Transcript
for the
Data Quality Webinar
held June 4 and 6, 2013

This transcript encompasses the introductory presentation as well as the presentations on protocol development, prior to live and live phases, and reporting and submitting the data. The substance of the last formal presentation on June 6, a question and answer session, is not here and has been incorporated into the companion Questions and Answers document which addresses all questions received. Transcript remarks related to procedural issues and speaker identification have been deleted along with those slides from the PowerPoint presentations.

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"Building Quality Data – Introduction"

presented by Marty Schoenemann

Slide 1 The Title slide.

Slide 2 Participants from AHI and its member companies who helped develop the content that was the basis of the presentations.

Slide 3 Participants from CVM who helped develop the content that was the basis of the presentations.

Slide 4 This webinar on data quality is the final workshop of the ten that are required by the Animal Drug User Fee Authorization Act of 2008. We have found this series of workshops to be extremely helpful in addressing issues of mutual concern. By way of example, three of the ten workshops held over the last five years included one on antimicrobial drugs for companion animals, one on manufacturing chemistry question−based-review process for sterile process validation, and a recent one on medicated feeds.

Slide 5 Why are we interested or concerned about high quality data? The short answer is faster drug approvals. Each data point is becoming more valuable. This is true because CVM is working to minimize the number of studies that are necessary to support approval. And in those remaining studies we're trying to minimize the number of animals we use and to focus on exactly what data are collected. The result is that the number of data points actually collected is decreasing dramatically. The other main reason is so that we will have a smoother review process.

Slide 6 It is a smooth review process because we are able to more easily reconstruct the data. We are able to determine that the data were collected appropriately and it permits an efficient analysis of the study results both from a statistical and a scientific perspective. And finally, we can confirm adherence to the laws, regulations, guidance, and policies.

Slide 7 To develop this webinar, AHI and CVM held a series of meetings to brainstorm different issues that were related to the lifespan of high quality data for target animal safety and clinical effectiveness studies. Our discussions ran the gamut from the conceptualization of the need for data all the way out to actually submitting that data to CVM.

Slide 8 From the results of those discussions there were five critical areas that we identified where improvements would be most effective. Those were study protocol development; prior to live and live phases of study conduct; reporting of the study results; and submitting of those results and data to CVM. These are the areas which will be covered during this webinar.

Slide 9 It's important to remember what this webinar does not cover. We received and thought of many different actions that could be taken to improve the quality of data, but we just didn't have the time to include all of them in our presentation. Therefore, this webinar is not an exhaustive examination of all the possible actions that can improve the quality of the data. Rather, it is the identification

and discussions of those actions that we believe are most likely to have a noticeable impact on data quality.

Slide 10 With that, thank you for participating today. Keep in mind that if you put the actions you learn today and Thursday into routine practice, we believe they can have a favorable impact on the quality of the data that you collect and submit to CVM and thus, should have a significant impact on the drug approval process.

"Building Quality Data **– Protocol Development"**

presented by Eden Bermingham

Slide 11 The Title slide.

Slide 12 Good morning. I'm going to talk about building quality into the protocol. Good protocol design helps you collect accurate, complete, precise, and orderly data. CVM's standards for quality data should be built into the protocol to help assure appropriate data are collected and analyzed. Our goal in this working group was to share and distribute best practices to ensure timely submission review.

Slide 13 So, the topics I will present today are presubmission conference and protocol meetings, sponsor review of the protocol, the overall study design, randomization, masking, adverse events, the inclusion and exclusion criteria, removal of animals, the choice, measurement, and timing of endpoints, data analysis, data capture forms, protocol training, and Standard Operating Procedures (SOPs).

Slide 14 And before I begin my talk, I will remind everyone that protocol concurrence is not required but it certainly helps to assure that the studies are adequate to support drug approval.

Slide 15 The presubmission conferences are scheduled for 30 plus days after receipt of the meeting request from the sponsor. CVM uses this time for internal meetings to review the meeting materials. The sponsor should define the indication and pivotal endpoints during the meeting. And there's usually discussion of possible label language during the meeting.

Slide 16 The presubmission conference is an opportunity for the sponsor to propose the development plan and general pivotal study designs. The sponsor can provide data summaries to support key protocol designs. At the end of the meeting, the Memorandum of Conference (MOC) summarizes the key points and agreements made during the meeting. And this is a reminder that if the sponsor has questions about the MOC, they should contact CVM for clarification.

Slide 17 There is also an early information option. This is where the sponsor can provide preliminary data, such as data from pilot or pharmacokinetic (PK) studies, approximately 100 days prior to the presubmission conference, to allow CVM to review the data and provide a more detailed discussion of pivotal studies during the meeting. The goal for this early information option is for sponsors to be able to submit the protocol immediately after the presubmission conference.

Slide 18 There are several resources available for protocol development, such as the Guidance for Industry numbers 85, 185, and 215. These provide guidance for general study designs. There are also species specific guidances, such as the species specific anthelmintic guidances. 21 CFR part 58 contains the Good Laboratory Practice regulations for non-clinical laboratory studies. There's also the AHI "points to consider" document which is titled "Protocol Submissions for the Division of Therapeutic Drugs for Non-food Animals." This is a helpful document but it is a few years old, so there are some outdated procedures. For example, there's no mention of the End-Review Amendment (ERA) or information about eSubmitter procedures. Appendix 1 of this document, which describes the statistics, also does not necessarily reflect CVM's current thinking.

Slide 19 There are also specific protocol development meetings where the sponsor may request a meeting after the presubmission conference to discuss specific protocol issues in more detail. These types of meetings are especially important for novel products, indications, or a complex study design. These types of meetings also allow CVM to provide specific feedback; however, they may not be necessary if sufficient early information is provided prior to the presubmission conference.

Slide 20 The internal review of the protocol by the sponsor is critical. It's very helpful to have input from statisticians, consultants, investigators, and monitors to help improve protocol quality and avoid mistakes. The quality assurance group can also help by reviewing the protocol. Sometimes it's just helpful to have another pair of eyes to see if there any possible misinterpretations of the protocol.

Slide 21 In drafting the protocol, it's helpful to identify the data capture forms (DCFs) in the text either by the title or the number. It's helpful to describe procedures consistently from one section to the next, using the same terminology. It's also helpful to organize and number the sections to help the investigator find the information more quickly.

Slide 22 With respect to overall study design, the sponsor should not base the protocol only on Freedom of Information Summaries (FOIs) from approved products because CVM's current thinking may have evolved since the approval. In addition, there may be important differences between the investigational drug product and the approved product, so that the studies cited in the FOI may not be appropriate. The sponsor should review protocols from third parties to confirm that they are acceptable. In the protocol, the sponsor should specify the pivotal and supportive variables for the proposed indication or safety.

Slide 23 The protocol should describe the experimental design, e.g. if it's a parallel or crossover study, and any blocking or stratification. The protocol should describe the treatment groups, e.g., the control groups and whether they are placebo or historical control groups. The protocol should also describe the sample size for the study and the treatment allocation, e.g., one-to-one or two-to-one treatment versus placebo groups.

Slide 24 The randomization section of the protocol should provide enough detail to illustrate the implementation and randomization restrictions such as blocking, stratification, or unequal treatment allocation, e.g., a 2:1 treated to placebo ratio. The protocol should specify that all details of the randomization will be included in the final study report.

Slide 25 The randomization section should also describe who will perform the randomization and how it will be implemented at the study site. For example, if the randomization is generated for each site prior to study initiation, or if it's generated centrally in real-time. If the study is masked, the treatment information should not be disclosed on DCFs other than the randomization sheet/treatment administration form.

Slide 26 For this webinar, masking includes both masking of treatment and the personnel. Masking is important for reducing observer bias and should be appropriate to the bias control needed for the study. Therefore, one approach may not fit all studies.

Slide 27 It's important to maintain separation of function between masked and unmasked personnel throughout the study. The protocol should specify the masking status of all key personnel, e.g., the sponsor, study director, monitor, treatment administrator, statistician, or owner.

Slide 28 The protocol should ensure that personnel making observations are not aware of the treatments. Personnel managing real-time data should remain masked throughout the study, e.g., the statistician, clinical investigator, or the study director.

Slide 29 For masking, it's important to use more labels or codes than the actual number of groups. For example, in a study with two treatment groups with equal allocation, use at least four treatment codes. In a study with unequal allocation, it's important that you use at least three treatment codes. This approach may vary depending on the number of treatments. It's important that the number of codes is not too great that it becomes confusing and increases the chance for error.

Slide 30 The protocol should specify conditions under which unmasking is allowed (for example, serious adverse events or human exposure), and how masking will be protected for the remaining subjects. Pay particular attention to protecting study integrity for interim analysis, such as using a separate statistician to perform the interim calculations.

Slide 31 And the protocol should also describe the timing and process for unmasking the study, e.g., after data locking.

Slide 32 The section I will discuss next is adverse events. The definition of an adverse event is included in the Good Clinical Practice (GCP) guidance (Guidance for Industry number 85). It is defined as any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product whether or not it's considered to be product related. Some protocols also define serious adverse events. It's important to train study personnel to report adverse events even if they appear to be unrelated to the treatment or if they are considered to be common diseases for that species or class of animal.

