OFFICE OF NEW ANIMAL PRODUCT EVALUATION AND OFFICE OF GENERIC ANIMAL DRUGS REVIEWER'S CHAPTER

REVIEW OF PROTOCOLS

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I. PURPOSE

This document describes the Office of New Animal Product Evaluation's (ONAPE) and the Office of Generic Animal Drugs' (OGAD) basic procedures for reviewing protocols. This document does not apply to qualitative risk assessments that are not protocols, comparability protocols, or method transfer trial protocols. It does apply to both general framework protocols and their subsequent site-specific protocols for field trials.

II. WHAT IS A PROTOCOL

A protocol is a plan for conducting a study that fully describes the objective(s), design, methodology, study endpoints, statistical considerations, and organization of a study.[1] Sponsors are not required to submit study protocols to us for review. However, sponsors often submit protocols for pivotal studies to us to obtain our concurrence.

Protocols are a submission type that is eligible for shortened review time (SRT) for resubmission as outlined in the ADUFA/AGDUFA Goals letter. Information in the Goals letter and P&Ps 1243.3060 and 1243.3070 should be considered when reviewing this submission type.

III. WHAT PROTOCOLS DO WE REVIEW?

We review every submitted protocol that we determine is for a pivotal study, including protocols that sponsors resubmit. Sponsors may submit protocols for our review and concurrence at any time between the planning stages and the start of the live-phase of the study. We do not review protocols for studies that have already begun. If you receive a protocol and believe the study has already begun, discuss the appropriate course of action with your branch chief.

A "pivotal" study is one that is essential to our decision to approve or deny an application, i.e., a new animal drug application (NADA), an abbreviated new animal drug application (ANADA), a supplement to an (A)NADA, or an application for conditional approval.

[1] Guidance for Industry (GFI) #85 includes definitions for "study protocol" and "study protocol amendments."

Whether a study is pivotal depends on, among other things, the specific new animal drug, the proposed intended uses, and other studies previously conducted or studies that the sponsor plans to conduct. We consider all protocols submitted to the Division of Manufacturing Technologies and the Division of Human Food Safety to be pivotal.

We determine whether a study is pivotal based on a cursory review of the type and objective of the study, not an in-depth examination of the protocol itself. If you cannot determine whether a protocol is for a pivotal study, talk to your branch chief (BC) and/or division director (DD).

Tables provided in Appendix 1 describe the action we should take when a sponsor submits protocols that we determine are for “pivotal” or “non-pivotal” studies.

IV. REVIEWING A PROTOCOL SUBMISSION

A. General

Per the Animal Drug User Fee Act (ADUFA) and Animal Generic Drug User Fee Act (AGDUFA) reauthorization agreements, CVM has agreed to review protocols and provide the sponsor with a letter that will include a “succinct assessment of the protocol; and will state whether the Agency agrees, disagrees, or lacks sufficient information to reach a decision that the protocol design, execution plans, and data analyses are adequate to achieve the objectives of the study.”

“Adequate” in this context means the critical scientific and regulatory elements of the study are acceptable. See Appendix 3 for additional information on the critical scientific and regulatory elements. CVM’s review is not intended to assure the protocol is perfect, nor that it offers the best or most efficient pathway to the study objectives. “Critical” in this context refers to the regulatory science and regulatory compliance elements of the protocol that assure the study can support a regulatory decision. CVM’s review is not intended to examine at all aspects of a protocol in depth.

Those parts of a protocol that do not impact whether critical regulatory science or regulatory compliance elements are adequate are the responsibility of the sponsor/contract laboratory. Our review of the protocol makes it more likely that the study will generate the information needed to satisfy the regulatory requirements for approval.

Sponsors may contact CVM to schedule a meeting to discuss any deviations from protocols made during the study to determine the effect on the study conduct, data collection, or subsequent analysis. If CVM determines it is appropriate for the sponsor to submit an amended protocol, it will be resubmitted as a new protocol. In this case, it is appropriate for the reviewer to review the amended protocol even though the study may have already started.

See Appendix 2 for information on the regulations that apply to protocols.

Protocols may contain justifications or be submitted concurrently with supporting data as described in P&P 1243.2200.

B. Upon receipt of the submission

1. Read the entire cover letter, if provided, to determine the purpose of the submission and whether the protocol is for a pivotal or non-pivotal study (see Section IV). If you are unsure whether you should review the protocol, consult your BC or DD.

2. If the protocol is for a pivotal study, conduct an initial assessment of the protocol and determine whether the protocol is sufficiently complete for review.

3. If you find that the protocol is deficient on its face and your BC and/or DD agree, do not review the protocol. Instead, issue a refuse to review (RTR) letter for the protocol.[2,3] The protocol is deficient if the number or types of errors in the protocol cause you to question the quality of the entire protocol and lead you to conclude that you cannot reasonably review the submission. Examples of these types of errors include lack of detail in the protocol, conflicting information between sections of the protocol, or the absence of important information.

4. If the protocol appears sufficient, determine whether you need to request any consults (e.g., biostatistics, pharmacokinetics, microbiology, manufacturing), and request consulting reviews through Appian.[4] If you are not certain whether a protocol needs a consulting review, ask your BC or the consulting reviewer's BC.

