OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF TARGET ANIMAL SAFETY OR EFFECTIVENESS DATA (P) SUBMISSIONS

I. PURPOSE

This document describes the basic procedures for reviewing an investigational new animal drug (INAD) target animal safety (TAS) or effectiveness data submission (STARS P submission, subclass TS or EF). It is intended to be a high level checklist for reviewers in the Division of Companion Animal Drugs (DCAD) and Division of Food Animal Drugs (DFAD) to use from submission assignment to close out. It is not intended to provide information on the scientific aspects of the review or how to determine if the submitted information is acceptable for concluding that a product is safe or effective.[1] For more information about principles of review, see ONADE Standard Operating Procedure (SOP) 1243.100.105 "Overarching Principles for Review and Documentation."

Note that although most TAS and effectiveness data submissions are made under the INAD phased review process, they may also be submitted as part of a non-administrative new animal drug application (NADA). Therefore, this document also includes information that may be useful for the review of TAS and effectiveness studies included in non-administrative NADAs.

II. INITIAL STEPS AT THE TIME OF ASSIGNMENT OF A DATA SUBMISSION

The data submission is assigned to the primary reviewer (PR) from the target animal division (TAD). Complete the following initial steps within the first few days after the submission is assigned to you:

A. Determine the Purpose of the Submission

Read the eSubmitter submission report, the cover letter (if included), and other summary information, if provided by the sponsor, in the submission to determine what the sponsor has submitted and what outcome they are requesting (i.e., technical section complete (TSC) vs. technical section incomplete/information acceptable (TSI/OK)).

[1] Some of the information in this P&P may also be applicable to INAD Reasonable Expectation of Effectiveness (RXE) P submissions or data submissions reviewed by ONADE divisions other than DCAD or DFAD.

B. Determine if the Submission is Acceptable for Review

If a submission is of such poor quality that it cannot be reviewed, we have 60 days from the correspondence date to issue a Refuse to Review (RTR) letter for an INAD P submission or 30 days to issue a Refuse to File (RTF) letter for an NADA. For example, we may find the submission unacceptable if there are significant pieces of information missing, if copies of the data are not readable, or if the number and types of errors in the submission call into question the quality of the entire submission. See ONADE Policies and Procedures (P&P) 1243.2050 "Refuse to File and Refuse to Review" for more information about the criteria and the administrative processes for RTR and RTF.

The RTR/RTF assessment for TAS P submissions is conducted by a consulting reviewer (CR) from within the Quality Assurance Team (i.e., a Quality Assurance Study Reviewer (QASR). For other P submissions, the TAD PR or a CR within the TAD may be responsible for conducting the RTR/RTF assessment. For the RTR/RTF assessment, follow the steps in P&P 1243.3100 "RTR and RTF Assessment of Submissions and Applications that Contain Data" and use the ONADE RTR/RTF template.

For QASR consults, see P&P 1243.3215 "Requesting a Quality Assurance Study Review from the Quality Assurance Team."

A reviewer in the Division of Scientific Support will identify the data files (XML or XPT files) in the submission as part of the RTR/RTF assessment, evaluate them for acceptability, convert them to reviewer usable Microsoft Excel files (XLSX), and notify the RTR/RTF reviewer of the file location. You do not need to request a consulting review for this process, and this is a separate process from the statistical consult.[2] See the Office Policy on data file conversion "Extensible Markup Language (XML) and SAS eXPORT (XPT) Data File Evaluation and Conversion Process".

C. Familiarize Yourself with the Contents of the Submission

Briefly look through the entire submission (table of contents and each file) to get an overall idea of what it includes and how it is organized. Check all the parts of the submission to determine which information may need to be reviewed by CRs. For example, there may be pharmacokinetic (PK) or human user safety information within a study file or in the All Further Information (AFI) section. Looking through the entire submission early can help identify the need for consults that might not be obvious from the eSubmitter report and helps to ensure all consults are identified and requested in a timely manner.

When looking through the submission:

1. Read the sponsor's technical section summary (if provided). If the results section does not seem to support the claim (e.g., >90% effectiveness for a companion

[2] The RTR/RTF reviewer does not need to request a formal consult for the data file conversion process. If you later identify additional files or file manipulation that would help with the review (e.g., creating one dataset out of multiple sets, renaming variables, paring down a large dataset into a smaller one with specific variables, graphical support for target animal safety studies, etc.), contact the appropriate Biostatistics Team directly and ask them to perform these tasks.

animal antiparasitic drug) talk to your team leader (TL). It may not be worthwhile reviewing the submission in this case.