Slide 33 A list of common terminology for investigators to use makes reporting easier. The protocol should state when to report adverse events (e.g., if they should be reported within a specific timeframe such as 24 hours), and to whom they should be reported to (e.g., the protocol may state to report adverse events to the monitor or a sponsor representative).

Slide 34 Dedicated forms for adverse events make the reporting easier. Multiple adverse event forms may be helpful to track the progress and resolution of adverse events. It may be helpful to use a follow-up form that documents the progress and resolution of the adverse event. Adverse event forms should include the date of occurrence and the date that the adverse event is reported. In some cases, these two dates are confused so there should be a separate space for each of these. The form should also include animal ID or the pen ID, the adverse event, the treatment of adverse event including concomitant medications, and the resolution.

Slide 35 The adverse event forms should be designed such that they do not compromise masking unless unmasking is necessary to treat the animal. Monitors should check for adverse events in other sources such as medical records and owners diaries.

Slide 36 Documentation of the removal of animals in the protocol is often a weak area and therefore the following items should be described clearly in the protocol: the criteria for removal, the procedures and documentation, who to contact in case of the removal, and how removed animals will be accounted for in the effectiveness or safety analysis.

Slide 37 The inclusion and exclusion criteria depend on the type of study and pivotal variables. The criteria may include reasonable diagnostics to ensure eligibility. It is important to list exclusionary medications, physiological conditions (such as pregnancy or lactation), and/or diseases.

Slide 38 The sponsor should consider the inclusion and exclusion criteria carefully so that they are appropriately restrictive or expansive as necessary to ensure suitable candidates are enrolled. And when choosing the criteria, it's important to think about how they may impact the final label.

Slide 39 In the next few slides I will be talking about the choice, measurement, and timing of endpoints. The endpoints should be consistent with the proposed indication and it should be measurable in a meaningful way, e.g., the endpoint may be clinically relevant. If it's a new endpoint, it's helpful to discuss this with CVM during the protocol development. In some cases, early information may be beneficial to justify the endpoint and when to assess it.

Slide 40 For the measurement of an endpoint, the methods and procedures should be well-defined, accurate, and reproducible. If equipment is used, then it must be properly calibrated. Consider contacting CVM if you are planning to use a new method because it may be helpful to discuss this before submitting the protocol. For example, if a sponsor wants to use a new glucometer to measure the primary endpoint, CVM may want some justification for its use or evidence of its accuracy.

Slide 41 The timing of the endpoint depends on the indication, e.g., if the endpoint occurs during the early versus the late stages of the disease. It's also dependent on the type of outcome, e.g., complete versus partial response. The timing of the endpoint may be dependent on drug levels in some cases, such as antimicrobials.

Slide 42 The data analysis section of the protocol should include the hypothesis to be tested, and the pivotal analysis should match the primary clinical hypothesis. The protocol should describe the treatment effect or effects to be estimated, it

should specify the significance threshold, and it should define the experimental unit, whether it's an animal or a group (e.g. pen, cage, or tank) of animals.

Slide 43 The data analysis section should also describe the principal features of the proposed pivotal analysis of the effectiveness variables. It should describe the statistical model, and fixed and random design factors that reflect any randomization restrictions. It should include the analysis details, such as covariance structures, and it should also include a plan for unexpected analysis problems, e.g., case of missing data or non-convergence issues.

Slide 44 The data analysis section should also prospectively define outcomes for animals removed prior to the final endpoint measurement. For example, animals that experience drug-related adverse events may be considered failures, and withdrawals unrelated to the treatment may be considered un-evaluable cases.

Slide 45 If the study includes an interim analysis, this section of the protocol should state the purpose of the interim analysis, such as if it is to be used for sample size calculations, or stopping for futility or remarkable effectiveness. Remarkable effectiveness refers to a drug that is so effective that all animals should benefit from the treatment. This section of the protocol should also describe the personnel involved and how study masking will be maintained. It should also state when the planned analysis will occur, in other words, if it's based on time or number of subjects.

Slide 46 The interim analysis section should also describe the process which includes the data freezing, which data will be analyzed, what type of analysis will be performed, and the plan for including the frozen data set in the final submission. The protocol should also describe any impacts on the final analysis. For example, any adjustments, such as when the alpha may be reduced to control a type one error.

Slide 47 The protocol should also include some direction as to data management. It should describe the timing and the process for the data freeze and data lock. For example, data audits or the QC process. The locked database is considered to be the electronic raw data, and any variable transformations or computations, e.g., unit conversion, should be planned for after the data lock.

Slide 48 And the entire electronic raw data set should be included in the submission, not the subset of the data that was analyzed.

Slide 49 I'm going to discuss designing data capture forms. Data capture forms that capture the primary variable data should be included with the protocol for concurrence. It's helpful to design the forms from the investigator's perspective to minimize errors. It's also important to understand how these forms will be used to ensure that they accurately capture the critical information.

Slide 50 Some sponsors have large data capture form databanks from which generic forms are modified for specific studies. Some sponsors create these forms from scratch. It's critical to train investigators how to use these forms because it's the most effective way to minimize errors. Therefore, a sponsor may want to consider a dry run to test the forms. As with the protocol, it's helpful to involve QA in the design and the review of these forms.

Slide 51 It's important to provide enough space for necessary information, and comments by laypeople may need more space. It's helpful to provide guidance on the type of comments the study participants need to add in the allotted space, and to provide enough space for the signatures and initials for both the observers and recorders, if that is applicable.

Slide 52 Most forms include the animal ID, date of documentation, and initials or signature of the participants. However, be aware of bias concerns; you should use a different form for each day rather than tracking data over time on a single form which would allow observers to see the previous days' documentation. Do not include treatment group identification on forms used by masked personnel.

Slide 53 CVM reviews the forms to see if they collect the appropriate information and preserve masking. We do provide comments if we feel that the forms are deficient. Numbering and titling the forms, and referring to them in the protocol, helps both the study participants and reviewers.

Slide 54 There usually is a greater variation in the forms used for field studies. However a sponsor should review the forms provided by a contract research organization (CRO) or any third-party to see if they are acceptable. In some cases for GLP studies, the site may have its own forms so they may be reluctant to use the sponsor forms. However, it is a sponsor's responsibility to ensure that the most appropriate forms are used for the study.

Slide 55 There are two main types of electronic data capture forms. In GLP studies, software is used to record toxicology data, like the Provantis and Xybion systems. In GCP studies, there's usually a form-based system with electronic forms that mimic the paper forms and data collection methods used in field studies.

Slide 56 It's important to remember that electronic data capture forms must be 21 CFR part 11 compliant. Some of the part 11 issues to pay particular attention to include ensuring that there is appropriate validation of the software, some indication of what signatures are considered valid, and inclusion of an audit trail to help monitoring. The sponsor may want to consider introducing CVM to their proposed software in a presentation. In some cases, the sponsor may want to include screenshots of the electronic data capture forms in the protocol.

Slide 57 Protocol training is the most effective and cost-efficient way to minimize errors and maximize consistency, because it gives the personnel the chance to point out problems with the protocol or forms. The sponsor may want to consider having an investigator or study personnel complete the forms using mock data to help debug the forms. Finally the sponsor should provide principles for rounding numbers when recording the data or the dosing of the drug.

Slide 58 Our next topic is protocol SOPs. "SOPs" stands for standard operating procedures. For both GLP and GCP studies, SOPs may not be necessary if the procedures are described adequately in the text of the protocol. If SOPs are to be used in the study, for both GLP and GCP studies, the SOPs critical to the study should be submitted with the protocol. The SOPs that pertain to the assessment of the primary variable should be submitted with the protocol for review. In that case, the sponsor may want to discuss which SOPs are considered critical before submitting the protocol. However, if the sponsor refers to using "standard methods" in the protocol instead of describing the method or including an SOP,

they assume the risk that the method may not be acceptable to CVM for the submission.

Slide 59 In some cases, for both GLP and GCP studies, procedures such as microbiological assays or other procedures as appropriate can be submitted separately for review. Sponsors should talk to the primary review division if they want to do this.

Slide 60 As a reminder for GCP studies, SOPs are not required by the CFR as part of the protocol, but may be used to support assessment of the primary variable or as part of part 11 validation. For GLP studies, there is a minimum of 12 critical areas required by 21 CFR part 58 that have to be addressed in the SOPs or in the protocol text itself.

Slide 61 The sponsor should ensure that all sites are able to meet the SOP requirements for GLP studies. In some cases, the SOPs may be considered proprietary by a CRO or electronic data collection vendor. The sponsor could then reference a submission outside the protocol such as in the Veterinary Master File.

Slide 62 So, in summary, the topics chosen for the presentation today are the areas where it's important to build quality into the protocol. The suggestions made today are based on feedback from both CVM reviewers and sponsors. Finally a well-written protocol decreases the potential for mistakes during the study and increases the chance of a one cycle review. Thank you very much for your attention.