5. If the protocol is a revised protocol, determine if a shortened review time (SRT) was offered and if the requirements for that have been met by the sponsor.[5]

   If we issue the sponsor a protocol non-concurrence letter, they may submit a revised protocol[6] after addressing the deficiencies we identified and any recommendations we made. The determination of whether a revised protocol is eligible for SRT was made when the protocol was previously reviewed.

   Although a revised protocol may be eligible for a SRT based on the comments from the previous review, the sponsor must also submit the revised protocol within 120 days of the non-concurrence letter to be eligible for a SRT. For an eligible revised protocol, if the sponsor resubmits the protocol within 120 days, the review clock is set to 20 days. If the sponsor resubmits the protocol after 120 days of the non-concurrence letter, the review clock is set to 50 days.

   If the revised protocol qualifies for SRT based on the two criteria mentioned above, ensure that the sponsor has certified that the only changes to the protocol are those requested in the non-concurrence letter.

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[2] If a submission is not acceptable for review, issue the letter within the 50-day STARS timeframe for the initial review of protocols.

[3] See P&P 1243.2050 for information on when we can use RTR. See P&P 1243.3030 for information on how to final-out the submission.

[4] See P&P 1243.3200 for information on routing a request for a consulting review through Appian.

[5] See P&Ps 1243.3060 and 1243.3070 regarding shortened review times for pioneer and generic drugs, respectively.

[6] A "revised protocol" refers to a new parent submission that the sponsor may submit following receipt of a CVM final action letter. Minor amendments are not CVM final actions.

If additional changes are present, the protocol may no longer be eligible for SRT. In this case, discuss the appropriate course of action with your BC.

C. Preparation for protocol review

1. Familiarize yourself with the investigational new animal drug (INAD) before you review the protocol. Describe in your review any pertinent information you examined. In addition to information the sponsor provides, some possible sources of information you should review include:

    a. The history of the INAD, any previous approvals of the new animal drug, and any related master file(s), using the administrative files (e.g., Corporate Document Management System (CDMS), Submission Tracking and Reporting System (STARS) Web, and Document Control Unit (DCU). Search the STARS Review Summary field to see if early information was submitted in an A-0000 or H submission that may inform your review. [7]

    b. If there are previous approvals for an (A)NADA with the same or similar active ingredient, familiarize yourself with the approved indications, pharmacology, warnings, contraindications, precautions, and adverse reactions. Look at the protocol review documents for these products. It may be helpful to talk to reviewers who have worked on similar products. Keep in mind that our thinking on protocol design and the conduct of studies evolves over time. You do not have to concur with a protocol simply because we previously concurred with a similar protocol if the science or policies have changed or if the previous determinations are no longer valid or appropriate.

        Several available sources that may contain information on approved drugs and chemicals under investigation are listed below.

        - The Animal Drugs @ FDA database is an electronic database of approved new animal drugs, which you can use to search for drugs with the same active ingredient or indications.

        - You may find related submissions by searching STARS using the chemical name. This search may locate information on similar new animal drugs that are still in the investigational stage.

        - Your BC may be a good source of information about related (J)INADs currently under review.

        - If you determine there has been a previous approval for a similar product, you should read the Memorandum Recommending Approval (MRA) for that (A)NADA. The MRA should include the number of the (J)INAD file. Use this number to find the original review documents.

    c. If there is an approved human drug with the same or similar active ingredient, read the package insert for information about indications, pharmacology, warnings, contraindications, precautions, and adverse reactions.

[7] See P&P 1243.2200

To find out if there is an approved human drug with the same active ingredient, go to the FDA/CDER website and search the Orange Book[8]. This should give you the product name and manufacturer. With that information, you can search the electronic Physicians' Desk Reference (PDR) for the package insert. The PDR, and other useful drug reference information, is available the FDA Library SharePoint Page Internal information redacted., and U.S. National Library of Medicine's Drug Information page.

2. Familiarize yourself with the disease, condition, parasite, or production parameter under investigation.

3. Understand where this study fits into the sponsor's overall development plan. Some information may be available in previous submissions or in the sponsor's cover letter. You can also contact the assigned project manager to discuss information including the project scope (e.g., target species, indication), the sponsor's plans for the project, and how the project fits into the sponsor's overall portfolio (e.g., whether there are related projects).

4. Sponsors are required to promptly report serious adverse events that occur during investigational studies.[9] As you review the protocol, consider under what circumstances you want the sponsor to report adverse events to ONAPE/OGAD as they occur, and what types of adverse events are acceptable to report at the time of the data submission. If the protocol does not address serious adverse event reporting, consider whether this is the appropriate time to communicate with the sponsor on this matter and whether an amendment to the protocol is needed.

5. As you review the protocol, keep in mind that CVM expects sponsors to maintain Part 11 compliance. CVM expects sponsors to comply with the recommendations outlined in the Guidance for Industry, "Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers.[10]. Additional guidance can be found at the following URL: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/guidance-industry-computerized-systems-used-clinical-trials

6. Contact the consulting reviewer(s) (CR) assigned to this submission and make arrangements to discuss the details of the protocol. Some protocols are straightforward and may not require discussion. Others are more complicated and require coordination between the primary reviewer (PR) and the CRs. You can find the names of the consulting reviewers by clicking on the "Amend/Consult" tab in the "Submission Location and Status" screen in STARS Web.
   Some reviewers may choose to review a protocol by inviting CRs to a meeting to discuss the protocol on a section-by-section basis. Participants are expected to read the protocol and prepare comments and/or questions before the review meeting. The primary reviewer or the Consumer Safety Officer (CSO) may

[8] https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

[9] 21 CFR 511.1(b)(8)(ii)

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions

document the discussion held during the protocol review meeting if they feel it is appropriate, the discussion can be documented in the meeting minutes or in a review. Some participants may also choose to write reviews relating to their area of expertise. Reference these meeting minutes and written reviews in your primary review. The primary reviewer or CSO should prepare a letter to the sponsor using the meeting minutes and the contents of any reviews.

