OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF PROTOCOLS

I. PURPOSE

This document describes the Office of New Animal Drug Evaluation's (ONADE) basic procedures for reviewing protocols.[1]

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.[2]

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. Our review of the protocol for a pivotal study makes it more likely that the study will generate information the sponsor needs to demonstrate whether the drug is safe and effective for the proposed conditions of use of the drug.

Protocols are a submission type that is eligible for shortened review time 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 protocol we determine is for a pivotal study, including protocols that sponsors resubmit. 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. Whether a study is pivotal depends on, among other things, the specific new animal drug, the proposed intended uses, and other studies

[1] This document does not apply to qualitative risk assessments that are not protocols, comparability protocols, and method trial protocols. It does apply to both general framework protocols and their subsequent site-specific protocols for field trials.

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

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 team leader, division director, or both.

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

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. Protocols are submitted to a sponsor's investigational file. For pioneer drugs this is an investigational new animal drug (INAD) file and for generic drugs it is a generic investigational new animal drug (JINAD) file. 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 team leader.

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 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.[3]

B. Immediately 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 team leader or division director.

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] P&P 1243.2200 Submission and Review of Early Information (EI) Prior to Presubmission Conferences and Protocol Review

If you find that the protocol is deficient on its face and have concurrence from your team leader and/or division director, do not review the protocol. Instead, issue a letter refusing to review the protocol.[4,5] 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.

3. If the protocol appears sufficient at the time when you first receive it, determine whether you need to request any consults (e.g., biostatistics, pharmacokinetics, microbiology, manufacturing, and request consulting reviews through Appian.[6] If you are not certain whether a protocol needs a consulting review, ask your team leader or the leader of the consulting team.[7]

4. If we issue the sponsor a protocol non-concurrence letter or refuse to review letter, they may submit a revised protocol[8] after addressing the deficiencies we identified and any recommendations we made. The determination of whether a revised protocol is eligible for shortened review timeframe was made when the protocol was previously reviewed.

   Although a revised protocol may be eligible for a shortened review timeframe 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 shortened review timeframe. 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 a shortened review timeframe based on the two criteria mentioned above, ensure that the sponsor certified that the only changes to the protocol are those requested in the non-concurrence letter. If additional changes are present, the protocol may no longer be eligible for a shortened review timeframe. In this case, discuss the appropriate course of action with your team leader.

C. Reviewing the Protocol

When you begin reviewing the protocol, consider the following information, as appropriate:

1. Familiarize yourself with the investigational new animal drug before you review the protocol. Describe in your review any pertinent information you examined.

[4] If a submission is not acceptable for review, you should issue the letter within the 50-day STARS timeframe for the initial review of protocols.
[5] See P&P 1243.2050 for information on when we can use refuse to review, and see P&P 1243.3030, for information on how to final-out the submission.
[6] See P&P 1243.3200 for information on routing a request for a consulting review through Appian
[7] For example, if you or your team leader are uncertain whether a protocol needs a biostatistics review, send the protocol to biostatistics as a consulting review.
[8] 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.

In addition to any information the sponsor provides, some possible sources of information you should review include:

a. The history of the investigational use of the new animal drug, 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.[9]

b. If there are previous approvals for an (A)NADA with the same or similar active ingredient, you should familiarize yourself with the approved indications, pharmacology, warnings, contraindications, precautions, and adverse reactions. You should also 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 conducting 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/appropriate.

   Several available sources that may contain information on approved drugs and chemicals under investigation:

   - 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.
   - In addition, 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 team leader 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 information about indications, pharmacology, warnings, contraindications, precautions, and adverse reactions.

   To find out if there is an approved human drug with the same active ingredient, go to the FDA/CDER website and search in the Orange Book. This should give you the product name and manufacturer. With that

[9] See P&P 1243.2200

information, you can search the electronic Physicians' Desk Reference (PDR) for the package insert. The PDR, and other useful drug reference information, is available on the inside.FDA website, the FDA Library 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. Make sure you 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 (target species, indication, etc.), the sponsor's plans for the project, and how the project fits into the sponsor's overall portfolio (for example, whether there are related projects).

4. Sponsors are required to promptly report serious adverse events that occur during investigational studies.[10] As you review the protocol, consider under what circumstances you will want the sponsor to report adverse events to ONADE 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 now is the time to communicate with the sponsor on this matter and whether an amendment to the protocol is needed.

5. In order to maintain Part 11 compliance, CVM expects sponsors to comply with the recommendations outlined in the May 2007 Guidance for Industry (GFI) #105, Computerized Systems Used in Clinical Investigations. The guidance is at the following URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computerized-systems-used-clinical-investigations.

6. Contact the consulting reviewer(s) 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 some coordination between the primary reviewer and the consulting reviewers. You can find the names of the consulting reviewers by clicking on the "Amend/Consult" tab in the "Submission Location and Status" screen in CDP STARS Web.