2. Spot check the final study report (FSR) and critical parts of the copies of raw data. For example, compare the FSR to the data summaries, looking for obvious errors and make sure the copies of raw data look “raw” and contemporaneously recorded. At this early stage you are not conducting a complete data audit you are confirming that the sponsor appears to have adequately performed a quality assurance check of the data and that the submission is acceptable for review.

   Raw data are defined as a record of the first place study information was recorded (for complete definitions of raw data, refer to 21 CFR 58.3(k) for laboratory studies and sections 1.24 and 8.3 of Guidance for Industry (GFI) # 85 (VICH GL9) “Good Clinical Practice” for clinical (effectiveness) studies). Raw data is not summary data but represents everything observed and recorded during a particular study and should include individual animal data. Whether handwritten or electronic, raw data should be attributable, legible, contemporaneous, original, and accurate (ALCOA).

3. Determine if the submission is complete and contains the expected information such as draft labeling, AFI, and draft Freedom of Information (FOI) Summary language. If any expected information is missing, discuss with your TL how to proceed, or if an amendment is appropriate.

4. If time allows, you may screen the notes to file and sponsor communications in the submission to see if there are any concerns or potential issues you may want to flag for further evaluation.

D. Issue Consulting Review Requests

Check the submission carefully upon receipt to determine if any scientific consulting reviews are needed. The consults needed will be based on the type of studies and the information submitted. If a particular subject matter expert (SME) was involved in the protocol review, they should be consulted during the review of the P submission. The most common scientific consults requested for a TAS or effectiveness data submission are from SMEs such as:

- Request a QASR and/or RTR/RTF assessment consulting review if needed, as described above in section II.B above.

- Biostatistics – If the submission includes pivotal study(ies) with a statistical analysis, send a consult request to the appropriate Biostatistics Team. There may be exceptions for division-specific studies; consult your division procedures or your TL. A biostatistics consult may also be needed for pivotal studies without formal analyses so that they can evaluate other considerations such as randomization and masking.

- Pharmacology – If the submission contains PK or bioavailability data (e.g., for TAS or dosage characterization), request a consult from the Clinical Pharmacology Team. See SOP 1243.166.001 “Clinical Pharmacology Team (HFV-166) Involvement and Communications During the Product Lifecycle”.

- Microbiology – If the submission contains microbiology information (e.g., bacterial culture, PCR data, etc.), commonly seen in effectiveness studies for products with antimicrobial indications, request a consult from the microbiologists in your division or in the Division of Human Food Safety (DHFS), depending on division procedures.

- Human User Safety – If the submission contains human user safety information or if there are potential human user safety concerns for this project, consider whether a human user safety consult is needed from DHFS. See SRD 1243.130.001 "Human User Safety Assessment".

- Chemistry and Manufacturing – If the submission includes TAS or effectiveness studies for medicated feeds or medicated water products (including immersion products for aquaculture), a consulting review should be requested from the Division of Manufacturing Technologies (DMT). DMT may review information such as homogeneity, segregation, stability, assays (including the analytical method) used to confirm correct inclusion or dosage levels, and mixing equipment validation for these products.

- Adverse Drug Experience and Product Defects – Consider requesting a consult from the Office of Surveillance and Compliance (OSC) Division of Pharmacovigilance and Surveillance (i.e., a DPS Adverse Drug Experience (ADE) and Product Defect (PD) Review) for adverse drug reports, including lack of effectiveness reports, which may impact our safety or effectiveness decision. This may be particularly useful if the active ingredient is already approved as an animal drug.

For consults within ONADE or from OSC, request consulting reviews through Appian. See the ONADE P&P 1243.3200 "Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission". In the "Instructions for Consulting Reviewer" section of the Appian template, clearly indicate what the CR should review. It is helpful for the CR(s) to know which portions of the data submission should be reviewed and your expectations (e.g., type of documentation such as formal review or comments by email). If there are multiple studies, let your consultants know what studies they need to review, and for what purpose. It is helpful to follow up with the CR(s) early in the review process.

For consults outside of ONADE, such as the Office of Applied Science (OAS), or another FDA center, follow the instructions in SOP 1240.106.004 "Office of New Animal Drug Evaluation's Intra- and Intercenter Consult Request Process."