D. Elements of protocol review

1. Review the protocol for completeness regarding the inclusion of all appropriate elements of study design, execution plans, and data analyses for the purpose of the study being proposed (target animal safety, effectiveness, residue chemistry, bioequivalence, etc.) with a focus on the primary variables that drive the study results and conclusions that will be used for regulatory decision-making. Check that the design, execution plans, and data analyses ensure the study is adequate to achieve the study objectives.

2. The protocol should state the standard of conduct to which the study will be conducted. The ultimate responsibility for following that stated standard of conduct and assuring the quality and integrity of the study rests with the sponsor who submits the application to CVM. Check to make sure the standard of conduct that will be followed is stated in the protocol. Refer to Appendix 3 for the listed elements of the protocol according to GLP and GCP standards (nonclinical laboratory studies and field effectiveness studies, respectively). CVM will review protocols with standards of conduct other than GCP or FDA GLP in a similar, consistent manner.

3. While reviewers will read the entire protocol submitted, CVM's review is focused on the regulatory science and regulatory compliance elements critical to ensuring that the data generated by the protocol are adequate to meet the study objectives and can be used to support a regulatory decision. **It is not CVM's responsibility to improve protocols or advise sponsors on minor deficiencies or omissions that do not directly impact CVM's ability to determine the adequacy of the protocol.**

    a. CVM will not provide editorial comments on protocols. These include comments regarding the formatting and corrections of typographical or grammatical errors unless they impact a critical study element.

    b. CVM will not require training records, curriculum vitae, or the names of the study director/investigators at the protocol review stage. Training records and curriculum vitae are not required or expected components of protocols (see GLP and GCP references above). Because CVM reviews a draft of a protocol and not the final protocol, it is acceptable for the version of the protocol that CVM reviews to not contain the name of the study director or clinical investigator. These names can and should be added before the final version of the protocol is signed by the appropriate personnel.

    c. CVM will not provide comments regarding compliance with the stated standard of conduct (GLP, GCP, etc.). We expect the sponsor to conduct the study in compliance with the stated standard of conduct and we will check to make sure the standard of conduct that will be followed is stated in the

protocol. The ultimate responsibility for following that stated standard of conduct and assuring the quality and integrity of the study rests with the person (sponsor) who submits the application to CVM. CVM's review focuses on the design, execution plans, and data analyses to ensure the study is adequate to achieve the study objectives. CVM has informed sponsors that CVM's concurrence with a protocol does not convey that CVM reviewed or agreed with the sponsor's compliance (or lack thereof) with the stated standard of conduct.

d. CVM will only consider if the design, execution plans, and data analyses are adequate when deciding whether to send a concurrence or non-concurrence letter, i.e., CVM will not send a non-concurrence letter solely to "improve" a protocol that is otherwise acceptable. If there are non-critical aspects of the protocol that are not adequate, missing, or unclear and we plan to send a non-concurrence letter, we can include comments that otherwise follow the principles of this document. Acceptable reminders for a concurrence letter are outlined in Section V.A of this document.

e. CVM will not provide comments regarding the inclusion of language to address a variety of potential occurrences. A protocol cannot account for every issue or event that may arise and the sponsor is expected to follow reasonable procedures for identifying, documenting, and evaluating all unforeseen issues or events that arise during the conduct of a study.

f. CVM only comments on data capture forms when the issue is believed to compromise the scientific or regulatory validity of the study (e.g., unmasking, or other introduction of bias, forms conflict with protocol procedures, and similar issues).

g. CVM will not require the attachment of all study standard operating procedures (SOPs) to a protocol. A brief description, or SOP excerpt, of sufficient detail for CVM to understand how the study procedure will be executed should be included in a protocol for each of the critical study science and regulatory compliance elements. SOPs could be provided but generally are not required unless that is the only way to provide sufficient detail for CVM to understand and determine the adequacy of a given procedure.

h. CVM will not provide additional comments, beyond the concurrence letter boilerplate language, regarding the creation of the final study report. It is the sponsor's responsibility to understand regulatory requirements and expectations for final study reports and there are a variety of publicly available resources that provide information on final study reports and submission preparation. Alternatively, the sponsor can discuss these topics with CVM outside the review of the protocol.

4. If during your review, you discover that a protocol is deficient (i.e., after the initial refuse to review assessment has been completed), conduct a complete review that is as detailed as possible considering the quality and level of detail of the protocol submission, and document the deficiencies.

If the deficiencies are minor or you have questions that the sponsor may be able to address quickly, follow your division procedures for contacting them. Document in your review all discussions you have with the sponsor, along with any requests for amendments to the protocol. Only request or accept a "minor" amendment if the amendment has a high probability of both making the parent submission complete and leading to a comprehensive review and decision within the initial STARS review timeframe.[11] The sponsor should submit an entire revised protocol including the requested changes for your review before we issue a concurrence letter.