"Building Quality Data – Prior to Live and Live Phases Presentation"

presented by Emily Smith

Slide 63 The Title slide.

Slide 64 Good morning. The following presentation focuses on the time of preparation for the study (following the development of the protocol), and the collection and management of data during the study. I would like to re-emphasize that the presentation is not an exhaustive discussion of all possible actions that could improve data but those areas that are most likely to have the greatest impact on data quality. The goal is to promote the submission of high-quality data which supports the efficient review of safety and effectiveness data and the expeditious approval of quality, safe, and effective drugs. My presentation highlights four areas of the prior to live and live phases of the study: 1) selection of sites and investigators, 2) training of personnel, 3) implementation of the protocol, and 4) data collection and management throughout the study.

Slide 65 The topics I will cover today relating to these four areas include site selection; personnel training; test and control articles; feed and water for the animals; concurrent medications; test animals; control of bias; data collection and management; amendments and deviations; adverse events; and quality oversight.

Slide 66 The selection of a site involves the selection of a Clinical Investigator for clinical studies (those conducted according to Good Clinical Practice (GCP) guidance); a study director for nonclinical laboratory studies conducted in accordance with Good Laboratory Practice (GLP) regulations, the evaluation of facilities in which a study will be conducted; the review of personnel qualifications, and, if it is a GLP study, additional considerations to ensure compliance with the regulations in 21 CFR part 58.

Slide 67 If the study is a clinical effectiveness study, the investigator should have sufficient knowledge, scientific training, and experience to conduct the study appropriately. These criteria should be evaluated as part of the selection process for the investigator. Please note the regulations require that studies submitted as part of substantial evidence of effectiveness are conducted by experts qualified by scientific training and experience.

As part of the selection process, it is useful to review the inspection history for the investigator. Clinical investigators are inspected under the compliance program that is referred to in Compliance Program Guidance Manual (CPGM) 7348.811. You can also review the FDA debarment list and disqualification proceedings for clinical investigators on the FDA website. Ultimately you should be confident that the clinical investigator you choose will be able to fulfill the responsibilities of the protocol and the applicable regulations and guidelines. They will be the one person responsible for all aspects of the conduct of the study at the study site.

Slide 68 A study director is defined by the regulations in 21 CFR part 58 and is the scientist of appropriate education, training, and experience, or a combination of those things, that has the overall responsibility for a nonclinical laboratory study (which I will refer to as a GLP study). GLP studies would include *in vivo* or *in vitro* safety studies, but do not include clinical studies or field trials in animals or basic exploratory studies.

The responsibilities outlined in 21 CFR 58.33 are separate from those of the test facility management and QA unit. All the responsibilities of the study director are defined in the regulations and include items such as ensuring that the protocol and any changes are approved and that the protocol is followed; all data including observations of unanticipated responses of the test system are accurately recorded and verified; unforeseen circumstances that may affect the quality and integrity of the study are noted when they occur and corrective action is taken and documented; test systems are as specified in the protocol; all applicable GLP regulations are followed; and all raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

Slide 69 When choosing a facility or study site for your study, there are a number of things to consider. One is the geographic location. The location or locations may have been discussed during meetings with CVM and depending on the project, the use of a variety of geographic locations may be important.

Another item to consider is the schedule. Does the facility have the time, particularly if there are seasonal considerations for the drug? For example, if the disease is more prevalent during a particular time of year.

And, you should also determine if the entire study will be conducted at one facility or if there will be contract laboratories involved. Contract laboratories are often used for procedures such as clinical pathology, necropsies or histopathology and you should ensure that these contract labs are following the appropriate standards.

The next thing for facility considerations relates to the inspectional history of the establishment if it is a GLP study. You should evaluate whether the site has been inspected previously, and if a FDA Form 483 was issued, determine whether those issues were resolved appropriately.

In terms of animal housing and handling, you should determine whether the facility has the appropriate facilities and experience to handle the species and also accommodate all procedures specified by the protocol.

Slide 70 As part of the facility evaluation, you should look at the SOPs at the site and determine if they are sufficient to meet the regulatory requirements for the study and, if they conflict with protocol specified procedures, that the facility can and will follow procedures specified by the protocol. There are particular requirements for standard operating procedures outlined in the GLP regulations that must be followed if it is a nonclinical laboratory study. You should also evaluate the equipment at the site to ensure that it meets the needs of the protocol, that it has been maintained and calibrated appropriately, and that scale checks and scale verifications are performed and recorded properly.

Slide 71 Additional facility considerations include confirming that the site has the ability to handle and store the investigational drug properly and the adequacy of their data handling procedures. You should determine if there is an appropriate storage available for the investigational drug and control products, and also ensure that the storage facilities allow for the drug to be stored at the appropriate temperature and in a secure environment. The data collected by the site should be stored to protect it from deteriorating, being destroyed, or tampered with and allow for easy retrieval. For GLP studies, there are specific archiving procedures that should be in place. If electronic data capture is used at the site, you should also confirm compliance with 21 CFR part 11.

Slide 72 When reviewing the qualifications of personnel at a study site, the key thing to remember is that there should be a sufficient number of personnel with the right qualifications to ensure compliance with the protocol and the applicable regulations. The substantial evidence of effectiveness regulations require that studies are conducted by experts that are qualified by scientific training and experience. Similarly, the GLP regulations require that each individual that is engaged in the conduct of or responsible for the supervision of a nonclinical laboratory have education, training, and experience or an appropriate combination of these, and the testing facility must also maintain a summary of this training and experience and a job description.

Slide 73 I want to take a few minutes to review and highlight some issues pertaining to site selection of GLP studies. Although there are many similarities between GLP studies and clinical studies, there are some items that require a greater level of preplanning and documentation during site selection. One of the important questions to answer is whether or not the site has the appropriate organizational structure and sufficient personnel. This includes test facility management, the

study director, the QA unit, and other supporting personnel. The test facility management, study director, and QA unit have specific and distinct roles outlined in the regulations. With reference to these three units, an individual cannot fulfill more than one of these roles within a single study and still be in compliance with the regulations.

The study director and test facility management have separate roles and the QA unit needs to be entirely separate from, and independent of, the personnel engaged in the conduct and direction of the study. For facilities with a small number of employees, preplanning (and potentially, discussions with CVM) is needed to ensure the development of a GLP-compliant infrastructure. It is helpful to create an organizational chart to show the various units at the establishment, their role in the study, and the management responsible for carrying out the study activities. I can't emphasize documentation enough. This should be readily available to inspectors and kept up to date at the study site.

Another question to answer is whether the facilities are sufficient to allow for proper study conduct. 21 CFR part 58 subparts C and E outline the requirements for facilities. Facilities include animal care and supply facilities, those facilities for handling test and control articles, laboratory operation areas, and specimen and data storage areas. These need to be of adequate size and design. The operation of the test facility is supported by certain required SOPs and animal care and reagent standards.

Slide 74 The next question related to site selection for GLP studies is whether the facility has appropriate equipment of adequate capacity that is suitably located and appropriately maintained and calibrated. The GLP requirements related to these issues are outlined in subpart D of part 58. Finally, does the site have adequate SOPs which are kept up to date? The minimum SOP requirements are listed in 21 CFR 58.81. The facility must establish and follow written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data.

Slide 75 After the site has been selected, personnel should be trained before the start of the study.

Slide 76 The training of study personnel may include training on GCP guidance or GLP regulations, with the depth of training dependent on the previous training and experience of the site. The training of personnel normally includes general overall protocol training for all study participants. Protocol procedure-specific training may also be done, particularly for personnel performing critical data collection procedures or for those procedures that may be new or difficult. Training on data capture forms may be most efficient if mock data capture forms are utilized. Doing such training may identify areas of the forms that need further clarification and help to avoid errors during the study. Documentation of all the training that is performed is essential. As part of this documentation, you should identify if personnel are trained in all aspects of the protocol, or only for some procedures.

Slide 77 Data quality considerations for test and control articles are found in both the "prior to live" and "live" phases of the study.

Slide 78 When preparing for your study, you should consider the implications of the timing of the study in relation to the submission of the Chemistry, Manufacturing, and Controls (CMC) technical section. For instance, if the stability testing and assay method validation are not complete and issues are identified following the study, these issues could jeopardize the acceptability of the study or lead to the need to conduct bridging studies.

At all times, the testing control articles should be stored properly and the storage conditions appropriately documented. If final stability data is not available, conservative expiry dating and storage conditions are recommended. Drugs used during the study should be labeled properly and the accountability of all drugs should be maintained during the study: from receipt of the drug at the study site through return of the drug back to the sponsor following the study.

Unapproved investigational new animal drugs are exempt from the requirements of an approved New Animal Drug application or Abbreviated New Animal Drug application and may be shipped in interstate commerce for use in clinical investigations if certain requirements are met. These requirements include proper labeling. Shipments of new animal drugs intended for clinical investigational use must be labeled with the following caution statement:

> "Caution. Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture."

Provisions are allowed for small containers.

