OFFICE OF NEW ANIMAL PRODUCT EVALUATION REVIEWER'S CHAPTER

REVIEW OF RAW DATA AGREEMENT H SUBMISSION FOR TARGET ANIMAL SAFETY AND EFFECTIVENESS STUDIES

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I. PURPOSE

A Raw Data Agreement H submission is a sponsor's agreement with the Office of New Animal Product Evaluation's (ONAPE) list of copies of raw data and study documents to submit to support their Target Animal Safety (TAS) or Effectiveness (EFF) technical section. This document describes what an ONAPE reviewer should expect in a sponsor's Raw Data Agreement H Submission and the procedures to review this H submission. The list of copies of raw data to be submitted for TAS studies are listed in Appendix 1 of this document and the list for EFF studies are listed in Appendix 2. Additional study documentation to be submitted with TAS and EFF studies is listed in Appendix 3.

This document only describes what information is expected to be submitted to ONAPE for a target animal safety or effectiveness study to support a new animal drug approval. 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. Additionally, this document does not account for any unexpected events outside the scope of the protocol that may occur during the conduct of the study and for which the Center for Veterinary Medicine (CVM) would expect the sponsor to provide full documentation, including copies of raw data.

II. TARGET ANIMAL SAFETY STUDIES

Sponsors submit copies of raw data and study documents from TAS studies conducted using the principles of Good Laboratory Practices (GLP) in the TAS technical section submission. Examples of TAS studies include:

- Margin of Safety Studies
- Reproductive Safety Studies

- Mammary Gland Safety Studies
- Injection Site Safety Studies
- Administration Site Safety Studies for Dermally Applied Topical Product
- Oral Tolerance Safety Studies for Topical Products
- Heartworm Positive Dog Safety Studies
- Avermectin Sensitive Dog Safety Studies
- Other (e.g., modified version of above studies, Ocular Safety Study, Vaccine Response Safety Study)

III. EFFECTIVENESS STUDIES

Sponsors submit copies of raw data and study documents from EFF studies, typically conducted using the principles of Good Clinical Practice (GCP) as described in Guidance for Industry (GFI) 85 VICH GL9, Good Clinical Practice, as part of the EFF technical section submission. Examples of EFF studies include:

- Clinical Effectiveness Studies
- Dose Confirmation Studies

IV. RAW DATA AND STUDY DOCUMENTS FOR TARGET ANIMAL SAFETY AND EFFECTIVENESS 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.”

Raw data are also defined in GFI 85, Good Clinical Practice, Section 1.24 as “Any original worksheets, calibration data, records, memoranda and notes of first-hand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from automated instruments, and hand-recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.”

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 ONAPE's List of Raw Data and Study Documents

ONAPE used a risk-based approach to determine which copies of raw data and study documents should be submitted to the TAS or EFF 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 ONAPE for TAS (Appendix 1) and EFF studies (Appendix 2). However, situations may arise where additional raw data or study documents are required to be submitted to complete the review of the TAS or EFF 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 aspects of study conduct or endpoints to reduce uncertainty in decision making to an acceptable level. Ideally, additional raw data considerations should be discussed with the sponsor prior to submission of the H submission. The following are examples but not an all-inclusive list:

    - water analysis and consumption for drugs administered in water;
    - feed composition and analysis for drugs administered in feed;
    - tests with specific requirements for sample handling, processing, or storage; and
    - equipment with specialized maintenance or calibration requirements.

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

V. RAW DATA AGREEMENT H SUBMISSION CRITERIA

ONAPE will only review this type of submission if the following criteria are met:

- the associated TAS or EFF study protocol has been submitted for review in advance of conducting the study (I-E-TS submission or I-E-EF submission),

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

- the review of the associated protocol submission is pending; and
- the associated protocol's submission number is clearly identified in the H raw data submission.

VI. RAW DATA AGREEMENT H SUBMISSION REVIEW PROCESS

A. Raw Data Agreement H Submission Content

The Raw Data Agreement H submission eSubmitter includes

- sponsors' agreement to provide copies of raw data listed in eSubmitter;
- sponsors' justification for exclusion(s) of copies of certain raw data, if they do not agree to provide copies of one or more raw data in the list; and
- sponsors' acknowledgement that they will submit the study documents listed in eSubmitter with their TAS or EFF technical section.