If the sponsor does not submit a minor amendment you have requested, your review should document the sponsor's failure to submit the amendment and you should prepare a protocol non-concurrence letter and, if applicable, use the SRT language.[12]

If a protocol contains anything other than "minor" errors or gaps (which may be corrected through a minor amendment as described above), you should consider the protocol not acceptable, and prepare a letter of non-concurrence and, if applicable, use the SRT language.

E. Elements of revised protocol review

For a revised protocol, focus on whether the sponsor addressed the comments we made in the non-concurrence letter for the previous submission. If the revised protocol was offered SRT and the sponsor has submitted it within the required 120-day timeframe, check to see if the sponsor has certified that they changed only what was requested. Ensure that those changes do not affect other parts of the protocol that you previously considered acceptable. Generally, you should not raise questions about parts of the protocol that we previously considered acceptable. However, if you find new issues or problems that we did not identify in the previous review, discuss with your branch chief whether it is appropriate to inform the sponsor about them in response to the current review. Document the reason(s) for transmitting or not transmitting these comments in your review.

If there have been significant changes in the relevant science or technology (e.g., new or improved assay methods, limits of detection, etc.) since the previous protocol submission, consider how these changes affect your evaluation of the protocol, and whether the sponsor should make additional revisions to the protocol.

Send consulting review requests through Appian to the appropriate branch(es). In addition, request any additional consulting reviews on the revised protocol for sections of the protocol that were not included in the previous version. Discuss the best approach for reviewing the resubmitted protocol with all CRs (See Section V.C.4. above).

F. Writing the protocol review

When writing a review for a protocol, there are certain standards of consistency that we need to sustain across ONAPE/OGAD. For specific types of protocols, follow the

[11] See P&P 1243.3026 for the definition of a "minor" amendment

[12] P&Ps 1243.3060 and 1243.3070 have information about how to decide if a submission qualifies for shortened resubmission or reactivation.

more specific division or branch SOPs. Those SOPs will incorporate these standards and provide additional details on writing reviews for specific types of protocols.

1. Format for the protocol review

   Begin with the ONAPE/OGAD Review template and follow the ONAPE/OGAD general review format, adding secondary or subordinate headings as necessary for clarity.[13]

   Protocol reviews for similar specific types of studies within a division or branch should follow a similar format. For example, all genotoxicity reviews should follow a similar format, but not all reviews written by the toxicology branch will follow the same format. The purpose of using a similar format is to make it easier for a reader to find specific information later.

   Your review should follow the review format for the specific type of protocol submission instead of using the format the sponsor uses. Following the appropriate format will ensure that the review is complete and contains all of the necessary information, including items the sponsors may have omitted.

2. General comments on content

   Describe the protocol by title and protocol or study number and its objectives. Summarize and comment on each critical scientific and regulatory element. In addition, include responses to any specific issues or questions raised by the sponsor in relation to the protocol in its cover letter. Provide comments on any related information or statements that the sponsor submits with the protocol. The review should contain three main points for each element:

   a. A brief summary of each protocol element and reference to the section or page number.

   b. An assessment as to whether the element is acceptable based on your knowledge of the area the element addresses, its consistency with the design of similar studies, and discussions with others in the office. We do not typically transmit these review comments to the sponsor, but you may use them as the basis for the Transmit to Sponsor section. The comments should provide the reader (e.g., branch chief, division director, and other reviewers now and in the future) an overview of the major issues identified in this particular study protocol and how you came to your conclusions. These comments should highlight any fatal flaws or other critical issues concerning the study design. These comments may also discuss specific parts of the protocol that are unusual or precedent setting.

   c. A determination of whether or not a comment should be transmitted to the sponsor, using the guidelines outlined in Section IV.D.3.

      In all cases, except where a decision was made to refuse to review the protocol, the review should be a complete review of the entire protocol.

[13] See P&P 1243.3009 for format information

Document any informal discussions you conducted that aided the review, as well as any additional information you used (for example, published information on disease processes, pertinent to the protocol or proposed indication) in your review. Many people may read your review, and in some cases, we may release it outside the Center.

d. Document any discussions with the consulting reviewers and refer to their written reviews.

3. Conclusions

For a protocol submission, you may: 1) concur with the protocol; or 2) not concur with the protocol.[14]

4. Recommendation(s)

The recommendation(s) section should state which type of correspondence (protocol concurrence, protocol non-concurrence, or protocol non-concurrence with SRT) you recommend sending to the sponsor, and any other administrative procedures you recommend.

5. Transmit to Sponsor

The Transmit to Sponsor section of the review should provide your comments to be included in the letter to the sponsor. Provide clear communication to sponsors through complete, succinct explanations that include relevant context and specific language or concepts, as appropriate.

See Section V below for details about what to include in the concurrence or non-concurrence letter.

V. COMMUNICATION WITH THE SPONSOR

The finalization of the review process includes issuing either a protocol concurrence letter or a protocol non-concurrence letter, with SRT offered, if applicable.

A. Protocol Concurrence

Concurrence is a fundamental agreement between ONAPE/OGAD and the sponsor that we agree with the design, execution, and analyses proposed in the protocol and we will not later alter our perspectives on these issues unless public or animal health concerns become evident that we did not recognize at the time we reviewed the protocol.[15] If CVM concurs with a protocol, concurrence is with critical study design elements but does not imply that CVM has reviewed, or concurs with, protocol details that are not critical elements of the study or that are beyond the scope of CVM's responsibility. A reviewer may note issues in their review but only a limited scope of "reminder" comments are acceptable for inclusion in the protocol concurrence letter.