Slide 79 While conducting the study, you should ensure that proper documentation is maintained. By now, you will see that the theme of "appropriate documentation" is expressed repeatedly throughout this section of the webinar. Examples of the types of documentation that should be maintained for the test and control articles include: lot/batch number; expiration/manufacturing dates; assay results; formulation details (which should be the final formulation); and source/manufacturer.

Slide 80 The test and control articles used during the study should be manufactured under Good Manufacturing Practices (GMP) or similar conditions. GMP compliance implies that an inspection has found the facilities and practices used to manufacture the material acceptable; therefore, the lots used for clinical studies are found to be manufactured under GMPs retroactively. CVM needs to have a CMC technical section in house before we request an inspection of the manufacturing facility, so practicality dictates that we have to make some concessions.

Although the clinical lots should be manufactured and tested using practices as close to GMPs as possible, the characteristics of GMP that the clinical lots may not always have include:

- Full production scale: usually 10% or more of production scale works for investigational products;

- Final production facility: the clinical lots may not be made in the same facility as will be used for production post-approval;
- The clinical lots may not be tested and manufactured using fully validated methods. There needs to be analytical testing for the certificates of analysis, but often the technical section with the validations doesn't come until years after the relevant studies are done; and
- They may not have all the relevant analytical tests done for the Certificate of Analysis. We can and do request additional tests after reviewing CMC data.

This approach I have outlined is consistent with CDER's "CGMP Guidance for Phase I Investigational Drugs. "GMP-similar" conditions would also be the expectation for those GLP studies in which intended product formulation is used. I'll discuss this a bit more in a moment.

Slide 81 Next I would like to mention a few additional issues specific to medicated feeds. First, you should ensure that you're using appropriate assay methods during the study. If the method used during the study is not fully validated prior to the study, you should consider the risks if there are changes needed later to the method. Secondly, assay results (which may come before or after the feed is used in some cases) should fall within the approved or investigational assay limits.

Additionally, during the mixing process you should take special care to avoid contamination with other drugs. In some cases, this will mean testing for last run study drug or using dedicated mixing equipment. Finally, as with dosage form drugs, accountability is very important and should include all phases of the mixing process. If there is an error or results that are outside the assay limits having everything documented is critical to the determination of in which step an error occurred.

Slide 82 GLP studies have some specific requirements for test and control articles. It is important to remember that there are a variety of types of non-clinical laboratory studies; some that use an active pharmaceutical ingredient (API) mixed with a carrier and others that use the drug product in the intended final formulation. Today we are discussing those studies that would be expected to use the drug product in the intended final formulation.

Current GLP regulations require that the:

- identity, strength, purity, and composition or other characteristics which define the test and control article be determined and documented (for each batch);
- test facility or sponsor must document methods of synthesis, fabrication, or derivation of the test and control articles;
- test facility or sponsor must determine stability of test and control article either before or during study;
- that the test and control articles are labeled and stored properly, and that
- reserve samples from each batch for studies of more than 4 weeks duration are retained.

Slide 83 Compliance program guidance manual (CPGM) 7438.808, which describes how nonclinical laboratories are inspected, states that the responsibility for test article characterization and stability testing may be assumed by either the facility performing the study or by the study sponsor.

What this means for the test facility performing a study with the intended final formulation provided by the sponsor, and for which test article characterization is performed by the sponsor, is that transparency and documentation at the test facility are critical.

The test facility should possess documentation of what tests were done by the sponsor and make it clear what information they have available to them (such as a Certificate of Analysis). They should also possess a statement from the sponsor regarding how the batch was manufactured, that all information related to the test article characterization exists with the sponsor, and that such information will be submitted to CVM at the proper time. It should be clear where the data reside in case it needs to be evaluated by CVM.

As part of the advanced notice of proposed rulemaking for GLP studies in 2010, FDA acknowledged that sponsors have requested the ability to cite compliance with the applicable good manufacturing requirements regarding the specifications, quality, and integrity of the test article. In that Federal Register notice, FDA stated that they are considering whether to accept compliance with either the specifics that would be required under a revised part 58, subpart F or the relevant good manufacturing requirements.

CVM understands that for the types of studies we are discussing today – studies in support of the target animal safety and effectiveness of new or abbreviated new animal drugs - GMP or similar conditions are expected. It is therefore critical to implement complete transparency and documentation of this process both for the protocol and at the test facility to demonstrate compliance with the spirit of the GLP regulations and to assure the quality and integrity of the safety data.

Alternatively, if the test article characterization is performed by test facility or contributing scientist, raw data should be archived with rest of study data and available for review.

Slide 84 The next set of considerations relate to the feed and water given to the animals during the study.

Slide 85 During the study you should ensure that personnel understand and implement feeding practices consistent with the protocol and that the data on nutrient content are collected per the protocol. In addition, study personnel should monitor for feed and water issues that could impact the study outcome. For example, regional variations in dietary ingredients could impact production drug studies and should be documented. Manipulations of mineral levels or extreme pH in water could impact drug activity in some cases.

Slide 86 If the study is a GLP study, take special care to ensure that the feed is stored separately from the areas of housing the test systems and protected from infestation or contamination and that established SOPs are available (for nutrition, for example). These requirements are described in 21 CFR 58.45 and 58.81(b)(2), respectively.

Slide 87 Additional requirements for GLP studies include the periodic analysis of feed and water for interfering contaminants and the confirmation that specifications for acceptable levels of contaminants are not exceeded. 21 CFR 58.120(a)(7) requires the protocol to contain a description or an identification of the diet including specifications for acceptable levels of contaminants. You should ensure that these levels are not exceeded as you are conducting the study.

Slide 88 Medications other than the test and control article are sometimes administered during the study.

Slide 89 These concurrent medications may be allowed depending on the protocol. It is important to follow the protocol specified procedures for concurrent medications because some medications could have an impact on the outcome of the study. If questions related to concurrent medications arise during the study, we encourage you to call us to discuss the situation. Regardless, you should be recording all treatments given prior to enrollment and during the study.

Slide 90 The test animals themselves are another area in which careful planning and documentation can improve data quality.

Slide 91 During the study, you should provide documentation of the source of the animals, their relevant history, and processing procedures (for example, those employed in a feedlot situation), as appropriate. In addition, you should ensure and document inclusion and exclusion of study animals based on protocol specified parameters.

Slide 92 The proper accountability of test animals is important to be able to demonstrate the proper frequency of observation, to explain missing data points, and follow the study conduct. The animal accountability should be documented until the end of the study or until the investigational withdrawal time is satisfied.

We recognize that animals are sometimes removed from a study prior to the end of that study. One of the main reasons to remove an animal is for welfare reasons. Animals may be removed consistent with protocol specified criteria and exit examinations and/or necropsies performed. If these examinations and necropsies are performed, they should be documented along with the reason for the animal removal. In a clinical field study, animals removed from a study after randomization should be documented. In these cases, the next enrolled animal cannot use the animal identifier or treatment code from a withdrawn animal. In a non-clinical laboratory study, animals removed from the study after randomization, but prior to treatment, can be replaced with adequate documentation. However, animals removed from the study post-treatment cannot be replaced.

Slide 93 The control of bias is the next area of emphasis for data quality.

Slide 94 As described earlier in the presentation focused on the protocol, the two main ways of controlling bias in the study are randomization and masking. Randomization is the process of assigning study animals (or groups of study animals) to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. This should be done in accordance with protocol specified procedures. Depending on the study, it may be better to

perform the randomization centrally (by the sponsor for all sites) or individually at each study site.

You should also employ procedures to ensure masking is protected during the study and pre-plan for situations where unmasking may occur.

Slide 95 Some examples of procedures designed to protect masking during the study include:

- Numbering or lettering vials so treatment identification is not seen;
- The use of more labels or codes than the actual number of groups. For example, a study with two treatment groups may use 4 codes, and if there is unequal allocation, it is important to use at least three codes;
- In some situations, the use of housing identification for animals that does not include any indication of treatment is appropriate. For example, you should not use a group code because it will inform observers which animals received the same treatment.

I would like to emphasize that there are other ways to protect masking and that these procedures need to be balanced with the need to ensure that animals are given the proper treatments.

Slide 96 Protecting the masking of personnel also includes planning for situations where unmasking may occur. This may include planned unmasking and unplanned unmasking.

Situations in which planned masking may occur include revealing the treatment assignment of an animal designated as a treatment failure in order to determine the future treatment of the condition or breaking masking for a preplanned interim analysis.

Unplanned unmasking may include situations such as the accidental identification of treatment assignments in audit reports.

If masking is broken during the study, you should follow the protocol specified procedures to minimize the impact on the quality and integrity of the data. Such procedures include documentation of the date, time, and circumstances around the masking (was it planned or unplanned?); confirmation of the animals or groups for which masking has been broken; and notification of the sponsor and sometimes CVM if appropriate.

Slide 97 Overarching many of the topics today is the topic of data collection and management.

Slide 98 The data and collection management plan for the study should be in place before starting the study.

Personnel should be trained appropriately on data quality to ensure that the data collected is attributable, legible, contemporaneous, original, and accurate. They should also be trained on data integrity principles so that they collect data that is credible, corroborative, and consistent. I will go into more detail regarding these principles in a moment.