If you are not sure whether a consulting review is needed for your submission, talk to your TL and/or contact the potential consulting TL to ask if they want a consult.

If your submission is a non-administrative NADA, you should coordinate with the CRs to make sure that all consults are returned with enough time to get any needed amendments (particularly labeling changes), prepare the FOI Summary and get sponsor feedback, and allow for the NADA administrative review steps to be completed. This may necessitate requesting for consults to be returned prior to the STARS consulting due date.

E. Complete the Bioresearch Monitoring (BIMO) Selection Tool

Complete the BIMO selection tool to help determine if a BIMO inspection may be appropriate for the studies included in your submission. Document the results of the BIMO selection tool in your review. See SOP 1240.3184.001 "Using the Bioresearch Monitoring (BIMO) Selection Tool" for more explanation and instructions.

F. Determine if the Submission is the Last Major Technical Section Submitted (last P) for the Project

If your submission is the last major P submission for an INAD project, be aware that the last P submission allows the sponsor to submit the minor technical sections, Labeling and All Other Information (AOI), which then signals ONADE to initiate submissions for the FOI Summary (Q submission) and the end game meeting (Q submission). Check the current Office procedures for the most current recommendations for timing and your responsibilities for these submissions. See section III.J. below for more information.

G. Create a Submission Timeline for Meeting Important Submission Milestones

For INAD P submissions and non-administrative NADAs, create a submission timeline for the submission. Use the submission timeline template for your submission type, located in ONADE SharePoint Templates page.[3] The timeline provides critical steps and interim deadlines as a helpful planning tool; however, you may need to modify them for your submission. Be sure to note important interim timeline dates (such as finalizing the database with consultants, administrative review, etc.). Talk to your TL (or other reviewers) for other specific interim steps and procedures that you should add to complete the submission.

Schedule a meeting of the review team (consultants and their TLs) to occur around Day 100 of the STARS timeframe. This meeting is helpful as a check-in to identify any major issues and coordinate any amendment requests and other components of the submission (e.g., labeling, FOI Summary, etc.).

III. REVIEWING THE SUBMISSION

A. Review Preparation

Familiarize yourself with the project so that you know how your submission fits into the overall drug development plan. If you are not sure what the context of the submitted information is, discuss the submission with your TL.

1. Check STARS and the administrative file (i.e., CDMS for completed electronic submissions or Document Control Unit for completed paper submissions that have not yet been scanned) to familiarize yourself with the overall project, looking at what was previously reviewed or discussed, and any other information that might be relevant to your submission. The project manager (PM) Drug Development Project portal in STARS CDP may also be useful. Things to look for include:

    - Formal meetings and informal sponsor communications,

[3] Internal information redacted.

- any memos to the file (typically Q submissions),
- protocol reviews for the studies in your submission,
- previous data reviews and letters (H or G submissions),
- NCIEs (typically B submissions) for the studies in your submission,
- BIMO inspections and associated establishment inspection report (EIR) reviews (K submissions), and
- serious adverse event reports (G submissions)

For projects involving more than one participant (e.g., public partners and a pharmaceutical company), you may have to look at each participant's INAD or master file to find the agreed upon requirements. Additionally, if there are more than one indication, species, and/or dosage regimen, there may be multiple Effectiveness and TAS technical sections that may or may not be relevant.

2. Look at the pertinent regulations, guidance documents, Office quality system tools (e.g., P&Ps, SOPs, Scientific Reference Documents (SRDs), Office policies, and templates) and division SOPs related to the submission.

3. Discuss with your TL (or other reviewers) if there are any recent approvals or projects under development which might provide good examples of how similar products were reviewed and any important precedents to consider. It may also be helpful to look at other information sources such as Animal Drugs @ FDA, foreign approvals, the CFR for the same drug or a similar drug in the same species.

4. If there is an approved animal or human drug (or an approved product in foreign markets), briefly familiarize yourself with the pharmacology, warnings, contraindications, precautions, adverse reactions and use information as listed on the labeling.

5. If necessary, familiarize yourself with the disease, condition, or organism under investigation through published literature, subject matter experts, textbooks, and other reliable references.

