR § 58), the study director cannot be the same person as the testing facility management. Some options in this situation may be to train another person to handle the more administrative duties of the testing facility management or collaborate with another small facility to share management resources. Other creative solutions are possible.

For facilities with a small number of employees, preplanning is necessary to ensure the development of a GLP-compliant infrastructure. The overall goal for the GLP regulations is to provide a quality system that can reliably produce study data of appropriate quality and integrity. Sponsors are welcome to discuss appropriate separation of function with CVM.

The documentation required by the GLP regulations allow CVM to reconstruct the conduct of the study so that we can confidently make regulatory decisions regarding the safety of the product based upon the data provided.

The standards and requirements in the GLP regulations are designed to provide evidence of acceptable managerial and scientific rigor in study conduct in the absence of direct agency oversight. Inconsistency in adherence to, or application of, these requirements will eventually lead to misaligned expectations and a decrease in the quality (and subsequently, the utility) of the study data collected. This ultimately degrades the efficiency of the approval process.

78. Please provide a listing of the 12 critical standard operating procedures for GLP studies.

SOPs must be established for, *but not limited to*, the following (21 CFR § 58.81(b)):

- Animal room preparation,
- Animal care,
- Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles,
- Test system observations,
- Laboratory tests,
- Handling of animals found moribund or dead during study,
- Necropsy of animals or postmortem examination of animals,
- Collection and identification of specimens,
- Histopathology,
- Data handling, storage, and retrieval,

- Maintenance and calibration of equipment, and
- Transfer, proper placement, and identification of animals.

The site should have the written SOPs necessary to carry out their study operations in a manner designed to ensure the quality and integrity of the data. GLP regulations in 21 CFR § 58 may be updated and it is the responsibility of the site and sponsor to assure adherence to current GLPs.

Study conduct

79. For GCP studies, if the clinical investigator needs to use a supporting facility to perform study related work (for example, using a diagnostic laboratory for MRI or CSF analysis) what type of documentation does CVM expect the investigator to collect before using the supporting facility to ensure the supporting facility is "qualified"?

In general, supporting facilities should be held to the same standard as the main facility. The type of documentation that we would expect is similar to the type of information that a sponsor uses to assess a facility. A sponsor should make the appropriate assessment (e.g., quality audits, qualification monitoring visits, etc.) that the personnel performing the work are qualified by training and expertise, that they are in compliance with GCP, and that the work done by the facility is accurate and reproducible. The degree of documentation for a supporting facility depends on the relationship of the work being conducted to the pivotal variable(s). If the supporting facility is responsible for measuring or evaluating the pivotal variable, then we would expect the sponsor to provide assurance that the results from the facility are accurate and reproducible. CVM does not typically expect the supporting documentation used to qualify the facility to be submitted; however, the clinical investigator should meet the responsibilities outlined in Section 3.2.8 of the GCPs, which states, sufficient documentation should be maintained to demonstrate compliance with GCPs.

80. What amount of information is necessary to appropriately document the use of concurrent medications in nonclinical and clinical studies?

If concurrent (concomitant) medications are used during the study, the reason for administration, identification of animals dosed with the medication, days dosed, dose administered, and any observed interactions should be documented following attributes of ALCOA. Documentation of the medication consists of its proprietary and established names, dosage regimen, and expiration date.

We recommend discussing the use of concomitant medications with CVM at the protocol stage. Any acceptable or prohibited concomitant medications should be clearly described in the protocol and all study conduct should comply with the protocol. CVM discourages the use of concomitant medications in Human Food Safety GLP studies.

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.

82. Is it acceptable if case numbers are not assigned to animals at the time they are screened for potential inclusion in a study?

It is acceptable to not assign a case number to animals being screened before enrollment as long as the animal has some sort of identification so that it can be tracked and accounted for in the final disposition records for the study. Additionally, if the pre- and post-assignment identification numbers differ, the sponsor should provide a list of both identification numbers in the FSR and/or in an electronic data file. The presence or absence of a predetermined randomization list does not affect these processes.

Final study report

83. Are there differences in the requirements for an FSR between pivotal and supportive studies?

We think that for any study to have utility there should be a written evaluation of the study results. Our requirements for the contents of pivotal effectiveness and safety FSRs can be found at 21 CFR § 514.117(b)(9) and 21 CFR § 58.185, respectively. For clinical studies, CVM GFI #85 (VICH GL9) provides further guidance on the FSR content. Supportive or corroborative (non-pivotal) studies are not used as a primary basis for approval decisions and therefore are not required to meet these standards, but sponsors should recognize that the potential utility of these studies is enhanced by high quality FSRs.

84. What exactly should be included as part of an FSR for a pivotal study? Are there other documents that CVM expects to be submitted in conjunction with an FSR?

In general, the contents of a nonclinical and clinical final study report are described in 21 CFR § 58.185(a) and section 7.3 of the GCP guidance document (CVM GFI #85 (VICH GL9)), respectively. Administrative and compliance items and additional information for a GCP FSR are described in sections 7.3.9 and 7.3.10. Copies of critical raw data should be submitted with the FSR and the FSR should summarize and reference the supportive raw data as necessary. Copies of raw data considered critical for CVMs review will depend on the requirements of the protocol and items that may have been agreed upon with CVM before the submission of the study.

85. Should the sponsor create a protocol with all amendments incorporated into the body of the protocol for submission with the FSR?

Generally, no. We expect the sponsor to include the original protocol, and all amendments with the FSR. We do not recommend or request that sponsors create a new “final version” with all of the changes incorporated. One exception is where a sponsor wishes to change the protocol before the start of the study.

In that case, the change may be "incorporated into the body of the protocol" to create a clean protocol for study personnel to follow when the study is initiated. If we concurred with the protocol before the pre-study change was made, we expect that the FSR will reflect the fact that the 'original' (now changed) protocol for the study is different than the protocol with which we concurred.

86. In situations where a sponsor uses both a contract research organization (as the test facility) and third-party contractors/contributing scientists, should the test facility expect to receive raw data and quality assurance reports from the third-party contractor/contributing scientist?

If a sponsor uses a test facility that meets the definition of a contract research organization (21 CFR § 511.1(f)(1)) by at least agreeing to assume the sponsor's responsibility identified in 21 CFR § 58.10, then, yes, that test facility must notify any third party that their service is part of a nonclinical laboratory study and must be conducted in compliance with 21 CFR § 58. In this case, the responsibilities of the testing facility and study director have not changed by the use of any third party. In general, the protocol should clearly define the role the third party plays in the study.

Per GLPs, there should be QA oversight for all aspects of the study including work performed at a third party facility. If the third party facility cannot provide QA oversight the testing facility should assume QA responsibilities. The QA inspection reports and the QA statement generated from the third-party contractor should be provided to the study director and the testing facility management as defined under 21 CFR § 58.35.

Copies of raw data generated by the third-party contractor should be provided to the study director upon request. The original data should be retained and archived as required by the study protocol and in compliance with 21 CFR § 58.195.

For example, a sponsor uses Firm A as the testing facility and Firm B as the contributing scientist for the histology phase (test site). The phase delegation and the QA's responsibilities in Firm B (test site) should be defined in the protocol. Typically, QA at the test site would perform a phase inspection, data and report audits. The audit reports should be reported to the contributing scientist (at the test site) and his/her management, study director and the testing facility management. At the end of the phase, if a contributing scientist report is provided to the study director, a signed QA statement should be included in the contributing scientist report. If no report is provided, the signed QA statement should be provided to the study director to be included in the study director's final study report.