When errors are found during data collection, correction should be done in accordance with the protocol.

Finally, it is important to remember that all data should be documented from the study, both expected (the data collected in accordance with the protocol), and unexpected. The documentation of unexpected data may occur through notes to file or protocol deviation documentation.

Slide 99 During the study, data is collected on the Data Capture Forms (DCF), many of which are designed specifically for the protocol, and, if concurrence was obtained from CVM, are part of the protocol concurrence. Signatures on the data capture forms generally include dated recorder and observer signatures or initials if both are involved in the data collection.

One thing to consider is that errors may be decreased during data entry if all of the observations on a single DCF form are entered into the same electronic file.

Slide 100 Owner diaries are data capture by animal owners used as needed for some types of clinical studies. Their primary purpose is to collect compliance and adverse event information. We understand that the data in these diaries is sometimes of more variable quality, but the quality can be improved through owner training, use of standard terminology, and communication with the animal owners throughout the study. Sometimes it can be difficult to get the diaries back from owners at the end of the study or in the case of treatment failure. Therefore, good communication with the owners throughout the study is important.

Slide 101 CVM requires that the raw data for pivotal studies are submitted. A common question then is, "which data are considered raw data?" For clinical effectiveness studies conducted in accordance with GCP guidelines, raw data includes "…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…" For GCP studies, facsimile transmissions and transcribed data are not considered raw data.

For non-clinical laboratory studies, raw data is defined as "…laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a non-clinical 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. The next slides provide the principles for collecting this raw data.

Slide 102 First are the data quality principles. These are often referred to as ALCOA, which stands for "Attributable, Legible, Contemporaneous, Original, and Accurate."

- Attributable means that the data can be traced through signature/initials and date to the individual(s) observing and recording the data;
- Legible means the data are readable and recorded in a permanent medium. If changes are made to original entries, the changes should be made appropriately. The changes should not obscure the original entry;

should indicate the reason for the change; and should be signed or initialed and dated by the person making the change;

- Contemporaneous means that the data are recorded at the time of the observation;
- Original means the first recording of the data; and
- Accurate means that the data are a true and complete observation. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or a written explanation for any empty fields should be retained with the study records.

Slide 103 The data integrity principles are referred to as the 3C's: Credible, Corroborative, and Consistent.

- Credible means that the data is based on real and reliable facts.
- Corroborative means that the data are backed up by evidence.
- Consistent means that the data demonstrate the required attributes consistently.

Slide 104 While collecting data during the study, you should pay attention to the units of measure. Data should be collected in units consistent with the equipment being used. You should use units of measure familiar to investigators to reduce errors and should maintain consistency within a study or across studies sites. For US submissions, you should talk to CVM prior to submission. CVM is open to discussing the submission of data reported in Standard International (SI) units.

Slide 105 Data derivations and conversions should not be performed during data collection and recording because of the potential for computation errors. Examples include such data derivations as unit conversions or the addition of several variables into a composite result. Such derivations or conversions should be completed after the data are frozen and locked which means after the time which changes and corrections can no longer be made to the data.

Slide 106 Rounding is sometimes necessary during data collection. If it is done, protocol specified procedures should be followed. The precision should be recorded in accordance with the limits of the equipment being used. All study personnel should follow the same process of how to record a number. This is an issue that is of particular concern for multi-site studies.

Finally, if rounding is performed during dose administration, it should be done as specified in the protocol. Procedures should be used which take animal weight, dose, and drug concentration into consideration. Rounding is often pre-planned for injectable drugs, but could be an issue for other formulations as well due to the increments on dosing syringes or bottles for topical preparations. The procedures should ensure accurate doses and dosing deviation of less than 10%.

Slide 107 Even with good planning, changes are sometimes needed and/or procedures are not conducted exactly in accordance with the protocol. In such cases, amendments and/or protocol deviations may be documented.

Slide 108 Such issues are not unexpected and do not always have a negative impact on the quality or integrity of the data. The GCP guidance defines a protocol amendment

as "A written change or modification of the study protocol effected prior to the implementation of the protocol or execution of the changed or modified task." A protocol deviation is defined as "A departure from the procedures stated in the study protocol."

GLP regulations require that any changes in or revisions to the approved protocol must be documented along with the reasoning for the change.

Note that unless provided for by the protocol, any changes nullify the CVM protocol concurrence. However not all changes may impact the acceptability of the data and CVM does not did need to be informed about minor issues such as typographical errors. It is important to remember that changes made without concurrence are made at the risk of the sponsor. We suggest talking to CVM and/or having a meeting if there are questions about changes that need to be made to a protocol.

If the protocol is for a minor use minor species study supported by grants, you should also consider the impact of the change on the designation status. If the modification to the protocol may impact the designation (for instance, the changes impact the indication) such changes need to be addressed through the regular designation modification procedure.

Slide 109 I want to make a couple of additional comments about deviations. It is important to ensure that all deviations are well-documented and evaluated for their impact on the study with relation to pivotal variables. The sponsor should make the final assessment of the impact of the deviations on the data when compiling the final report.

Some deviations may be found by the monitor or quality assurance unit and should be addressed by the investigator or study director during the course of the study

The sponsor should have clear guidelines for their notification during the study. If a deviation is occurring at one site, they may be able to implement procedures to prevent it at another site.

Slide 110 Adverse events are another area in which careful documentation is key.

Slide 111 According to the GCP guidance, an adverse event is defined as "Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, whether or not considered to be product related."

For adverse events, it is important to ensure that the appropriate people are notified. This includes CVM, if necessary. The notification of CVM, in some cases, is required as described in 21 CFR 511.1.

Slide 112 As part of adverse event reporting during the live phase of the study, the training of personnel in the identification and documentation of these adverse events is very important. Adverse events should be recorded without reclassification or categorization. This will be discussed in more detail in the next presentation.

Slide 113 The final topic in this section is quality oversight.

Slide 114 An independent QA unit is required by the GLP regulations. Similarly, monitoring is recommended by the GCP guidance. The sponsor is ultimately responsible for all of the data, but there are different ways to accomplish this.

Slide 115 In a clinical study, good monitoring may help sponsors catch issues early and potentially keep issues from perpetuating throughout the study. Monitors should keep records of communication at the site and sites with high enrollment or more deviations should be monitored more frequently.

Slide 116 In a GLP study, the QA unit has a distinct role separate from the role of the study director and test facility management in terms of the documentation of compliance with the regulations. I want to take a moment to highlight the different roles with regard to documentation of compliance or noncompliance.

As described in 21 CFR 58.35, the QA unit is required to assure compliance with the regulations and to inform the study director and test facility management of problems that occur during the study.

The study director's responsibilities are described in 21 CFR 58.33. Those responsibilities related to documentation of compliance include assuring that all GLP regulations are followed and noting and documenting corrective action for unforeseen circumstances that may impact the quality and integrity of the data.

The third piece is the test facility management. Their responsibilities are described in 21 CFR 58.31. They are responsible for assuring that deviations from the regulations are communicated to the study director and corrective action is taken and documented.

So, you can see that these three units in the GLP study have roles that are intertwined, but distinct with regard to ensuring compliance with the regulations.

Slide 117 Noncompliance with the GLP regulations may be pre-planned or identified during or after the study. If the noncompliance is preplanned the protocol stage, sponsors should provide justification for why the provision of the GLP regulations cannot be followed and how the GLP regulations will be followed in spirit as much as possible. For example, one reason for planned non-compliance is if a procedure could compromise proper science in that particular situation.

If the noncompliance is identified during the conduct of the study, the study director must describe the procedures by which the problem was corrected and discuss the impact on the establishment's operations, study conduct and data integrity. Regardless of whether preplanned or not, this information should be made available to the FDA inspector at the time of an inspection.

Slide 118 I would like to highlight two specific reasons why this documentation is critical. First is for the generation of the required sponsor GLP compliance statement. The sponsor GLP compliance statement is described in 21 CFR 514.1(b)(12)(iii) and includes either a statement from the sponsor that the study was conducted in compliance with GLP regulations, or if not in complete compliance, a brief statement explaining the reason for the noncompliance. This sponsor GLP compliance statement will be discussed in more detail in the Report/Submission presentation on Thursday. However, I wanted to note here that documentation

and transparency during the study will assist the sponsor as they review the study and compile this statement in preparation for submitting the study to CVM.

Slide 119 Secondly, this documentation is important for discussions with FDA inspectors. As described in CPGM 7348.808, not all findings of noncompliance are significant enough to be listed on an FDA Form 483. Issues are not generally 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 have no impact on the firm's operations, study conduct, or data integrity. Having the appropriate documentation on site will assist the facility in discussions with FDA inspectors and may assist the inspectors in making decisions regarding which observations should be included on an FDA Form 483. If you have any questions about inspections or specific questions about an FDA Form 483, we recommend that you contact Vernon Toelle, leader of Pre-Market Compliance and Administrative Actions Team at CVM at 240-276-9238.