[14] While we do meet with sponsors to discuss protocols, you should not reach agreements on the details of a protocol or concur with a protocol during a meeting. Advise sponsors to formally submit a protocol for our review if they wish to get our concurrence.

[15] Concurrence does not mean that we concur with the dose interval or withdrawal times that the sponsor proposes.

Reminder comments are limited to:

- reminders on specific items for the data package or corresponding technical section.
- reminders regarding the drug development process (for example, GMP inspection)
- reminders, not related to the current study, that we would like the sponsor to consider for future protocols.

Our concurrence letter should not include suggestions or recommendations to the sponsor for improving the particular protocol.

Include the boilerplate paragraphs regarding the appropriate submission of electronic data and analysis files in the protocol concurrence letter template, as well as other boilerplate paragraphs as appropriate. Any additional reminders can be inserted after these boilerplate comments where indicated by the comment bubble.

If you concur with the submitted protocol, complete the CVM BIMO Selection Tool, which will assist you in determining whether a BIMO inspection should be requested for the study. For further details on this process, refer to SOP 1240.184.001.[16]

B. Protocol Non-concurrence

If any critical scientific or regulatory elements are unacceptable, issue a protocol non-concurrence letter.

Note that the ONAPE/OGAD template for protocol nonconcurrence can be used for protocol non-concurrence letters when SRT is offered and when it is not offered.

Our non-concurrence means that there is no agreement about the protocol design, execution plans, or data analyses and/or that we lack sufficient information to reach a decision that the protocol design, execution plans, or data analyses are adequate to achieve the objectives of the study.

Our non-concurrence letter should be as detailed as possible considering the quality and level of detail of the submitted protocol, and should state whether we disagree, and/or we lack sufficient information to reach a decision about the protocol. Provide feedback to the sponsor on the concerns identified during review that preclude CVM's ability to concur with a protocol. It is critical that our letter provides enough information so that the sponsor understands the basis for our comments. Additionally, the letter can include comments that may improve the quality of the study protocol but are not required for protocol concurrence.

Whenever possible, number the comments in the letter and reference the particular section of the protocol that they address. Our letter should also address any specific protocol-related questions or issues the sponsor included in their cover letter.

The letter will likely include comments to transmit to the sponsor from the consulting reviewers. If changes or clarification, other than minor non-substantive edits, to a consulting reviewer's comments are necessary, obtain concurrence from the consulting reviewer(s) regarding the modifications. If you and the CR cannot agree on

[16] See SOP: 1240.184.001 Using the BIMO Selection Tool

the transmittal, then discuss the issue with the consulting reviewer(s) and their supervisor(s). When you do not use the CR's original language, document in the primary review the actual language that will be in the letter, and how the decision was reached. Identify who was involved in the decision and how those involved reached agreement on the language. If a consulting reviewer's comments are not sent to the sponsor, document in the primary review why that decision was made.

If a protocol qualifies for SRT, send a protocol non-concurrence SRT offered letter.

VI. COMPLETING THE FINAL ACTION PACKAGE

Follow the procedures in P&P 1243.3030 when you complete the final action package. If you are offering SRT for resubmission, also follow the procedures in P&Ps 1243.3060 or 1243.3070, for INADs and JINADs, respectively. For INAD protocols that are associated with raw data agreement H submissions, the PR enters the STARS submission ID for the H raw data submission (I-H-RD) in the Review Summary field in Appian.[17]

VII. REFERENCES

Code of Federal Regulations (Title 21)

Part 58 – Good Laboratory Practice for Nonclinical Studies

§58.1, Scope

§58.120, Protocol

Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals

Part 226 – Current Good Manufacturing Practice for Type A Medicated Articles

Part 514 – New Animal Drug Applications

§514.8, Supplemental new animal drug applications

§514.111, Refusal to approve an application

§514.117, Adequate and well-controlled studies

Guidance for Industry

#3 General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals

#35 Bioequivalence Guidance

#63: Validation of Analytical Procedures: Definition and Terminology

#64: Validation of Analytical Procedures: Methodology

[17] Refer to P&P 1243.4095 Review of Raw Data H Submission for Target Animal Safety Studies.

#85 Good Clinical Practice (VICH GL9)

#106 The Use of Published Literature in Support of New Animal Drug Approvals

#119 Guidance for Industry and Reviewers: How the Center for Veterinary Medicine Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug

#185 Target Animal Safety for Veterinary Pharmaceutical Products

Guidance for Industry: Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers

CVM Standard Operating Procedures

1240.184.001 – Using the Bioresearch Monitoring (BIMO) Selection Tool

CVM Program Policy and Procedures Manual – ONAPE and OGAD Reviewer's Chapter

1243.2050 – Refuse to File and Refuse to Review

1243.2200 – Submission and Review of Early Information (EI) Prior to Presubmission Conferences and Protocol Review

1243.3009 – Format and Style Conventions for Reviews and Submission Summaries

1243.3026 – Amending and Resetting the Clock on Submission Tracking and Reporting System (STARS) Submissions

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

1243.3060 – Implementing Shortened Review Times for New Animal Drug Application Reactivations and Investigational New Animal Drug Resubmissions Using eSubmitter

1243.3070 – Implementing Shortened Review Times for Abbreviated New Animal Drug Application Reactivations and Generic Investigational New Animal Drug Resubmissions

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

1243.4095 – Review of Raw Data Agreement H Submission for Target Animal Safety Studies

VIII. VERSION HISTORY

October 24, 2005 – original version

April 26, 2010 – revised to incorporate ERA processes. The information currently in the P&P was updated as necessary to conform with current ONADE practices.