B. Conduct the Scientific Review

Reviewing data from a regulatory perspective is a skill that is learned over time as you work with your TL, interact with your team and division members, and review data submissions independently. You need to consider the veterinary medical and biological aspects of the data, and the impact of applicable laws, regulations, guidance, policies, and precedents. Regulatory science is a combination of these factors. We do not review to ensure pure or perfect science, rather to ensure that the studies conducted for approval meet the applicable regulatory standards.

<u>FSR and records for each study</u>

After familiarizing yourself with the project and submission materials, you should begin review of the data by reading the FSR(s). The FSR(s) should give a good overview of the study(ies) and conclusions. Remember, as you read and consider the

sponsor's evaluation and conclusions, you are responsible for determining if those conclusions support the intended conditions of use.

You should verify the accuracy of the FSR with regard to the primary variable(s) by comparing it with the information provided in the copies of raw data. For example, for an anthelmintic dose confirmation study, you should verify that the worm counts in the copies of raw data match the information the sponsor provided in the FSR. For a drug with a low margin of safety, you may be particularly interested in ensuring that all adverse reactions as reported in the copies of raw data were captured in the final study report. The depth of your raw data audit may vary with the nature and size of the submission, the QASR review, if performed, or any concerns you may have with the study design or with the disease or drug.

Determine how the study(ies) contributes to the decision regarding the safety or effectiveness of the drug product. The terms pivotal and non-pivotal are sometimes used to describe whether the study contributes to the approval decision. The contribution of each study towards the basis of our conclusions may depend on the quality and the clinical relevance of the data. Many things may (but do not automatically) make a study unacceptable as evidence to establish safety and effectiveness, for example:

- the study was not adequate and well controlled[4] (effectiveness) or did not comply (or exceptions were not acceptable) with U.S. GLP[5] (TAS). Check the regulations, office policies, and/or applicable guidance documents for the applicable standards;
- the study was a pilot study;
- the study was not conducted with the final formulation, or with the intended dosage regimen (dose, frequency, duration, and route of administration); or
- the study was conducted outside the U.S. and does not provide inferential value for the intended U.S. population (e.g., animal breeds, animal management, or pathogens are not representative of U.S. breeds, management, or pathogens).

For each study used to support approval, summarize the study design and review the data. Document any major inconsistencies or problems with the data, protocol amendments and deviations, and issues that require discussion or further consideration.

Review of supporting information

For supportive information (e.g., non-pivotal studies, scientific literature, etc.), briefly summarize what was submitted and its significance in the submission or for the project. Note in your review any study or supportive information in the submission that was not reviewed.

[4] 21 CFR 514.117
[5] 21 CFR 58

Data review tools

The XML and/or XPT files containing the raw data for the study(ies) will be converted to Microsoft Excel (XLSX) spreadsheets shortly after the submission is received (see section II.C.). If you determine that additional tools would facilitate your review of the data, such as custom data tables, summary statistics, and data visualization plots, contact the Biostatistics team.

Data audit

Although you may not need to conduct a complete audit comparing the copies of raw data to the information in the final study report for every study parameter, you are still responsible for conducting a complete review of the submission. You should evaluate the information contained in every document of the submission to the depth necessary to make an informed decision on the data. If non-traditional types of information are provided (e.g., scientific literature, data from foreign studies, or real-world data), there are resources available within ONADE to assist in the review of this type of information, including several GFIs.[6]

Review documentation

If a division review template is available, copy and paste the applicable sections into the ONADE review template. Using a template will help to ensure that your reviews are consistent and address the important aspects of each study. Always keep in mind that the template is just a starting point. Data review is not a fill in the blanks process. You may also need to address things that are not mentioned in the template, and it's possible that not all parts of the template will be applicable to your data package. To ensure that readers know that all sections of the template were addressed and not overlooked, write 'Not Applicable' (and if needed, a brief explanation) next to those headings that do not apply to the study rather than deleting it. For example, if you are reviewing a study where the personnel were not masked to treatment, do not just write 'Not Applicable' next to masking. Because data collection in most pivotal studies is conducted by personnel that are masked to treatment group, you should explain why this particular study deviates from the regular approach to ensure that you provide enough context.

Documenting your regulatory decision

In many cases, you will need to make a final decision without all the information you might like to have. When faced with such uncertainty, your conclusions should be based on the information in the submission combined with your scientific and medical knowledge, precedent, possible outcomes (risks and benefits), discussions with other team members, etc.