B. Timing of Raw Data Agreement H Submissions

We will only review a raw data agreement H submission under this review process if the submission meets the criteria in Section V above. Therefore, the sponsor may submit the raw data agreement H submission after the associated TAS or EFF protocol has been submitted, until the protocol submission is closed out, or on the same day the protocol submission is made. The raw data agreement H submission will have a 100-day review time assigned in the Submission Tracking and Reporting System (STARS).

C. Upon Receipt of Raw Data Agreement H Submissions

Raw data agreement H submissions will be assigned to a primary reviewer (PR) in the Division of Companion Animal Drugs or the Division of Food Animal Drugs. The PR follows the procedures outlined below.

1. Assess the associated protocol submission to determine if it is acceptable for review. If the protocol submission is not acceptable for review and the final action is Refuse to Review (RTR), then the raw data agreement H submission will be RTR as well. Each submission (protocol and raw data agreement H submission) will have its own RTR final action letter,[2] with the protocol letter issued before the H submission letter.
2. Because the raw data agreement H submission may be submitted with or after the protocol submission, we may not know that the protocol final action will be RTR when the raw data agreement H submission is submitted.
3. If the protocol and raw data agreement H submissions appear acceptable for review, send a consult request[3] to the same review team members consulted on the associated protocol submission, and to the Quality Assurance (QA) Branch

[2] See P&P 1243.2050 Refuse to File and Refuse to Review.
[3] See P&P 1243.3200 Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission.

for QASR review. The PR and consulting reviewers (CRs) for the raw data agreement H submission are the review team.

4. Schedule a meeting for the raw data agreement H submission review team to occur between day 60 and day 70 from receipt of the submission. At this meeting, the review team discusses the sponsor's eSubmitter responses to ONAPE's list of copies of raw data and study documents. This meeting may be cancelled if the review team determines it is not necessary.

D. Reviewing Raw Data Agreement H Submissions

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

1. Read the associated protocol in its entirety. Continued review of the raw data agreement H submission depends on the following information:

   a. If a protocol concurrence letter has been or is expected to be issued for the associated protocol, the review team members work to complete their review of the H submission.

   b. If a protocol nonconcurrence letter with shortened review time (SRT) has been or is expected to be issued for the associated protocol, and:

      i. the comments in the protocol nonconcurrence letter would not impact the raw data or study documents being collected in the study, the review team members should generally work to complete their review of the raw data agreement H submission when an SRT letter is issued for the protocol with the assumption that the sponsor will make the changes requested in the SRT letter.

      ii. the comments in the protocol nonconcurrence letter would impact the raw data or study documents being collected in the study, the review team members end review of the raw data agreement H submission (see instructions in section VII.C. below).

   c. If a protocol nonconcurrence letter without SRT has been issued for the associated protocol submission, the review team members end review of the raw data agreement H submission (see instructions in section VII.C. below).

2. The nature of the protocol may result in our determination that the sponsor should submit copies of additional raw data and study documents not listed in eSubmitter. Decisions on which additional raw data and study documents are needed should be made based on the individual study design.

3. The review team should meet between day 60 and 70 following receipt of the raw data agreement H submission to discuss whether the sponsor's submission is acceptable. If the previously scheduled meeting is not necessary, it may be cancelled once this goal has been met.

E. Writing the Review for Raw Data Agreement H Submissions

The PR prepares a review document.[4] CRs should prepare a review document if they have transmittal comments to provide to the PR. If a CR chooses not to prepare a review document, they will state that they agree with the sponsor's proposal in eSubmitter and concur with previous review team communications/agreements in an Appian comment.[5] Review documents should be prepared according to division procedures.

The PR includes the following information in their review:

1. the associated TAS or EFF protocol by title, protocol, or study number, and the STARS submission ID in the submission summary.
2. whether the sponsor agrees to submit copies of the raw data and documents listed in the eSubmitter template (i.e., Appendices 1, 2, and 3) to the TAS or EFF technical section.
3. if the sponsor does not agree to submit copies of one or more raw data and/or study documents listed in the eSubmitter template, document whether their justification is acceptable; and
4. whether the sponsor has proposed to submit additional copies of raw data in addition to the items listed in the eSubmitter template.