   Some reviewers may choose to review a protocol by inviting consulting reviewers to a meeting to discuss concerns on a section-by-section basis. We expect participants to read the protocol and prepare some comments or questions before the review meeting. The Consumer Safety Officer (CSO) or primary reviewer may document the discussion during the protocol review meeting if they feel that it is appropriate, using whatever format they feel is appropriate (i.e., meeting minutes, documented in the review). Some participants may also choose to write reviews relating to their area of

[10] 21 CFR 511.1(b)(8)(ii)

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 minutes of the meeting and contents of any formal reviews.

7. Review the entire protocol. If during your review, you discover that a protocol is deficient (i.e., after the initial assessment was 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 (telephone or e-mail), along with any requests for amendments to the protocol. Only request or accept a "minor" amendment if the amendment has a high probability both to make the parent submission complete and to lead 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 with shortened review timeframe language, if applicable.[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, with shortened resubmission review timeframe language, if applicable.

8. For a revised protocol, specifically 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 they changed only what was requested. Ensure those changes do not affect other parts of the protocol 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 team leader 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.

[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.

Generally, for a revised protocol, send consulting review requests through Appian to the appropriate team(s). 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 consulting reviewers (See section V. C. 4. above).

D. Writing the Review for the Protocol Submission

When writing a review for a protocol submission, there are certain standards of consistency that we need to sustain across ONADE. For specific types of protocols, a reviewer should follow more specific division or team 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 ONADE Review template and follow the ONADE 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 team should follow a similar format. For example, all genotoxicity reviews should follow a similar format, but not all reviews written by the toxicology team will follow the same format. The purpose for 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. The review should summarize and comment on each important protocol or study design 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 element of the sponsor's protocol and reference to 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 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., team leader, division director, and other

[13] See P&P 1243.3009 for format information.

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. If an element of the protocol is unacceptable, state the reasons, and determine whether the item should be transmitted to the sponsor, using a risk-based approach. What is the risk of not transmitting the comment? What is the value added in transmitting the comment? 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.

   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.

3. Conclusions

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

4. Recommendations

   The recommendation(s) section should state which type of correspondence (protocol concurrence, protocol non-concurrence, or protocol non-concurrence with shortened resubmission review timeframe) 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 for the letter to the sponsor. If changes or clarification to a consulting reviewer's transmit to sponsor language are necessary, obtain concurrence from the consulting reviewer(s) regarding the modifications. If you and the consulting reviewer cannot agree on the transmittal, then discuss the issue with the appropriate reviewer(s) and their supervisor(s). When you do not use the consulting reviewer's original transmit to sponsor language, document in the final review the actual language that will be in the letter, and how we made that decision. Identify who was involved in the decision to use this language and how those involved reached agreement on the language.

   If you do not concur with the protocol, this section should include specific comments for the sponsor identifying any sections that are missing or need revision and should tell the sponsor if we need any additional information.

[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. You should advise sponsors to formally submit a protocol for our review if they wish to get our concurrence.

Comments should refer to the sponsor's numbered sections of the protocol, when possible.

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 shortened resubmission review timeframe offered, if applicable.

A. Protocol Concurrence

Concurrence is a fundamental agreement between ONADE 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 are evident that we did not recognize at the time we reviewed the protocol.[15] Protocol concurrence does not guarantee that the results of the study will support a particular finding or approval of the new animal drug.

Our letter should not include suggestions to the sponsor for improving the particular protocol or a similar protocol, if and when, it is submitted in the future. Include the boilerplate paragraph regarding the appropriate submission of electronic data and analysis files in the protocol concurrence letter template.

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 1240.3610.001.[16]

B. Protocol Non-concurrence

If you do not concur with a submitted protocol, you should issue a protocol non-concurrence letter.

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, or we lack sufficient information to reach a decision about the protocol. It is critical that our letter provide enough information so that the sponsor understands the basis for our comments.

Whenever possible, number the comments in the letter and reference the particular section of the protocol they address. Our letter should also address any

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

[16] Link to the SOP:
Internal information redacted

specific protocol-related questions or issues the sponsor included in their cover letter.

If a protocol qualifies for shortened resubmission review timeframe, send a protocol non-concurrence shortened review timeframe offered letter.

Note: that our ONADE template for protocol nonconcurrence can be used for protocol non-concurrence letters when shortened review timeframe is offered and when shortened review timeframe is not offered.

VI. COMPLETING THE FINAL ACTION PACKAGE

Follow the procedures in the P&P 1243.3030, when you complete the final action package. If you are offering a shortened review timeframe, also follow the procedures in 1243.3060 INADs or 1243.3070 for JINADs.

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

#85 Good Clinical Practices

#105 Computerized Systems Used in Clinical Investigations

#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

CVM Standard Operating Procedures

1240.3184.001 – Using the Bioresearch Monitoring (BIMO) Selection Tool

CVM Program Policy and Procedures Manual – ONADE 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

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.