Your review should present the results of the study along with your evaluation and conclusions and recommendations based on a thorough review of the entire

[6] Some examples of available resources are GFI #106, "The Use of Published Literature in Support of New Animal Drug Approval"; GFI # 265 "Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs", and GFI #266 "Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs".

submission. Conclusions and recommendations should be concise and include the rationale for the decisions.

C. Request and/or Document BIMO Inspections

If BIMO inspections have not been requested previously for the pivotal study(ies) in this submission (i.e., for the clinical investigator(s) or non-clinical laboratory(ies) that conducted the study(ies)), determine if an inspection(s) is needed. See P&P 1240.3610 "CVM Bioresearch Monitoring Program – General Procedures for the Preparation, Assignment, and Completion of Bioresearch Monitoring (BIMO) Inspections" and the BIMO selection tool.

If a BIMO inspection for the study was conducted previously, or if there is other relevant BIMO inspection history for the involved clinical investigator(s) or laboratory(ies) available in the CDP BIMO module, include a summary of the inspection(s) (i.e., study or entity inspected, inspection dates, and final classification) in your review.

For each pivotal study, state in your review why a BIMO inspection will or will not be requested.

D. Meet with the CR(s) per the Timeline or as Needed

If you think a meeting to discuss the submission with the review team would be useful, schedule a meeting in Outlook with the CR(s) at an appropriate time point in the review cycle (approximately Day 100) to discuss the submission. Things to discuss may include:

- Agreement on the database (e.g., exclusion of certain animals or study sites from the final analysis).
- Use of appropriate methods for data summary and analysis.
- Initial opinion of the sponsor's conclusions and draft language for FOI Summary section and label/labeling (if provided).
- Discussion of any issues that have come up during review.
- Any amendments or informal clarifications needed from the sponsor.
- Preliminary opinion of whether the submission may be complete or incomplete (and if incomplete, whether shortened review time (SRT) be offered or not (non-SRT) if the review is far enough along).

E. Incorporating Consulting Reviews

When you receive a completed consulting review, read it and if needed, discuss it with the CR so that you understand the comments and how to incorporate them in the transmittal to the sponsor. Although you may not fully understand all content of the CR's review, it is important to know what is being recommended and why. In some cases, after your discussion with the CR, some of the CR's comments may not be transmitted or are no longer relevant.

If changes are made to the CR's comments, ensure the CR agrees with these changes (sometimes a minor change can make a big difference in the meaning). Document the outcome of the change either by including the CR's concurrence with the changes as an appendix to the review or note it in the Submission Summary, Reviewer's Discussion, or Consulting Reviews section of your review. Spelling and grammar changes may be made without consultation.

F. Request Amendments if Needed

If you need additional data or information to complete your review, and you determine an amendment is the appropriate step to obtain the information, follow P&P 1243.3026 "Assessing Submission Quality and Amending and Resetting the Clock on Submissions" to request an amendment. When possible, bundle the requests to minimize the number of amendments needed and contact the CRs to see if they have amendment requests which can be incorporated. If you are unsure if an amendment is appropriate, talk with your TL.

G. Document the Test Article Information

Communicate with the Division of Manufacturing Technologies as needed to confirm the test article information. Complete the target animal division section of the Test Article Information template to include in your review appendix. See SOP 1243.118.001 "Documenting and Confirming Test Article Information (Including Formulation) for Pivotal Data Submissions".

H. Review the Draft Labeling, AFI, and Draft FOI Summary Language

1. Draft Labeling

   Draft labeling language should be submitted with the Effectiveness and TAS technical sections. Although it is not required, if the sponsor did not provide draft labeling, talk to your TL about whether to request draft labeling in an amendment.

   Review only the parts of the draft labeling relevant to the technical section, for example:[7]

   - Indications for Use
   - Dosage and Administration
   - Contraindications
   - Warnings (animal safety, user safety, or other warnings related to animal safety and effectiveness)
   - Precautions
   - Adverse Reactions

[7] Not all sections will apply to all labeling components or all products. Sections such as Clinical Pharmacology and Microbiology should be reviewed in conjunction with the applicable CRs. It may be appropriate to review other sections as well, depending on the product and the proposed labeling language. A complete review of all labeling components will be conducted under the Labeling technical section.

- Information for Animal Owner
- Target Animal Safety
- Effectiveness

Provide labeling comments to the sponsor in the letter or draft labeling language in a separate document, per your division procedures. It may be helpful to include explanations for significant changes being requested.