VII. RAW DATA AGREEMENT H SUBMISSION REVIEW OUTCOMES

Use the Raw Data Agreement H submission acknowledgement letter template to respond to the H submission, depending on one of the following scenarios:

A. Sponsor Agrees to Submit Copies of Raw Data and Study Documents on ONAPE's List with the TAS or EFF Technical Section

If we issued a concurrence letter for the associated protocol (or a nonconcurrence letter with SRT where revisions will not impact the raw data or study documents being collected in the study), the review team completes the review and issues an acknowledgement letter.

B. Sponsor Agrees to Submit Copies of Raw Data and Study Documents on ONAPE's List with the TAS or EFF Technical Section

If the sponsor does not agree to submit one or more raw data or study documents, they should provide a justification. There are two potential responses for this scenario.

1. The Review Team Agrees With the Sponsor's Justification Not to Submit Copies of One or More Raw Data or Study Documents:

   If we issued a concurrence letter for the associated protocol (or a nonconcurrence letter with SRT where revisions will not impact the raw data being collected in the

[4] See P&P 1243.3009 Format and Style Conventions for Reviews and Submission Summaries.
[5] See P&P 1243.3029 Closing Out Consulting Reviews for Submission Tracking and Reporting System (STARS) Submissions for information on providing comments in Appian instead of a written review.

study), CVM issues an acknowledgement letter to inform the sponsor that we agree with the justification.

2. The Review Team Does Not Agree With the Sponsor's Justification Not to Submit Copies of One or More Raw Data or Study Documents:

   If we issued a concurrence letter for the associated protocol (or a nonconcurrence letter with SRT where revisions will not impact the raw data being collected in the study), CVM issues an acknowledgement letter. In the acknowledgement letter, we will include comments addressing why we do not agree with the sponsor's justification to not provide copies of one or more raw data and study documents on ONAPE's list.

C. ONAPE Does Not Concur on the Associated Protocol

If we issue a nonconcurrence letter without SRT for the associated protocol (or a nonconcurrence letter with SRT where revisions may impact the raw data and study documents being collected in the study), the review team ends the review of the H submission and CVM issues an acknowledgement letter.

VIII. COMPLETING THE FINAL ACTION PACKAGE

To identify both the protocol(s) and raw data agreement H submission(s) that are associated to one another for this process, the PR enters in the Review Summary field in Appian the following:

- for the protocol submission (I-E-TS or I-E-EF), enter the STARS submission ID for the H raw data submission (I-H-RD); and
- for the H raw data submission (I-H-RD), enter the STARS submission ID for the protocol submission (I-E-TS or I-E-EF).

To identify which raw data agreement H submission were found to be acceptable and which were not, the PR enters in the Review Summary field in Appian one of the following:

- submission acceptable; or
- submission unacceptable

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

IX. 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 Program Policies and Procedure (P&P) Manual – ONAPE Reviewer's Chapter

1243.2050 Refuse to File and Refuse to Review

1243.3009 Format and Style Conventions for Reviews and Submission Summaries

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

1243.3200 Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

X. VERSION HISTORY

September 29, 2023 – Original version.

December 11, 2025 – Major revisions to add clinical effectiveness information to the document, which had previously only addressed target animal safety.

APPENDIX 1. COPIES OF RAW DATA EXPECTED TO BE SUBMITTED TO CVM FOR TARGET ANIMAL SAFETY STUDIES

Table 1. Target Animal Variables

General Variable Name	Definition
Clinical Observations	Documentation of original records of animal observations including routine daily observations and post-dosing observations. These are typically more detailed health evaluations than General (Daily) Health Observations and less detailed than physical examinations. These are not typically done by a veterinarian but done by an individual with some medical training such as a technician.
Adverse Events	Documentation with descriptions of any observation in animals that is unfavorable and unintended and occur after the use of an article, whether or not considered to be product related.
General Health Observations	Documentation of routine health checks for signs of ill health that include assessment of limited physical parameters (e.g., mortality/ moribundity checks).
Physical Examinations	Documentation of the physical exam conducted by a veterinarian documenting health status of an animal, usually conducted prior to assignment 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 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.
Special Tests	Documentation that is based on the individual drug and species, e.g., blood pressure, telemetry.