Slide 120 In summary, I hope you've learned today that the quality of data is enhanced through the careful selection of the site and clinical investigator or study director; training of personnel is imperative; you should carefully follow the protocol throughout the study and follow the regulations and applicable guidances as you conduct the study; that all study personnel should use good data collection and management practices; and you should carefully monitor the study and document areas of compliance or noncompliance. We are going to move in a moment to a short time for questions and answers.

"Building Quality Data – Reporting and Submitting"

co-presented by Veronica Taylor and Marty Schoenemann

Slide 121 Good morning everybody and thank you for the fabulous introduction. I guess it is time to get started. We will continue talking today about building quality data. This section is specifically going to target reporting and submitting your data. At this point we know that you developed a stellar protocol, it was complete, easy to follow, and had well-defined endpoints. You have collected the data complying with all regulations and it is thoroughly documented. And now you are going to put together your information to prepare a report to send to CVM. Also, most importantly, the report is to help you evaluate your understanding of your submission. So let's get started.

Slide 122 We have divided this presentation into reporting and submitting data. The reporting section will include compiling the data that you have so arduously collected. And after you have collected the data, you need to review the data, prepare an electronic file to send to CVM, and analyze the data. Then, based on your analysis, you will prepare the report. When all of that is ready, you then submit all of your reports and your data to CVM.

Slide 123 As we talked about on Tuesday, there are several possible sources for raw data. Raw data can be paper records. These are typically data capture forms, chromatograms, photographs, written records of unexpected observations or adverse events or any other data that you have collected that is pertinent to your submission. Electronic raw data (electronic records) are files that have been put

directly into the electronic data set. These should be part 11 compliant and include an audit trail that is needed to verify the part 11 compliance. The audit trail should be submitted with your final study report to CVM as a text file.

Slide 124 Raw data are verified for appropriate signatures to verify masking and accountability. For the electronic forms, we verify that the audit trail exists and is available. These data are typically reviewed for validity and adherence to ALCOA principles: attributable, legible, contemporaneous, original, and accurate. The sponsor may use any effective method that they find available to audit their data. But, it is the sponsor's responsibility to validate the data.

Slide 125 After the data are checked, start to prepare the electronic file. We will refer to the electronic raw data files as e-files. Those are the data files you will submit for review. The files contain the transcribed data records or the other original electronic raw data records.

Slide 126 We have some suggestions for preparing the electronic files. Keep the file size manageable. eSubmitter requires that files be 100 MB or smaller. We would suggest that in your preparation of electronic data files for what we refer to as paper submissions also be limited to 100 MB. I will be referring to "paper submissions" as basically any submission that does not come through eSubmitter.

If you need to divide the submission into multiple files, make sure that they have a logical structure. For example you could create a clinical data file, a hematology data file, or other related observations. And how many data files are needed for any one submission is driven by the complexity and the scale of your submission.

Large data sets may need to be reduced in size or small data sets might be compiled together. That is up to you. For multi-site studies, often times it is convenient to keep files for each site separate from each other with a special name. Just be sure that whatever files you create are driven by rational considerations.

If you're wondering about the limitation of the 100 MB file size, it was chosen because the limited size allows review both in-house and from remote locations. The small data files will facilitate our review and we appreciate your consideration.

Slide 127 Another property that is desirable in the e-files is that they are self-contained. What that means is that they can be independently reviewed. They have enough demographic information such as treatment, sex, block, site, animal identification, so that if a file is opened it can easily be searched for animals of chosen treatments, sex, etc.

We discourage the inclusion of the same non-demographic variable in multiple files because the data then have to be verified over and over again. We do appreciate that in some instances it may be appropriate. For example, body weight might be included in the dosing file and the physical examination file. Just limit the number of files that include the same variable(s).

Let's do a quick recap about data files. Please keep them small, 100 MB or less. Make sure that they're self-contained, that they contain all records, and variables do not appear in multiple data files.

Slide 128 Please do not send duplicate copies of data files. For example, do not send a copy with all of the data and an additional analysis data file which has all the data deleted for an excluded animal or individual data points deleted.

Slide 129 To clarify, freezing data can be performed multiple times during the course of your data compilation. For example, the data may be frozen to perform an interim analysis. The data are locked after the changes, corrections have been made and questions have been resolved; but before the data are unmasked. As a statistician, I don't think the study is over until the data have been compiled, locked down, and the unmasking point has been reached. Be sure you follow the process you have detailed in your protocol for freezing and locking data.

Slide 130 Oftentimes, sponsors have an exclusion meeting with CVM after locking the data. Having the meeting after data locking and prior to unmasking will maintain the integrity of the data set. Sometimes the exclusion discussion is included in other meetings sponsors have prior to filing the submission. These meetings are not pre-submission conference meetings. So please indicate that these are other ONADE (OO) meetings.

At exclusion meetings we can discuss the exclusion of subjects from the data file. For example, subjects that may have been noncompliant with pretrial inclusion or exclusion criteria that are inadvertently assigned to treatment or animals that receive non-compliant concomitant medication may be excluded from analysis. Data points that have been collected outside the range of the protocol specified data time interval might be considered for exclusion. After discussion of these exclusions with CVM prior to the analysis and interpretation of the data, we are fairly confident that the data you're using will be found acceptable. This is quite a help for both of us because it will be more likely that we will reach the same conclusions. However, you should be aware that because CVM has not had access to all available information, decisions made during the exclusion meeting are not considered final.

Slide 131 We want to remind you that analysis is considered any assessment of results where a sponsor makes decisions about the data and study. This analysis does not require calculation or performance of a statistical test (calculating a p-value). In fact, any summary of data is considered an assessment whether it is performed on frozen or locked data sets.

Changes to the analysis strategy specified in the protocol need to be documented as a protocol of amendment or deviation. CVM Biostatistics is always open to a discussion of how to handle problems should they arise in regard to your data analysis.

Slide 132 Basically reporting the data is telling the story. We are asking you to present all of the study actions, results, and conclusions in some format that seems logical to you that best tells the story. There is no single best way to do this. You need to remember that because we cannot be at the study site while the study is ongoing, this report becomes our eyes into the conduct of the study.

When you are writing a report you should keep in mind a couple of points. First, can we reconstruct the study? Does the report include enough detail that would allow us to understand exactly what you did? Second, be expansive in scope. If you're in doubt about whether something should be included, put it in.

Be aware that many times we have seen that individual values and the tabular values in the report cannot be traced back to the primary data. This means that there is some kind of error occurring, either in the presentation of the information in the final study report, or in the raw data itself.

If you're looking for a guideline to follow in the construct of the study, the GCP guidance suggests that it may be helpful to follow the study protocol as a potential outline.

Slide 133 The basic sections of an adequate study report include: the executive summary where you hit the high points, the materials and methods section where you describe how protocol requirements were met and executed, the results section where you summarize the observations that were collected, and the conclusion sections where you try to tell us what it all means.

Slide 134 The executive summary content is straightforward. You need to include a brief description of the study design. Talk about the treatments, the number of animals, the number of sites, the drug dosage, and these sorts of basic things.

You should also highlight the major results of the study. Include what you expected to see that supports your hypothesis. Also include those things that you did not expect to see and that might provide information that may not put your drug in the best possible light.

Finally, you need to highlight the most important conclusions of the study. Can you tie these conclusions back to the question of "Did the results support the purpose of the study"?

Slide 135 In the materials and methods, I will go over some issues that we often see. For drug administration, we like to see formulas and examples so that we can be assured calculations are done correctly and that those calculations will indeed return the correct levels of drug.

You also need to discuss how you can provide sufficient bias control. Bias control comes partly in the form of appropriately masking your study personnel. Some of the people may only need to be masked to certain aspects of the study and others will need to be masked completely. For the randomization, we need to know that the animals were assigned to treatment in an appropriate manner. We also need to know that the location of pens/cages/tanks of the animals are randomized or are appropriately distributed based on the needs of the study.

Another area we often have concerns is the documentation of adverse events. We are asking that you use clear terminology for the adverse events. This helps with consistency at the study site and across study sites within a multi-site study.

Slide 136 Care should be taken to provide descriptions of study processes that are somewhat subjective. For these, you need to define the scoring or coding systems that are used. Scores and codes are often used in addressing pain,

depression, or other success criteria that are not readily obtained from using a piece of equipment. In other words these, observations are based on some judgment by the observer.

We also ask that you prepare and provide formulas and sample calculations for derived variables and transformations used in your study and/or analysis. Simple things like converting from one unit to another unit, i.e., SI to the US or vice versa should be recorded. Some of the other more involved calculations, e.g., average daily gain or feed consumption when you are trying estimate average daily weight gain or feed efficiency need to be documented.

The materials and methods section should also have a pretty good summary of the statistical analyses that are going to be used to summarize the data that you collected. You do not have to have all of the data or data analysis descriptions in the final study report. Sometimes it's actually more clear and easier for the final study report to be understood if a lot of the details of those analytical procedures are actually placed in a statistical report.

A statistical report is a type of report called a contributing scientist report in GLP studies. I think it is becoming more common to see reports of that nature being supplied for GCP studies as well.