2. AFI

   Any further information pertaining to the drug's effectiveness and safety should be submitted with the Effectiveness and TAS technical sections, respectively. The sponsor must disclose all information, both favorable and unfavorable, that is pertinent to an evaluation of the drug's effectiveness and safety (per 21 CFR 514.1(b)(8)(iv)). If the sponsor does not provide AFI in the P submission, talk to your TL about whether to request AFI in an amendment.

   The most common information submitted as AFI is reports or abstracts for other studies (e.g., non-pivotal, pilot, foreign, etc.) that have been conducted by the sponsor, or results of a literature search. They may also submit foreign market experience information such as Periodic Safety Update Reports (PSUR) lists. Look at these materials to see if there are any concerns regarding effectiveness or animal safety that would alter our conclusions, or information that might need to be added to the labeling. Comment on any additional safety or effectiveness information submitted.

   For projects that will result in a supplemental approval, the sponsor should submit any new information since their last submission to the Drug Experience Report (DER).

3. Draft FOI Summary Section

   We encourage sponsors to submit draft FOI Summary section(s) relevant to the respective technical section with the TAS and Effectiveness (including dosage characterization) technical sections. In the P submission, if the study(ies) is acceptable, revise the section (TAS or Effectiveness) of the draft FOI Summary as appropriate. CVM prepares the final FOI Summary as an agency-initiated Q submission, once the major technical sections are complete or are nearing completion, usually, at the same time as the minor technical sections (Labeling and AOI) are reviewed.

   In your review, explain if needed per division processes, significant differences between your documents and those submitted by the sponsor, such as factual discrepancies, differences in the statistical results, observations or adverse events, or other information that the sponsor included but is not pertinent to the approval.

   After you have prepared the draft FOI Summary section(s) and your management (and any consultants if needed) has cleared it, send it to the sponsor via email so that they may review it and request revisions or corrections before we close out the P submission. The main purpose of sending the draft language to the sponsor

is to find and correct errors; CVM makes the final decision about the content of the FOI Summary. If the sponsor does not reply by the requested date or requests revisions beyond factual corrections, refer to your division processes or discuss how to proceed with your TL.

I. Sponsor Communications During the Review Cycle

Reviewers may correspond with sponsors while a submission is under review, and request that sponsors submit additional clarifying information directly to reviewers via e-mail. Substantive (or unsolicited) information should be submitted as an amendment through eSubmitter. However, answers to simple clarification questions may not need an amendment. Discuss with your TL if you are unsure.

Document e-mails and informal phone calls with sponsors in your review if the discussion is pertinent to the review or outcome. In addition, it may be appropriate to include a copy of e-mails with the review documents (e.g., as an appendix) for inclusion in the administrative file. When including email copies in the review, only include the relevant portions of the email chain.

J. Additional Considerations for the Last P Submission

The last P is the last remaining major technical section for a project once all the other technical sections have been completed in the INAD. If the last P is submitted under the INAD, the project is considered to be in the end game, in which an end game meeting will occur, and as noted above, the sponsor will submit the minor technical sections (Labeling and AOI M submissions) and the TAD will prepare the complete FOI Summary (Q submission).

Note: If the last P is submitted as part of a non-administrative NADA, the labeling and AOI will be included in the application, and preparation of the FOI Summary will occur as part of the application review.

Navigating the INAD end game requires the TAD PR to coordinate completion of the last P, the Labeling and AOI, and the FOI Summary simultaneously, and consider the following:

1. Timing of Consulting Reviews

   Communicate with the CRs early in the process about the timelines for the M and Q submissions. Coordinate amendments for the Labeling M submission and assemble the FOI Summary which may necessitate getting input from CRs prior to the consulting due dates.

2. Coordinating the Reviews of the Last P, Labeling M, and FOI Summary Q Submissions

   When reviewing the last TAS or effectiveness P, Labeling M, and FOI Summary Q submissions at the same time, it may be more efficient to review the labeling under the M submission and write the FOI Summary under the Q submission instead of duplicating the reviews in the P, M, and Q submissions. Similarly, if the AFI information in the last P is duplicated in the AOI M submission, it may be more efficient to review it under the M submission. In both cases, you can reference the

M and Q submissions in the P submission instead of duplicating the review in the P submission review.

