OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF RAW DATA FOR BIOEQUIVALENCE STUDIES TO SUPPORT AN ABBREVIATED NEW ANIMAL DRUG APPLICATION

I. PURPOSE

This document describes what a reviewer in the Division of Generic Animal Drugs (DGAD) should expect in a sponsor's Bioequivalence (BE) technical section or P Submission and the procedures to review the submission. This document only describes what information is expected to be submitted to DGAD for a BE study to support a generic or abbreviated new animal drug application (ANADA). It does not impact what raw data and study documents should be generated or collected during the study conduct per the protocol and the standard of conduct.

II. BIOEQUIVALENCE STUDIES

Sponsors submit copies of raw data and study documents from BE studies conducted using the principles of Good Laboratory Practices (GLP) (or the equivalent in other jurisdictions) in the BE technical section submission using a Question-based Review (QbR) format.

III. RAW DATA AND STUDY DOCUMENTS FOR BIOEQUIVALENCE STUDIES

A. Raw Data

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

CVM expects copies of certain raw data be submitted for evaluation. Copies of raw data include data collected manually on paper forms and data collected electronically via an electronic data capture system. The audit trails of electronic records must be submitted as part of the raw data for those electronic records. The sponsor should

demonstrate how the collected data maintained the attributes of being attributable, legible, contemporaneous, original, and accurate (also known as ALCOA) throughout the internal handling of the data files through the submission of the data files to CVM for review.

CVM published a document that provides responses to questions asked by industry regarding data quality, including raw data and submissions to CVM. For additional information, please refer to the Question-and-Answer Document for the Data Quality Webinar held June 4 and 6, 2013 (UPDATED April 2021).[1]

B. Process Used to Determine ONADE's List of Raw Data and Study Documents

ONADE used a risk-based approach to determine which copies of raw data and study documents should be submitted to the BE technical section.

In general, the copies of raw data and study documents listed in Appendices 1 & 2 of this document are expected to be submitted to ONADE for BE studies. However, situations may arise where additional raw data or study documents are required to be submitted to complete the review of the BE technical section submission. The two most likely situations in which additional raw data may be requested are described below.

1. The study has design components that result in additional data needs. Certain studies may require copies of additional raw data related to critical study endpoints to reduce uncertainty in decision making to an acceptable level. An example of this is feed composition and analysis for drugs administered in feed.

2. Significant information gaps are identified during review of the BE technical section submission. Reviewers may identify omissions, inconsistencies, or questions related to the raw data that should be addressed by the sponsor before ONADE can complete the review of the studies and make scientific and regulatory decisions.

IV. BIOEQUIVALENCE SUBMISSION REVIEW PROCESS

A. Submission Content

Before the primary reviewer (PR) and consulting reviewer (CR) begin reviewing the submission, they will perform an assessment of the submission content to determine if the submission is fit for review. This should occur within the first two weeks of submission assignment. In alignment with the specifics outlined in P&P 1243.3100 (Refuse to Review (RTR) and Refuse to File (RTF) Assessment of Submissions and Applications That Contain Data), the reviewers will determine if the submission meets the following minimum criteria for review:

- It is properly organized with either a table of contents or bookmarks,
- All applicable QbR sections are present,
- Content is legible and in English,

[1] CVM Data Quality Webinar Q&A: https://www.fda.gov/media/147451/download

- A signed Final Study Report and protocol are present,
- All relevant compliance statements are present and signed,
- Raw data aligns with items listed in Appendix 1 & 2, and,
- Electronic data files are in the appropriate file format.

If one or more of the above elements are not present, then the PR can consider a final action of Refuse to Review (see P&P 1243.2050 Refuse to File and Refuse to Review for further information). This decision should be made in conjunction with applicable division procedures.

B. Reviewing Bioequivalence Submissions with Raw Data

When the review team begins reviewing the submission, they will assess the following information, as appropriate:

1. Background – determine if prior studies were performed under the same generic investigational new animal drug (JINAD) file and consider any impact they may have on the BE study under review. Look for past sponsor communications and meetings related to the study as well as previous reviews of the study protocol and bioanalytical method validation.
2. Read the included protocol under which the study was conducted and identify any differences from the previously concurred upon protocol if applicable. Evaluate any deviations and amendments in their entirety to determine if any could have impacted the study quality or the validity of the results.
3. Evaluate the Final Study Report and included data regarding the following, as applicable:
    a. Study design and conduct to determine if the overall design and implementation of the study is consistent with the study protocol and appropriate for the drug product being investigated.
    b. Randomization and masking procedures to determine if they were carried out in a way that minimizes concern for introduction of bias.
    c. Animal husbandry and overall health status of the animals throughout the study including clinical observations, diagnostic lab work, physical exams, and adverse events.
    d. Dosing and sampling procedures to determine if they were conducted appropriately and per the protocol. Also evaluate any dosing failures to ensure that they are documented and handled appropriately and consistent with the protocol.
    e. Plasma processing, sample storage and transport information to determine if sample handling was appropriate and is supported by stability data.
    f. Bioanalytical phase information to determine if the method used for incurred sample analysis was implemented consistently with the

conditions and parameters which supported the method validation and that the method performance was consistent with the performance during the validation experiments.