Table 2. Study Quality 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: ▪ When a deviation occurred, on what date ▪ Description/explanation of the deviation (what happened?) ▪ Was anything done to address the deviation, if appropriate ▪ Discussion on the impact the deviation had on the study ▪ Meets 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.
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.
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. COPIES OF RAW DATA EXPECTED TO BE SUBMITTED TO CVM FOR EFFECTIVENESS STUDIES

Table 1: Target Animal Variables

General Variable Name	Definition
Effectiveness/Clinical Endpoints (as listed in the protocol)	Documentation of observations or recordings for variables specified in the protocol to determine the effectiveness of the drug, such as a behavioral assessment, scoring of a clinical sign, measurement, or laboratory results.
Owner Diaries (companion animal studies only)	Documentation generated by the owners of study animals that typically record drug administration and/or observation of the effects of the drug on the animal, such as dosing records, routine overall health and activity descriptions, and questionnaires.
Adverse Events	Documentation with descriptions of any observation in animals that is unfavorable and unintended and occur after the use of an article, whether considered to be product related or not.
General Health Observations	Documentation of routine health checks for signs of ill health that include assessment of limited physical parameters (e.g., mortality/moribundity checks).
Physical Examinations	Documentation of the physical exam conducted by a veterinarian documenting health status of an animal. These are usually conducted prior to assignment to the study to determine eligibility. However, these may be conducted as needed during the study to identify health problems, or at regular predetermined intervals to assess animal health. The veterinarian or scribe typically records notes from the exams 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.
Special Tests	Documentation that is based on the individual drug and species, e.g., blood pressure, telemetry.

Table 2. Critical Study Data

General Variable Name	Definition
Documentation of deviations and copies of raw data to support the deviations	Documentation of departures from GCP and the protocol during the conduct of the study. CVM expects all deviation documentation should have the following information: ▪ When a deviation occurred, on what date ▪ Description/explanation of the deviation (what happened?) ▪ Was anything done to address the deviation, if appropriate ▪ Discussion on the impact the deviation had on the study ▪ Meets 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 GCP and/or protocol occurred during the conduct of the study.
Enrollment Documentation	Documentation that includes checklist for enrollment (inclusion/exclusion) criteria (e.g. physical exams, certain scoring, etc.) indicating the animal is or is not eligible to enroll in study. May also include a list of all animal identifiers included in the study.
Owner Consent Forms	Documentation of informed consent signed by owners prior to study enrollment.
Documentation of randomization procedures performed and the outcome of all randomizations	Documentation of randomization procedures performed and the outcome of all randomizations, i.e., the randomization table(s) and other records related to randomization procedures required by the protocol.
Dose Calculation and Preparation	Documentation of how doses were calculated and prepared (e.g., 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 that indicates (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.
Test/Control Article Accountability	Documentation of test article receipt, dispensing of test article, and remaining or returned test article at end of study.

Notes to File	Documentation of study procedures and important issues or events 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 investigator and contributing scientists, and Quality Assurance Unit for the study.

APPENDIX 3: STUDY DOCUMENTS

The following study documents will need to be submitted within the TAS or EFF technical section.

- Final Study Report: The final study report (FSR) submitted to support target animal safety or effectiveness decisions for the new animal drug should follow the requirements set forth in the applicable standard of conduct (typically 21 CFR Part 58.185 for TAS and Guidance for Industry 85 VICH GL9, Good Clinical Practice, Section 7 for EFF). In addition, CVM reminds sponsors to make sure the following are included in the FSR:
    - Protocol and amendments
    - Contributing scientist reports (TAS only)
    - Dates of monitoring visits (EFF only)
    - 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
    - Description of all calculation, 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 TAS or EFF 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 or the investigator. 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 or the investigator 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.