Additionally, it is not always necessary to include labeling comments or a copy of the draft FOI Summary section in/with the P technical section response letter. Instead, if consistent with your division's processes, you may modify the letter boilerplate to state that comments will be provided as part of the M or Q submissions, or a similar acknowledgement and clarification.

3. Executive Summary for the Complete FOI Summary

   If your submission is the last P or a non-administrative NADA, contact the Executive Summary writer early to initiate the executive summary preparation process. See P&P 1243.5760 "Process for Preparing an Executive Summary for a Freedom of Information Summary".

4. End Game

   When reviewing the last P, Labeling M, and FOI Summary Q submissions you will also need to prepare for the end game meeting, which is led by the project manager. See P&P 1243.3051 "Verifying Scope and Technical Section Status for Phased Review Projects in the End Game" for more details on the information you will need to have for the meeting.

IV. PREPARING THE FINAL ACTION PACKAGE

1. Determine the final action for the P submission and prepare the documents accordingly:

   a. If all the submitted pivotal study(ies) is acceptable and all requirements for the technical section are completed, the final action will be technical section complete (TSC).

      i. Write a "technical section complete" letter using the Office template. You may include comments (from your review and CRs) in the letter related to the studies, labeling, and the draft FOI Summary section, as appropriate. Check with your division for specific language if applicable. In the TSC letter, describe what the section is complete for (i.e., clearly identify the dosage regimen, indication(s), and species/class that the TSC letter is in reference to). A sponsor can work on multiple projects under the same INAD; therefore, it can be confusing to determine which technical sections are complete for each project without detailed CVM documents.

      ii. Obtain division management concurrence on the wording for the FOI Summary section and labeling if those will be shared with the sponsor.

      iii. Email the sponsor an advance copy of the CVM changes to the pertinent labeling section(s) and FOI Summary section language so they can inform us if there are errors or if they would like to propose any modifications. Inform the sponsor of the turnaround time for comments.

   b. If at least some study(ies) is acceptable, but all requirements for the technical section have not yet been completed, the final action will be technical section

incomplete, submitted information acceptable. The technical section incomplete (TSI) letter comments should clarify which (if any studies) are acceptable and which are not.

Write the letter using the Office TSI letter template. This should be used when there are multiple components needed for a technical section and not all of the required components have been submitted, e.g., an antiparasitic product with multiple parasite species, but the current P submission includes studies for one species, or aquaculture projects with multiple target animal species; projects where multiple types of studies are required. You may include comments in the letter related to the studies, labeling revisions, and the draft FOI Summary section (for any acceptable studies), as appropriate (if labeling comments or FOI Summary language will be provided follow steps a.ii. and a.iii. above). Check with your division for specific language if applicable.

c. If the study(ies) is not acceptable, the final action will be technical section incomplete, submitted information not acceptable. Write the letter using the ONADE technical section incomplete letter template. Also determine whether shortened review time (SRT) will be offered. Include comments in the letter related to the studies, and whatever next steps need to be taken, as appropriate. Typically, draft labeling comments and draft FOI Summary section language are not included. Check with your division for specific language if applicable.

2. Prior to submitting your draft final action package to the TL, ensure that you have addressed ALL sponsor requests and review concerns. The sponsor does not have the benefit of reading the primary and consulting reviews, so it is critical that the letter provides enough information so that they understand the basis for our comments. Read your review again and ensure that it is complete, internally consistent, and that clear conclusions are drawn. Also make sure it is consistent with applicable Center and division policies, guidance documents, and precedents.

3. Place all documents that need division clearance in the shared folder location according to your division procedures (e.g., S: drive folder or SharePoint page). The folder should contain clean, ready for final documents, as applicable:

   - primary review;
   - response letter;
   - draft labeling document (if applicable); and
   - draft FOI summary section (if prepared).

   The folder may also contain reference documents (or links to the documents) that the TL or division director (DD) may need, such as:

   - consulting reviews;
   - a copy of the submission timeline;
   - referenced documents (e.g., memoranda, emails, etc. related to the submission that were not incorporated into your review).

4. The TL will comment on the draft documents and let you know when they are ready for revisions or next steps (e.g., DD review). Discuss any questions, concerns, or disagreements[8] with TL comments with your TL. After your TL's comments have been addressed, let your TL know that the documents are ready for the next step in the clearance chain or send them forward according to your TL's communicated expectations for the submission.