Slide 137 If we look at the results sections, I have just a few points to make about the content and how things can be improved. First, we would like you to discuss all of the data that you collected. You need to keep in mind that brevity of the discussion or even the omission of a discussion of certain types of data will lead to unnecessary questions. By that I mean that our reviewers are quite inquisitive. If they see that you collect data and notice that it is not discussed in the final study report, they will wonder why. So they will go back and dig through the data to see if it was an attempt to obscure or hide some inconvenient observations. Oftentimes that is not the case, but it does slow down the review process. If all of the data collected are discussed in the final study report, then that minimizes the need of the reviewers to go back and dig through the raw data itself.

Second, have you grouped the adverse events appropriately? I think this was discussed in some detail on Tuesday. In your final study report, it would be helpful if you discuss any trends that were observed in the adverse events. Remember that the report is supposed to reflect the report author's assessment of causality. The assessments may be wrong or they may be right but an assessment should be included. Where the sponsor was not one of the study authors, they have the opportunity in the submission itself to provide the final recommendation from the sponsor specific perspective about adverse events. We will take the sponsor's final recommendation into consideration when we evaluate those adverse events.

Of course, none of us are perfect. So we expect there will be protocol amendments and deviations. When those happen, we expect that the impact on data collection and results will be fully described. Many of these may not have an impact on data collection, study integrity, or interpretation of results. But, we would like to see a statement detailing why you believe that the amendment or deviation has no impact on data collection, study integrity, or interpretation of results.

Slide 138 For the results section, you should use the summaries, statistical analyses, and graphs to guide interpretation of your results. Why is this good idea? When the protocol was written and, ultimately, concurred on, the study design and the statistical analysis were an integral part of that. The selected analyses were intended to provide the desired hypotheses testing. So the statistical analyses you use should lend themselves to easy telling of the results of the study.

When you are reporting means for interpretation, make sure you use the appropriate means and associated p-values. One example of appropriate use of means, is reporting covariate adjusted least square means with p-values rather than reporting the simple arithmetic means. These covariate adjusted means are often different from the arithmetic means especially in the case of an unbalanced design.

Use tables and graphs to aid in the interpretation of the information in the final study report. You can use tabulation for several reasons. The first is for increased impact of important information. The next is to consolidate secondary observations – that while necessary for the full understanding of the study – the observations themselves have no large direct effect on the outcome of the study.

Finally, you may have contributing scientist reports. Please make use of them. Make appropriate connections in the final study report to minimize the need for CVM reviewers to go back and figure out exactly the purpose of the contributing scientist report. You need to draw in the observations or the opinions of the scientist and make them part of the final study report.

Slide 139 In the conclusions section, I think this is again fairly straightforward. The main part of the conclusion is to answer the question about whether the results support the hypotheses or the purposes of the study. In other words, did you find what you expected to find?

We suggest that you prepare the most persuasive scientific argument that you can draw from the conclusions of the study. You have to keep in mind that when we look at the data, we may be inclined to interpret the data in a very slightly different manner. This is your best opportunity to persuade us to your point of view. When you have multiple studies this becomes particularly important because this overall persuasive argument is not necessarily captured in any of the individual study reports.

Slide 140 So sometimes, for shorthand, we talk about the need for you to submit the final study report for a pivotal study. It is not always clear what we mean when we say "please submit the final study report" for a pivotal study. So, this slide is trying to address all of these concerns. So, holistically speaking, the final study report contains the study report itself, it also contains a number of appendices that should be attached or associated with the final study report. That would include a copy of all of the raw data and any reports from contributing scientists. It would include a copy of the study protocol, as it has been amended. In other words, don't submit the protocol that you started the study with. Submit a copy of the study protocol that you ended the study with.

And sometimes it is useful to submit the important SOPs. I want to make it clear here that we are not asking for all SOPs. We are only asking for those SOPs that might be critical to explaining some facet of the study. For instance are you

using some original procedure to measure an analyte of some type? Or are you using an unusual procedure as the basis for a measurement of one of the critical variables? Or, are you taking an unusual approach to more common requirements?

Slide 141 The last issue for me in this presentation is a discussion of the sponsor's GLP compliance statement. I wanted to address this because this is an issue whose visibility has been increasing over the last several years. So, what exactly is the issue?

There has been a long-standing ambiguity or confusion within both CVM and, I daresay, the regulated industry as to the nature and necessity of what some people would consider seemingly duplicative requirements regarding assessments of the quality of nonclinical studies.

Slide 142 So, exactly what is the sponsor's GLP compliance statement? It is a statement required of the sponsor for each GLP study that is submitted to the CVM in support of the application. The exact wording is found in part 514 section 1, and I'll just read it here.

"With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with … [the GLP regulations]…, or if the study was not conducted in compliance, a brief statement of the reason for the non-compliance." (21 CFR 514.1(b)(12)(iii))

That is it in a nutshell, the language that has apparently befuddled everybody at this point.

Slide 143 So, why do we have this requirement? What is the intent of the sponsor's GLP compliance statement? A look at some of the related documents make it clear that the intent of the regulations was to ensure that sponsors are aware of, and actually take responsibility for, the quality of nonclinical data they are submitting. The perceived need for such a requirement is a direct outgrowth of the Industrial Biotest Labs (IBT) scandal back in the early 1970s. The quality of the studies conducted at IBT was extremely poor. In some cases the study documentation was poor to nonexistent and in others there was outright fabrication of the results. Sponsors were apparently unaware of the quality of the data they were actually receiving from IBT, yet they submitted reports of those studies to the agency for consideration.

So just to be clear, this requirement is not a new requirement. It may seem that way because we have not talked about it much in recent years. But, this requirement has existed since the GLP and the associated changes to existing regulations were finalized back in 1978.

Slide 144 So I think the intent of this sponsors compliance statement was made most abundantly clear in a comment that is present in the preamble to the final GLP regulations, 43 Federal Register page 60013.

"…The revisions [of existing regulations] highlight the fact that although studies not conducted in compliance with the regulations may continue to be submitted to FDA, the burden of establishing that the non-compliance did not affect

the quality of the data submitted is on the person submitting the noncomplying study."

The agency was talking about the revisions conforming to the conventions of existing regulations. And they wanted to make it clear that sponsors can still submit studies to the agency that were not conducted in compliance with the GLP.

The bolded section here is that the burden of establishing that the non-compliance did not affect the quality of the data submitted is on the person submitting the non-complying study. On this it is clear, it is a sponsor's responsibility to actually do the check and confirm the validity of the noncomplying GLP study.

Slide 145 Is this sponsor's compliance statement really important? I think it is quite clear the answer is "yes." Its importance is reflected in the seriousness of the actions that can be taken when that statement is not present. For example, if you don't include a statement for each of the nonclinical laboratory studies in your application, then it is considered an untrue statement in the application. Not having the sponsor's compliance statement in your application is also grounds to refuse to file an application if the sponsor fails to include the statement for each study. It is also grounds to refuse to approve an application.

Slide 146 So, why are we talking about this now? Why have we not been dealing with this all along? I think the first reason is the current inconsistency in its requirement. I think we can place that at our feet and at your feet because we have not consistently required, nor have sponsors consistently provided, the statements as part of their submitted applications.

We are implementing increased flexibility in how we help sponsors meet our requirements. In doing so, we are taking CVM and the sponsors out of our individual comfort zones. The use of the novel approaches that come out of this flexibility may make the regulatory requirements seem less certain which leads to more confusion. And, I think this applies both to CVM and the sponsor.

One of the novel approaches that we have seen the increasing use of is what we term "nontraditional testing facilities," or laboratories that are doing a one-off GLP study. But they likely do not have the history of conducting studies that are subject to the GLP regulations. So their knowledge of the GLP regulation, and their experience with it, may simply not be adequate.

For instance, in these situations, where and who is the quality assurance unit? What is their level of experience? What is their professional or personal relationship with the testing facility management and the study director? Do those individuals in those three roles have appropriate independence? These are the sorts of issues that exemplify why we have concern about getting a high-quality statement as to the validity of these noncomplying GLP studies.

Slide 147 All of these issues and actions have created what you might call a perfect storm. We have the current level of ambiguity within CVM and the industry about what the compliance statement is, why we need to use it, and what does it need to look like, etc. We also have increasing use of testing in these non-traditional

facilities. And our flexibility is leading to a faster tempo of work and decisions in the drug approval process.

All of these factors have come together to create an environment in which it is no longer possible to assure that that the quality of the nonclinical data have not been adversely impacted by all of these non-routine processes.

So we believe that returning to, or actually now enforcing, the use of the sponsor's compliance statement will rightly put the burden of data quality back on the sponsors. We believe this is consistent with the intent of the experts who wrote the GLP regulations.

Slide 148 Several other statements pertaining to data quality have been suggested as meeting this requirement, or perhaps as being an acceptable substitute. They are neither. For instance, in the first case, there is a similar statement required to be included in the final report of the nonclinical study, which is intended to be a description of all circumstances that may affect the quality or integrity of the study [21 CFR.185(a)(9)]. Ultimately, this statement comes from the study director and the testing facility management, not from the sponsor.