g. Statistical analysis and results including pharmacokinetic profiles for each subject.

h. Sponsor and study personnel communication notes and notes to file.

i. Sponsor's conclusions to determine if bioequivalence criteria have been met and if any aspects of the study conduct may have impacted the interpretability of the results.

C. Writing the Review for BE Submissions

The PR prepares a review document. CRs should prepare a review document or work with the PR to determine if another method of conveying information would be appropriate (see P&P 1243.3029 Closing Out Consulting Reviews for Submission Tracking and Reporting System (STARS) Submissions for further information). Review documents should be prepared according to division procedures.

The PR includes the following information in their review:

1. Identity the pivotal study by title and study number, the reference listed new animal drug (RLNAD), and the STARS submission ID in the submission summary.

2. Description of the study design and any differences in conduct, implementation, and analysis from the concurred upon protocol.

3. Description of the sponsor GLP compliance statement and any other included compliance statements. Identify any areas of non-compliance identified by the sponsor or indicated in the submitted information and assess if these observations impact the overall data quality of the study.

4. Observations related to aspects of the study described in section IV.B. above, as applicable, including impact assessments of those observations on the overall outcome of the study.

5. Any additional observations and assessments identified during review of the submitted information that may impact the outcome of the study.

6. An assessment of the results and conclusions presented in the Final Study Report.

7. An Agency conclusion regarding whether the submitted information supports a technical section complete determination.

The PR also drafts a technical section complete or incomplete letter as appropriate and in accordance with division procedures.

V. COMPLETING THE FINAL ACTION PACKAGE

The PR enters the following in the Review Summary field in Appian:

- Technical section outcome
- Description of the proposed generic product and dosage form
- If the technical section is incomplete, include a brief description of any deficiencies that led to that determination.

Follow the procedures in the P&P 1243.3030, when you complete the final action package.

VI. REFERENCES

CVM Question and Answer Document for the Data Quality Webinar held June 4 and 6, 2013 (Updated April 2021) at https://www.fda.gov/media/147451/download

CVM Policies and Procedures Manual – ONADE Reviewer's Chapter

1243.2050 - Refuse to File and Refuse to Review

1243.3029 - Closing Out Consulting Reviews for Submission Tracking and Reporting System (STARS) Submissions

1243.3030 - Completing Final Action Packages for Submission Tracking and Reporting System (STARS) Submissions

1243.3100 - Refuse to Review (RTR) and Refuse to File (RTF) Assessment of Submissions and Applications That Contain Data

VII. VERSION HISTORY

October 17, 2024 – Original version.

APPENDIX 1. COPIES OF RAW DATA EXPECTED TO BE SUBMITTED TO CVM FOR BIOEQUIVALENCE STUDIES

Table 1. Observational Data

General Variable Name	Definition
Clinical Observations	Documentation of original records of animal observations including routine daily observations, post-dosing observations, and unscheduled observations (if applicable). Post-dosing observations are typically more focused on monitoring study animals for dosing failures as defined in the protocol and for adverse events associated with the drug product. These may be performed by a veterinarian or by an individual with some medical training such as a technician.
Adverse Events	Adverse events are generally considered any unfavorable or unintended observation in a study animal following the use of an article, whether or not considered to be product related. CVM expects adverse event documentation to include description of the event and classification with respect to severity and likelihood of relationship to test/reference article.
Physical Examinations	Documentation of the physical exam conducted by a veterinarian documenting health status of an animal, usually conducted prior to study inclusion to the study to determine eligibility or as needed during the study to identify health problems. For study inclusion, the veterinarian or scribe typically records notes on a designated form. As needed, exams may be on a form or the veterinarian's notes.
Animal Body Weights	Documentation of the weight of individual or small groups (e.g., litter weight) of animals taken at protocol-defined times during the study using a calibrated scale and weights.