December 14, 2015 - discontinue ERA procedures and incorporate shorter review times and Appian procedures. The sponsor notification email is removed from the process.

July 1, 2016 – Updated formatting and redacting internal information.

November 28, 2018 – Updated to put into current format and to remove references to the retired P&P 1243.3022 Implementing the User Fee Acts (ADUFA III, AGDUFA II) of 2014.

April 16, 2019 – Updated information regarding shortened review and provided other minor edits for clarity.

August 15, 2019 – Edited to include information on serious adverse event reporting and update the titles of references in the reference section.

April 20, 2020 – Updated to reference that early information may have been submitted in an A-0000 or H submission and can be found by searching review summaries in the STARS history for the file and that may inform the person doing the protocol review.

August 12, 2020 – Updated to include information about the new CVM BIMO Selection Tool and reference the SOP about the Tool.

September 23, 2020 – Updated to reflect that there is now one protocol non-concurrence letter that can be used for non-concurrence letters when shortened review is offered and when it is not offered.

April 22, 2021 – Updated to include reasonable expectation of effectiveness information in Section III. Updated to Change reference to Appendix A and B to Appendix 1 and 2.

July 14, 2022 – Quality systems review for minor formatting updates.

March 12, 2025 – Update to ONAPE/OGAD reorganization. Updated formatted template style, Arial font size: 11. Updates included changes made to the P&P as a result of the Protocol P&P working group which had representation from each Division. These updates include reorganization, revisions, and added parameters (or boundaries) of protocol review to provide clarification to help reviews understand how to implement the principles of protocol review when completing their reviews.

July 30, 2025 – Updated to add the Office of Generic Animal Drugs (OGAD) to both the header and footer.

July 13, 2026 – Added the following sentence to Section VI, “For protocols that are associated with raw data agreement H submissions, the PR enters the STARS submission ID for the H raw data submission (I-H-RD) in the Review Summary field in Appian." A footnote was also added to the sentence to refer back to P&P1243.4095 Review of Raw Data Agreement H Submission for Target Animal Safety Studies.

APPENDIX 1. DECISION

Table 1: Action ONAPE/OGAD will take when ONAPE/OGAD determines a protocol is pivotal

Sponsor action	**ONAPE/OGAD will:**
Sponsor requested a review of a protocol they think is pivotal *OR* Sponsor requested a review of a protocol without stating whether or not it is pivotal	1. Examine the submission AND: • Refuse to review the submission (final action code REFUSE REV) if the protocol is insufficient or of unacceptable quality; *OR* • Perform a "complete review" within the STARS timeframe. Notify the sponsor of our decision using the appropriate letter: • protocol concurrence; • protocol non-concurrence; or • protocol non-concurrence with SRT.
Sponsor requested a review of a protocol they think is non-pivotal	Inform the sponsor that the protocol is for a study we consider to be pivotal and see if we can reach agreement. If we cannot reach agreement and the sponsor has not convinced us the study is non-pivotal, follow the steps in the first cell in this column.
Sponsor did not specify whether or not to review a protocol they think is pivotal *OR* Sponsor did not specify whether or not to review a protocol without stating whether it is pivotal or not	Inform the sponsor that we will review the protocol. Then follow the steps in the first cell in this column.
Sponsor requested we file a protocol they state is pivotal without review *OR* Sponsor requested we file a protocol without review and did not state whether or not they think it is pivotal	Inform the sponsor that we will review the protocol. Then follow the steps in the first cell in this column.
Sponsor did not specify whether or not to review a protocol they think is non-pivotal *OR* Sponsor requested we file a protocol they think is non-pivotal without review	Inform the sponsor that the protocol is for a study we consider to be pivotal and see if we can reach agreement. If we cannot reach agreement and the sponsor has not convinced us the study is non-pivotal, then follow the steps in the first cell in this column.

Table 2: Action ONAPE/OGAD will take when ONAPE/OGAD determines a protocol is non-pivotal

Sponsor action	**ONAPE/OGAD will:**
Sponsor requested a review of a protocol they think is pivotal *OR* Sponsor requested a review of a protocol without stating whether or not it is pivotal	Inform the sponsor that the study is not pivotal. Unless the sponsor convinces us that the protocol is for a pivotal study, we will refuse to review the submission (final action code REFUSE REV) and will explain in our letter to the sponsor that we do not consider the protocol to be reviewable because it is for a non-pivotal study.
Sponsor did not specify whether or not to review a protocol they think is pivotal *OR* Sponsor did not specify whether or not to review a protocol without stating whether or not it is pivotal	Inform the sponsor that the study is not pivotal. Unless the sponsor convinces us that the protocol is for a pivotal study, we will refuse to review the submission (final action code REFUSE REV) and will explain in our letter to the sponsor that we do not consider the protocol to be reviewable because it is for a non-pivotal study
Sponsor requested review of a protocol they think is non-pivotal *OR* Sponsor did not specify whether or not to review a protocol they submitted they think is non-pivotal	Refuse to review the submission (final action code REFUSE REV) because the protocol is for a non-pivotal study and we do not consider the protocol to be reviewable.
Sponsor requested we file a protocol they think is pivotal without review	Inform the sponsor that the study is not pivotal. Unless the sponsor convinces us that the protocol is for a pivotal study, we will RTR the submission (final action code REFUSE REV) and explain in the letter that we do not consider the protocol to be reviewable because it is for a non-pivotal study.
Sponsor requested we file a protocol without review and did not state whether or not it is pivotal *OR* Sponsor requested we file a protocol without review and stated they think the protocol is non-pivotal	Write a memorandum to the file that indicates we believe the protocol is for a study that is not pivotal and thus not reviewable. We then close the submission with the final action code FNR/MEMO.