   If the TL or DD make changes to a CR's transmittal, labeling, or FOI Summary language, obtain concurrence from the CR before moving to the next step.

V. CLOSING OUR THE P SUBMISSION

Once documents have been cleared at the division level, upload the final action package documents into Appian for close-out. Refer to P&P 1243.3030 "Completing Final Actions for Submissions", the Appian User Guide,[9] and any division SOPs related to Appian close-out procedures.

VI. REFERENCES

Code of Federal Regulations

21 CFR 58.3(k) - Definitions

21 CFR 514.1(b)(8)(iv) - Evidence to establish safety and effectiveness

CVM Guidances for Industry (GFIs)

GFI # 85 (VICH GL9) - Good Clinical Practice

GFI #106 - The Use of Published Literature in Support of New Animal Drug Approval

GFI # 265 - Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs

GFI #266 - Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs

CVM Program Policies and Procedures (P&P) Manual – ONADE Reviewer's Chapter

1243.2050 - Refuse to File and Refuse to Review

1243.3026 - Assessing Submission Quality and Amending and Resetting the Clock on Submissions

1243.3030 - Completing Final Actions for Submissions

[8] See SOP 1243.100.005 "Scientific Advisory Committees" for procedures to follow if you and your TL cannot reach agreement on a specific issue.

[9] Internal information redacted.

1243.3051 - Verifying Scope and Technical Section Status for Phased Review Projects in the End Game

1243.3100 - RTR and RTF Assessment of Submissions and Applications that Contain Data

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

1243.3215 - Requesting a Quality Assurance Study Review from the Quality Assurance Team

1240.3610 - CVM Bioresearch Monitoring Program – General Procedures for the Preparation, Assignment, and Completion of Bioresearch Monitoring (BIMO) Inspections

CVM Standard Operating Procedures (SOP)

1240.106.004 - Office of New Animal Drug Evaluation's Intra- and Intercenter Consult Request Process

1240.3184.001 - Using the Bioresearch Monitoring (BIMO) Selection Tool

ONADE Standard Operating Procedures (SOP)

1243.100.005 - Scientific Advisory Committees

1243.100.105 - Overarching Principles for Review and Documentation

1243.118.001 - Documenting and Confirming Test Article Information (Including Formulation) for Pivotal Data Submissions

1243.166.001 - Clinical Pharmacology Team (HFV-166) Involvement and Communications During the Product Lifecycle

ONADE Scientific Reference Documents (SRD)

1243.130.001 - Human User Safety Assessment

ONADE Policies

Extensible Markup Language (XML) and SAS eXPORT (XPT) Data File Evaluation and Conversion Process

Other Resources

Appian User Guide

VII. VERSION HISTORY

July 19, 2024 – Original version.

APPENDIX 1. – CHECKLIST OF MAJOR P SUBMISSION TASKS

INITIAL STEPS UPON RECEIPT

- ☐ Determine the purpose of the submission.
- ☐ Conduct (or request a consult for) the RTR/RTF assessment.
- ☐ Briefly familiarize yourself with the submission contents.
- ☐ Request consulting reviews within 5 days of receipt.
- ☐ Complete the BIMO selection tool.
- ☐ Identify if this submission is the last P submission.
- ☐ Create a submission timeline.
- ☐ Schedule review team meeting for approximately Day 100.

SUBMISSION REVIEW

- ☐ Familiarize yourself with the project.
- ☐ Conduct the scientific review.
- ☐ Request BIMO inspections if needed.
- ☐ Meet with the CRs (Day 100 review team meeting and as needed).
- ☐ Resolve any differences between reviewers if needed.
- ☐ Request amendments (if needed and appropriate).
- ☐ Document the test article information.
- ☐ Review the draft labeling, all further information, and draft FOI Summary section if provided.

For last P submissions:

- ☐ Communicate timelines to CRs for the Ms (Labeling and AOI) and FOI Summary Q submission reviews.
- ☐ Request preparation of the executive summary for the FOI Summary.
- ☐ Prepare for the end game meeting.

FINAL ACTION PACKAGE

- ☐ Determine the final action for the submission.
- ☐ Prepare the appropriate final action letter.
- ☐ Email the sponsor draft labeling changes and the draft FOI Summary section per division procedures.
- ☐ Submit the final action package for division clearance per division procedures.
- ☐ Upload the final action package documents in Appian for close-out.