Slide 149 Another statement that has been proposed as being an acceptable substitute is the statement required to be prepared by the quality assurance unit and to be included in the final study reports [21 CFR 58.25(b)(7) and 58.185(a)(14)]. This statement's content is clearly inadequate because it simply contains the dates that the quality insurance inspections were performed and reported to the testing facility management and the study director.

Slide 150 So, what do we expect this statement to look like? Here a model statement that I think meets our needs. Part one of it includes a personal declaration of responsibility and a clear statement regarding the compliance or noncompliance of the study.

"I have personally inspected the final study report (including all raw data) and other study-associated information for compliance with the GLP regulations found at 21 CFR part 58. Based on my review, my assessment is that this non clinical laboratory study (was/was not) conducted in full compliance with the regulations found in part 58."

Slide 151 The second part of it is a listing of those areas of noncompliance and a brief statement for the reason for noncompliance. We have tried to strike a balance with this listing between brevity and utility. We did not want this listing or this compliance statement to become a long or complicated document. Just to be clear, when we are talking about a list of those sections of the GLP regulations we are talking about identifying those sections, such 58.105 for test article characterization or 58.35 for QAU unit issues. We are not asking you to identify a particular sub paragraph, citing the section will be sufficient.

"My review of this information revealed non-compliance with the following sections of the GLP regulations: (provide a list of those section(s) where non-compliance was noted and a brief statement of the reason for the non-compliance)."

This statement should be signed by the individual performing the review.

Slide 152 To recap, the submission should be organized. A "paper submission" should have a cover letter included and a Form FDA 356v. If you are using eSubmitter, no cover letter or 356v is required because the responses to the eSubmitter queries are sufficient. Please include a table of contents for the entire submission and the regulatory summary drawing conclusions about all of the information from the submission. Include the appropriate compliance statements, final study reports, and the appropriate appendices (including expert summaries) associated with each final study report.

Slide 153 Now, we will concentrate on submission of electronic files. The files you submit become the official records of your submission. The file types for electronic submission were chosen by CVM to provide the greatest chance for being readable and usable in the future with minimal effort. For these reasons, nonproprietary files that are less dependent on software version and are accessible using free software were chosen.

Again the purpose of choosing these file is to preserve their electronic form so that they may be used in the future by both the sponsor and CVM. Software dependent electronic files may not be readable/useable if the software version changes.

Slide 154 So to briefly go over selected file types.

Portable document format (PDF) files can be used for text and image files. These are not TXT files. The term "text" refers to actual text documents and not to files with the "txt" extension. The text (PDF) file can include reports, scanned material, data capture forms, a "Read Me" file, and log and output files from executed programs. Log and output files from executed programs are not required anymore. But, if the sponsor thinks they facilitate the evaluation of the data analysis, then those should be provided in a PDF format.

Data and program files can also be provided in extensible mark-up (XML) format. Please note that submitted XML files must be nonproprietary files and cannot be generated simply by saving data file with an XML extension or renaming the file with an XML extension. Data files saved or renamed with an XML extension are proprietary files.

Note that data may also be provided as SAS transport (XPORT, XPT) files. I think the XML data files are preferable.

If you're having difficulty converting files into a format that is useful or usable, please contact the Biostatistics group. We can help you, and we look forward to interacting with you.

Slide 155 Some of the limitations of the XPT files are: variable names are limited to eight characters and SAS or SAS Universal Viewer software is needed to review these files. SAS Universal Viewer is free and nonproprietary but SAS is not free and is proprietary.

Note that XPORT XPT files and CPORT XPT files are different. For example, each XPORT XPT file must be generated individually. CPORT XPT files can be generated as compressed files but these are not acceptable to CVM. Compressed

files are not acceptable because they have to be opened outside the protected read-only drive to be used.

Slide 156 The other data format is XML. XML files allow a more generous variable length and XML files can be read in Excel, notebook, and other text readers.

Slide 157 To recap, for your electronic files, eSubmitter only accepts PDF, XPT, and XML files. For "paper submissions" (submissions not using eSubmitter), we strongly recommend using the XML and XPT file formats for data. If you want to use other data file formats when not using eSubmitter, please contact CVM Biostatistics to discuss the formats you want to use.

Slide 158 Here is a resource for electronic file creation for both eSubmitter and other submissions:

http://www.fda.gov/downloads/ForIndustry/FDAeSubmitter/UCM332980.pdf

Slide 159 Do not use special characters, e.g., #, %, when naming files for eSubmitter. Limit the file path length by limiting the number of directories, subdirectories, and folders that must be navigated to access the file. Limit the length of the file name. We can recognize PDF files as text files. But, both analysis programs and data files may use the XML format. So, it is also useful if you indicate in the name if it is a data or program file.

Remember, the maximum permissible file size for eSubmitter is 100 MB.

I want to talk more about the blanks in file names and limiting the number of subdirectories used to access a file. If the file name, which includes all the directories, subdirectories, and folders, becomes overly long, eSubmitter truncates the physical file name (the name used to directly access the file) to a numeric value, i.e., 1.PDF, 2.XML, or 3.XPT. The only access we have to the complete file name is the eSubmitter HTML report. We have to cross-reference the HTML report with the truncated name to understand any description you provide about your files or to access electronic data for analysis.

Slide 160 Submit the text files as PDFs. Organize your physical files with logical breaks with simple descriptions. Remember, PDF files must be subjected to optical character recognition (OCR) to allow for more convenient text searches and bookmarks. And, it is very useful for the reviewers if your PDF files are bookmarked for reference purposes.

Slide 161 Submit analysis programs as XML profiles. Unlike data files, for SAS programs, you can simply save the file an XML file in your SAS window or rename the SAS extension to XML. (SAS program files are nonproprietary if renamed.) Note that generally data files can NOT be converted to nonproprietary XML file by renaming the file extension and files created in this way are not usable for data analysis.

Slide 162 The next slides will have SAS program language for generating and reading XML and XPT files. I would like to say that the conversion can be done in other software too.

So this is the SAS code for generating nonproprietary XML and XPT files.

SAS code to generate non-proprietary XML files

```
libname in 'file location';
libname out xml 'file location\filename1.xml';
data out.dataset1; set in.filename; run;
```

SAS code to generate XPT files

```
libname in 'file location';
libname out xport 'file location\filename1.xpt';
data out.filename1; set in.filename; run;
```

Slide 163 Here is the SAS code for reading the XML and XPT data files into a SAS program:

SAS code to read non-proprietary XML files

```
libname in xml 'file location\filename.xml';
data filename1; set in.dataset1; run;
```

SAS code to read XPT files

```
libname in xport 'file location\filename.xpt';
data filename1; set in.dataset1; run;
```

Slide 164 We strongly recommend that all of the pivotal studies include a "Read Me" section or text file. The "Read Me" information identifies all data and analysis program files by name and describes the purpose of each file.

Slide 165 Also in the description of the data file; please include complete variable names, truncated variable names, and units of measure. For example, if you used BWT to identify body weight, please make that association. It is also helpful if you identify the data files used in each analysis program and the variables analyzed in each program.

Slide 166 Your analysis program should contain internal documentation sufficient to explain data manipulation and any specialized procedure that might be executed in the program. If programming is used exclude data, it would be useful to document the reason for the exclusion and the person who directed that the data be excluded.

When multiple files are called into a single program file, please identify the purpose of each of the files that is being included in the program.

Slide 167 We at CVM are going to analyze the XPT or XML files you submit. So, we recommend that you analyze the data using the same files. Rather than using SAS or Excel files in your programming, convert your files to the same XPT or XML files that we are going to use for analysis.

Also please include conversion programs and any programs used to generate statistical tests and data summaries in your submission. Just a reminder, simple programs are often best.

Slide 168 Summarizing what we talked about this morning, we have discussed reporting and submitting data including verifying raw data to make sure it was captured accurately in the electronic files. We discussed creating complete and accurate final study reports, providing the sponsor's GLP or GCP compliance statements, and submitting compliant PDF, XML, and XPT files.

Question and Answer Session

presented by Marty Schoenemann

Slide 169 Reminder that the questions and answers from this session have been incorporated into the Questions and Answers document.

Closing of Webinar

presented by Marty Schoenemann

Slide 170 With that, I think we have come to the end and it is time to wrap up this two day webinar.

First of all, I would like to thank each of you for your participation and particularly your perseverance with some of our self-inflicted problems this morning. We have also noticed over the last couple of days that there have been instances where some individuals have lost audio for some period of time. I am not sure what the answer to that is.

With regard to the content of the webinar, it is always a difficult test trying to strike a balance between the needs of our newer members and those of us who consider ourselves grizzled veterans. Hopefully, we have succeeded and that each of you has found the presentation useful. If each of you were able to find one or two nuggets to make part of your routine practice, I think I would count that as a major success. And, by the way, your submitted data will be better for it.

With regard to access to the webinar documentation, we have committed to making all of the information available within 30 days. The information that we will provide in 30 days are a set of the slides, a transcript of our presentations, and written answers to all of the questions that have been asked. Please go to the website announcing this webinar for a link to the documentation.

There have been some requests that we provide the slides sooner, and I think we will try to post an early version of those slides by Friday, or Monday at the latest.