APPENDIX 2. REGULATIONS THAT RELATE TO SAFETY AND EFFECTIVENESS

A. Non-clinical Laboratory Safety Studies

Sponsors must conduct all non-clinical laboratory safety studies that support or are intended to support an approval in accordance with Good Laboratory Practice (GLP) regulations (21 CFR Part 58).[18] 21 CFR §58.120 describes the requirements for protocols for these studies.

B. Adequate and Well-controlled Effectiveness Studies

We may refuse to approve an NADA if it does not include "substantial evidence" of effectiveness.[19] Substantial evidence consists of one or more "adequate and well-controlled studies".[20] 21 CFR §514.117(b) describes the characteristics required for protocols for adequate and well-controlled effectiveness studies. Effectiveness studies include clinical studies intended to evaluate effectiveness for a pioneer product using bioequivalence methodologies. Adequate and well-controlled studies include studies such as, a study in target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study. Sponsors should conduct these studies in accordance with Good Clinical Practice (see GFI #85).

Adequate and well-controlled foreign studies may provide substantial evidence that a new animal drug is effective.[21] The utility of such studies depends upon whether the sponsor sufficiently addresses the potential differences such as animal breeds, genetic composition within a breed, diseases, nutrition, and husbandry practices between the foreign country and the United States. Where these differences have no impact on an animal's response to a new animal drug, adequate and well-controlled foreign studies may support a finding by substantial evidence that a new animal drug is effective. Sponsors may also use published literature as substantial evidence of effectiveness if we have access to the necessary documentation. [22]

C. Bioequivalence Protocols for Generic New Animal Drug Approvals

Sponsors demonstrate the safety and effectiveness of a generic new animal drug by showing that the generic new animal drug is bioequivalent to an approved pioneer new animal drug. Sponsors must conduct all non-clinical laboratory bioequivalence studies they submit in support of an ANADA approval in compliance with GLP regulations, 21 CFR Part 58.

[18] With respect to each nonclinical laboratory study contained in an application, the submission must contain either a statement that the sponsor conducted the study in compliance with the good laboratory practice regulations set forth in part 58 of this chapter, or, if the sponsor did not conduct the study in compliance with such regulations, a brief statement of the reasons for noncompliance [21 CFR 514.1(b)(12)(iii)].

[19] See 21 CFR §514.1(b)(8)(ii)

[20] See 21 CFR §514.4(a)

[21] See 21 CFR §514.4 (b)(3)(ii)

[22] See GFI #106

APPENDIX 3. CRITICAL ELEMENTS FOR A SAFETY OR EFFECTIVENESS PROTOCOL

This section includes requirements and recommendations but is not intended to be an all-inclusive list for you to consider when reviewing a protocol.

Note that for both safety studies and effectiveness studies, the requirements include the name and address of the testing facility or study sites, study contacts, and records to be maintained (handling of records). Testing facilities, study personnel, study locations, and details on the handling of records do not have to be specifically identified in a draft protocol for CVM to concur. Note, as part of our regulatory review of an effectiveness protocol we will need to understand how the sponsor plans to address the overall requirements of the substantial evidence regulations, including inferential value and independent substantiation. While the details may not be known at the time of our protocol review, the sponsor should provide enough information in the protocol, in a meeting or in other documented communication with CVM so that we understand their plans for meeting these regulatory requirements.

A. Safety Studies

1. 21 CFR §58.120 requires protocols for all non-clinical laboratory safety studies to contain the following information, as applicable:[23]

    - descriptive title and statement of the study's purpose;
    - identification of the test and control articles by name, chemical abstract number, or code number;
    - sponsor name and the name and address of the testing facility at which the study is being conducted;
    - number, body weight range, sex, source of supply, species, strain, sub-strain, and age of the test system;
    - procedure for identification of the test system;
    - description of the experimental design, including the methods to control bias;[24]
    - description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description must include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than those established by the specifications;

[23] Draft protocols for safety studies may not contain all details listed here [e.g., location of study, name of study director (investigator if for effectiveness studies), or signature, etc.], but we still may consider them sufficiently complete for review and concurrence. Final protocols must contain the required information identified in a regulation. Talk with your BC if you have questions about information missing from a protocol.

[24] Masking (blinding) personnel to treatment is one method for reducing bias. GLP regulations do not require that personnel involved in the study be masked to treatment. However, for certain types of safety studies it may be appropriate for the sponsor to address masking of personnel in the protocol. If it is unclear whether the protocol provides adequate methods for controlling bias, discuss with your BC or DD.