APPENDIX 1: DECISION MATRICES

Table 1: Action ONADE will take when ONADE determines a protocol is pivotal

Sponsor action	ONADE will
Sponsor requested a review of a protocol they think is pivotal OR Sponsor requested a review of a protocol without stating whether it is pivotal or not	Examine the submission AND: Refuse to review the submission (final action code 065) if the protocol is insufficient or of unacceptable quality; OR Perform a "complete review" within the STARS timeframe. Notify the sponsor of our decision by issuing the appropriate letter: protocol concurrence protocol non-concurrence protocol non –concurrence with shortened review timeframe
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, and 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 they think it is pivotal or not	Inform the sponsor that we will review the protocol, and 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, follow the steps in the first cell in this column.

Table 2: Action ONADE will take when ONADE determines a protocol is non-pivotal

Sponsor action	ONADE will
Sponsor requested a review of a protocol they think is pivotal OR Sponsor requested a review of a protocol without stating whether it is pivotal or not	Inform the sponsor that the study is not pivotal. Unless sponsor convinces us that the protocol is for a pivotal study, we will refuse to review the submission (final action code 065) 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 to review a protocol without stating whether it is pivotal or not	Inform the sponsor that the study is not pivotal. Unless sponsor convinces us that the protocol is for a pivotal study, we will refuse to review the submission (final action code 065) 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 to review a protocol they submitted they think is non-pivotal	Refuse to review the submission (final action code 065) 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 sponsor convinces us that the protocol is for a pivotal study, we will refuse to review the submission (final action code 065) and will explain in the letter to the sponsor 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 it is pivotal or not 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 FNR w/memo (final action code 009).

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).[17] 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.[18] Substantial evidence consists of one or more "adequate and well-controlled studies."[19] 21 CFR §514.117(b) describes the characteristics 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 lab animals, field study, bioequivalence study, or an in vitro study. Sponsors should conduct these studies in accordance with Good Clinical Practice (GFI #85).

Adequate and well-controlled foreign studies may provide substantial evidence that a new animal drug is effective.[20] 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 necessary documentation.[21]

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 Good Laboratory Practice regulations, 21 CFR Part 58.

[17] 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)).

[18] See 21 CFR §514.1(b)(8)(ii).

[19] See 21 CFR §514.4(a).

[20] See 21 CFR §514.4 (b)(3)(ii)

[21] See GFI #106.

APPENDIX 3: INFORMATION A SAFETY OR EFFECTIVENESS PROTOCOL SHOULD CONTAIN

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

A. Safety Studies

1. 21 CFR §58.120 requires protocols for all non-clinical laboratory safety studies to contain the following information, as applicable:[22]

   - A descriptive title and statement of the purpose of the study
   - identification of the test and control articles by name, chemical abstract number, or code number;
   - the name of the sponsor and the name and address of the testing facility at which the study is being conducted;
   - the number, body weight range, sex, source of supply, species, strain, sub-strain, and age of the test system;
   - the procedure for identification of the test system;
   - a description of the experimental design, including the methods for the control of bias;[23]
   - a 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 established by the specifications;
   - each dosage level, expressed in milligrams per kilogram 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;[24]

[22] Draft protocols for safety studies may not contain all of the details listed here (for example, 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 team leader if you have questions about information missing from a protocol.

[23] 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, you should discuss it with your team leader or division director.

[24] 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).

- records to be maintained;
- date of approval of the protocol by the sponsor and the dated signature of the study director. Sponsors must make certain all changes in or revisions of an approved protocol are documented and the reasons for them and the study director must sign and date them and maintain them with the protocol; and
- a 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 Principals 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,
      - GFI #64: Validation of Analytical Procedures: Methodology, Final Guidance,

      Consult with your team leader to determine which guidances are applicable, or if you need further instruction.

B. Effectiveness Studies

1. A protocol for an adequate and well-controlled study must contain:[25]

   - 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 which can be correlated with the specific formulation and production process used to manufacture the new animal drug used in the study;

[25] See 21 CFR §514.117
[26] GFI #85: contains the standard of conduct we currently recommend.

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

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

- a description of the method of assignment of animals to an experimental unit to account for pertinent variables and 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). Therefore, the protocols for these studies must contain the information we describe in section A. above.

2. We have developed the following guidance documents 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 team leader for guidance.

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

[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.

- For food safety studies, specifically tissue residue depletion studies to establish drug withdrawal/milk discard periods, see GFI #3: General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals. See also section A 2., human food safety studies, above.

Consult with your team leader 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 team leader or division director to determine whether a sponsor may amend a protocol which 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 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, etc.) 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.[30]

[30] See GFI #85: for a checklist of items we recommend including in protocols for clinical studies.