Table 2. Procedural Data

General Variable Name	Definition
Documentation of deviations and copies of raw data to support the deviations	Documentation of departures from the GLP and protocol during the conduct of the study. CVM expectation on all deviation documentation should have the following information: ▪ The date the deviation occurred ▪ Description/explanation of the deviation (what happened?) ▪ Description of what was done to address the deviation, if appropriate ▪ Discussion of the impact the deviation had on the study ▪ Information should meet the basic standards we expect for all raw data, e.g., attributable, legible, contemporaneous, original, and accurate (ALCOA) Copies of the raw data where the documentation of departures from the GLP and/or protocol occurred during the conduct of the study.
Feed Consumption	Documentation recording daily feed issued. Additionally, when possible, documentation should include a qualitative assessment of proportion of feed consumed per animal or group of animals housed together.
Dose Calculation and Preparation	Documentation of how doses were calculated and prepared (e.g., rounding to the nearest 0.2 mL to achieve X dose, the actual dose calculation table listing animal ID, body weight, calculated dose, administered dose, etc.).
Dose Administration	Documentation may include treatment (e.g., when/where/how it was injected, mixed, given orally, etc.) and data capture form of list of animals and an indication (check box, etc.) that each animal received its assigned dose per treatment group assignment, per body weight. For medicated feed and medicated water studies, documentation should include feed or water issuance and consumption records (respectively), as well as batch preparation records and drug concentration assays.
Blood Collection	Documentation of collection of blood samples used in bioequivalence evaluation. This includes documentation showing the point or instance at which each sample is obtained, consisting of the actual date and time of samples collected based on the target time-point.

General Variable Name	Definition
Blood Processing	Documentation of processing of blood samples used in bioequivalence evaluation.
Sample handling and transfer	Documentation showing the condition(s) at which the sample was maintained from the time of sample collection to analysis including transfer, shipping, and storage conditions. Should also include documentation that tracks chain of custody of the samples.
Sample Storage	Documentation of how the sample was stored, including temperature and other conditions as required for the specific type of sample. This information should generally include a summary of the storage temperature range and any excursions.
Sample Processing	Documentation of the preparation of the final extract (before instrumental analysis) of a sample involving various manipulations (e.g., extraction, dilution, concentration) of the original study sample.
Storage Stability Data for Samples and Reference Standard Solutions	Documentation of any data not previously submitted to CVM demonstrating the chemical stability of the analyte in a given matrix including the effects of collection, handling, and storage of the analyte. Additionally, documentation of storage conditions for standard solutions, duration of storage, and any testing to determine a standard is fit for use should be submitted.
Chromatograms (including re-assayed samples)	Copies of chromatograms generated from the study. Currently CVM typically requests a minimum of 20% of the chromatograms be submitted (including 100% of chromatograms pertaining to re-assayed samples). The method of determining which chromatograms will be submitted should be specified a priori. All run summary tables of accepted and failed runs should be submitted.
Note to File	Documentation of study procedures that occur during the study which may affect study outcome or information relevant for reconstruction of the study.
Communication Records	Documentation of emails, summary of telephone calls, such as communication between the study director and contributing scientists, and Quality Assurance Unit for the study.

APPENDIX 2. STUDY DOCUMENTS

The following study documents will need to be submitted within the BE technical section.

- Final Study Report: The final study report (FSR) submitted to support bioequivalence decisions for the generic new animal drug should follow the requirements set forth in 21 CFR Part 58.185. In addition, CVM reminds sponsors to make sure the following are included in the FSR:
    - Protocol and amendments
    - Animal housing diagram
    - Contributing scientist reports
    - Description of any issues that may have affected the outcome of the study. A statement of no impact should include an explanation of the no impact assessment.
    - Description of all randomization procedures performed and detailed description of how masking was maintained.
    - Description of all calculations, transformations, formulas, programs, etc., to reconstruct final reported values
    - Tables, graphs, or other representations that present a summary of the data. These summary representations of the data can provide clarity to the final study report and aid in the comprehension of the statements and conclusions in the final study report.
- Additional documents expected to be submitted within the BE technical section submission:
    - Reference ranges
    - COAs for investigational drug or label if already approved (both need to include lot number or batch identification) and medicated feed/medicated water drug concentration assay results for drugs administered in feed/water.
    - Curriculum Vitae (CV) or description of qualifications for study personnel – A copy of the resume or CV is still expected for the study director. A brief explanation of the qualifications of other study personnel is sufficient.
    - Signature page with initials (for manually recorded data) – Personnel responsible for recording data manually and the study director provide samples of their signatures, initials, and numbers for accountability, to ensure authorized personnel conducted the observations, and aid in the interpretation of the observations.