- each dosage level (expressed in mg per kg of body weight or other appropriate units) of the test or control article to be administered and the method and frequency of administration;
- type and frequency of tests, analyses, and measurements to be made;[25]
- records to be maintained;
- approval date of the protocol by the sponsor and the study director's dated signature. Sponsors must document all changes in or revisions of an approved protocol and the reasons for them, and the study director must sign and date them and maintain them with the protocol; and
- statement of the proposed statistical methods to be used.

2. In addition to the above required elements of a protocol, the following final guidance documents contain recommendations relating to safety study protocol elements:

   a. For animal safety studies:

      - GFI #185, Target Animal Safety for Veterinary Pharmaceutical Products.

   b. For human food safety studies:

      - GFI #3: General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals may be applicable;
      - GFI #63: Validation of Analytical Procedures: Definition and Terminology; and
      - GFI #64: Validation of Analytical Procedures: Methodology.

   Consult your BC to determine which GFIs are applicable or for further instruction.

B. Effectiveness Studies

1. A protocol for an adequate and well-controlled study must contain the following (per 21 CFR §514.117):

   - a clear statement of the study objectives;
   - a statement acknowledging the applicability of, and intention to follow, a standard of conduct acceptable to FDA; [26]
   - an identification number correlated with the specific formulation and production process used to manufacture the new animal drug used in the study;

[25] To allow you to adequately review the protocol, the sponsor should include in this information the rationale for conducting the particular tests and analyses or measurements the sponsor includes in the protocol. You may do this by referring to the appropriate guidance document(s).

[26] GFI #85 contains the standard of conduct we currently recommend.

- a description of the precise nature of the study design; e.g., the treatment period durations, whether it is a parallel, sequential, or crossover design; and the determination of the sample size;[27]

- the method description for selecting animals for the study;[28]

- the method description for the assignment of animals to an experimental unit to account for pertinent variables and the method of assignment of a treatment or a control to the experimental units;

- an explanation of the methods of observation and recording of the animal response variables,[29] and documentation of the methods, such as "blinding" or "masking," used in the study for excluding or minimizing bias in the observation; and

- a description of the methods for conducting the study, including any appropriate analytical and statistical methods used to collect and analyze the data resulting from the conduct of the study, a description of the criteria used to assess response, and, when appropriate, a justification of the selection of the methods to assess animal response.

2. In addition to the characteristics above, the following guidance contains recommendations relating to effectiveness study protocol characteristics:

    - GFI #85: Good Clinical Practice provides recommendations relating to the design and review of protocols for effectiveness studies.

C. Bioequivalence Studies for Generic New Animal Drugs

1. Non-clinical laboratory bioequivalence studies intended to support generic new animal drug approvals must comply with GLP regulations (21 CFR §58.1). Thus, the protocols for these studies must contain the information we describe in Section A.

2. We have developed the following GFIs relating to the review and approval of generic drugs. For in vitro dissolution testing of solid oral dosage forms, palatability studies, and other studies (solubility profile), consult your BC for guidance.

    - For bioequivalence studies for generic new animal drugs, refer to GFI #35: Bioequivalence Guidance. This GFI also provides guidance on human food safety considerations for generic new animal drugs.

    - For food safety studies, specifically tissue residue depletion studies to establish drug withdrawal/milk discard periods, see GFI #3: General Principles for Evaluating

[27] An adequate and well-controlled study uses a design that permits a valid comparison with one or more controls to provide a quantitative evaluation of drug effects. When describing the precise nature of the study, the sponsor should describe the control used. Possible controls (placebo concurrent control; untreated concurrent control; active treatment concurrent control; historical control) are described in 21 CFR §514.117(b)(4)(i)-(iv).

[28] This should include the inclusion and exclusion criteria for the study.

[29] This should include an explanation of what animal responses the study will record and how often the study will record the responses. In addition, if appropriate to the protocol under review, the sponsor should explain why they selected to record those responses and document the level of training the observer of the animals or person documenting the responses is expected to have.

the Human Food Safety of New Animal Drugs Used in Food-Producing Animals. See also Appendix 3, Section A.2. above.

Consult your BC if you need further instruction.

D. Additional Information

You may need additional information to review any protocol. Although the regulations do not require that sponsors submit the following information as part of a protocol for a safety, effectiveness, or bioequivalence study, you may find that this information is important or even critical to your review and the conduct of the sponsor's study. Review this information if the sponsor provides it. If the sponsor does not provide it, you may request some or all of this information. Consult your BC or DD to determine whether a sponsor may amend a protocol that lacks this additional information or whether you should send a non-concurrence letter.

1. Copies of data capture forms to record treatment assignment, drug administration, clinical examinations and observations, sample collection, animal recovery, necropsy, and other data that will contribute to the determination of safety, effectiveness, or bioequivalence;

2. Standard operating procedures (SOPs) referenced in the protocol; specific examples may include copies of:

    - SOPs pertaining to the collection of primary variables or other data that will contribute to the determination of safety, effectiveness, or bioequivalence;

    - SOPs describing the criteria by which sponsors will select samples (e.g., tissues, blood, feed, water) for laboratory reanalysis;

    - SOPs describing the criteria by which sponsors will designate values or samples as outliers to exclude from the data analysis; and

    - The methods the sponsor proposes for dealing with missing or incomplete data from the study due to various causes, such as lack of compliance, illness or injury resulting in removal, or human error.

3. Other information you consider necessary to complete the review. See GFI #85: for a checklist of items we recommend including in protocols for clinical studies.