REVIEW OF PROTOCOLS

I. PURPOSE

This document describes our (the Office of New Animal Drug Evaluation's (ONADE)) basic procedures for reviewing protocols and we provide appendices detailing the review of safety and effectiveness protocols submitted by sponsors.[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] The term protocol includes the original protocol and all related amendments. The protocol may include plans for presenting study results in the final study report or submitting study results to us in electronic format.

[1] This document does not apply to qualitative risk assessments that are not protocols (i.e., E or F submissions), 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."

We code protocols submitted by sponsors to their investigational files (INAD/JINAD-investigational new animal drug and generic investigational new animal drug respectively) in our Submission Tracking and Reporting System (STARS) using the submission type code "E" for protocols without data, and "F" for protocols with data.[3]

III. ARE SPONSORS REQUIRED TO SUBMIT A PROTOCOL?

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.

IV. 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 (a new animal drug application (NADA), an abbreviated new animal drug application (ANADA), or a supplement to either). Whether a study is pivotal depends on, among other things, the specific new animal drug, the proposed intended uses, and other studies already conducted or studies that the sponsor plans to conduct.

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. We consider all protocols submitted to the Division of Manufacturing Technologies and the Division of Human Food Safety to be pivotal. If you (the reviewer) cannot determine whether a protocol is for a pivotal study, you should talk to your team leader, division director, or both. If you still cannot reach a decision on whether a protocol is for a

[3] We do review protocols for aquaculture drugs that sponsors include as part of annual project plans. ONADE will only review protocols for pivotal studies for a drug (including aquaculture drugs) that we code as an "E" or "F" submission. Follow division SOPs if you are a reviewer in the Division of Manufacturing Technologies and ask about submissions we allow others to submit protocols under NADA example old approvals that did not have an INAD submit protocols to NADA to HFS receive a protocol under the NADA, ANADA, or VMF.

pivotal study, you should discuss the matter with the Science Policy Advisor or a member of the Policy Team.

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

V. REVIEWING A PROTOCOL SUBMISSION

A. General

Sponsors may submit protocols for our review and concurrence at any time between the planning stages and completion of the study. As a reviewer, you should review a protocol for a pivotal study, regardless of the stage of conduct. If we receive a protocol electronically, you are to process it in accordance with procedures we established for electronic submissions.

B. Immediately upon receipt of the submission:

1. You should read the entire cover letter to determine the purpose of the submission and determine whether the protocol is for a pivotal study or not (see Section IV). If you are still unsure whether you should review the protocol, consult your team leader or division director.

   Sometimes sponsors will include multiple requests in the protocol submission. If we would normally code these in STARS as individual submissions, you should separate the requests and get them appropriately coded in STARS so that you (or other reviewers, if appropriate) can review and track each request.

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

   If you find that the protocol is deficient on its face, you should not review the protocol. You should instead issue a letter refusing to review the protocol.[4,5]

[4] Although the timelines in P&P 1243.3022 and GFI #119 allow 60 days to determine if a submission is acceptable for review you should issue the letter within the 50 day STARS timeframe for the review of protocols.

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, you should, determine whether you need to request any consultations (e.g., biometrics, pharmacokinetics, microbiology, pathology) and make such requests through STARS.[6] If you are not certain whether a protocol needs a consulting review, you should ask your team leader or the leader of the consulting team.[7] Consulting reviewers often provide input about the study design, proposed measurements, and other aspects of the protocol that can save review time and review cycles. For example, a biometrics review can help avoid serious problems with invalid or inappropriate study designs that sponsors cannot correct at the analysis stage.

C. Reviewing the protocol

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

1. You should be familiar with the investigational new animal drug before you review the protocol. You should describe in your written review any pertinent information you examined. 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),

[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 STARS

[7] For example, if you or your team leader are uncertain whether a protocol needs a biometrics review, you should send the protocol to biometrics as a consulting review. In the "For Reviewer Use" field on the document tracking form, indicate that you would like an assessment of whether or not a biometrics review is necessary.

using the administrative files [Document Control Unit (DCU) and Records ("R:") drive[8]].

b. If there are previous approvals for a NADA (or ANADA) 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 you disagree with the previous reviewer's basis for concurrence.

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

   - The Green Book On-line Database on the CVM website is an electronic database of approved new animal drugs, which you can use to search for drugs with the same active ingredient or indications. Once you learn the NADA number of the new animal drug, you should search the STARS database to find the related INAD file number.

   - 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 the various 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 NADA. The MRA should include the

[8] Although the R: drive is not the official record, and may not be a complete history, it may still be useful as a resource for locating certain reviews and other documents.

number of the INAD file. You should use this number to find the original review documents.

c. If there is an approved human drug with the same or similar active ingredient, you should 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, you should go to the FDA/CDER website and search in the Orange Book. 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 on the FDA intranet, FDA Libraries Live, WebLERN, and Drug Information page.

2. You should familiarize yourself with the disease, condition, parasite, or production parameter under investigation. If the indication is new or unique, you need to understand how it does or does not relate to other indications. You should be aware that we do not permit derivative claims.[9]

3. You should make sure you understand where this study fits into the sponsor's overall development plan. This information may be available in previous submissions or in the sponsor's cover letter. If not, contact the sponsor for clarification or talk to your team leader.

4. You should contact the consulting reviewer(s) assigned to this submission and make arrangements to discuss the details of the protocol, if warranted. 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

[9] A Derivative claim is an indication that is based on an indirect result of a drug's mechanism of action or is an indirect measurement of the drug's action(s). This type of indication represents an observation that is incidental to, but coincident with, achieving the stated indication. This observation would not occur in the absence of the primary effect. This type of indication may also be a surrogate for the direct action of the drug. An example of a derivative claim is the treatment of flea allergy dermatitis with a flea control product. In this example, any resolution of dermatitis is an indirect result of killing the fleas and not a direct result of the drug's mechanism of action.

by logging into STARS and checking the Document Overview for Pending Submissions.

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 should document any concerns regarding the protocol and prepare minutes of the protocol review meeting, and place them on a shared drive for all meeting participants to review and modify. Alternatively, the CSO or primary reviewer can e-mail a copy of the meeting minutes to meeting participants for their comment. Some participants may also choose to write reviews relating to their area of expertise. You should 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.

5. You should review the entire protocol. If during your review, you discover that a protocol is deficient (i.e., after the initial assessment was completed), you should conduct a complete review that is as detailed as possible considering the quality and level of detail of the protocol submission,[10] and document the deficiencies in a protocol non-concurrence letter.

   If you find minor errors or have questions that the sponsor may be able to address quickly, you should follow your division SOPs for contacting them. You should document in your review all discussions you have with the sponsor (telephone or email), along with any requests for amendments to the protocol. You should only request or accept a "minor" amendment without resetting the clock 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 STARS review timeframe. The sponsor should submit a clean, revised protocol including the amended section for your review before we issue a concurrence letter. If the sponsor does not submit an amendment you have requested, your review should document the sponsor's failure to submit the amendment and prepare the non-concurrence letter.

[10] See P&P 1243.3022 for information on implementing the Animal Drug User Fee Act of 2003 (ADUFA).

If a protocol contains anything other than "minor" errors or gaps, you should consider the protocol incomplete, and prepare a letter of non-concurrence.

D. Reviewing a revised protocol

1. If we issue the sponsor a protocol non-concurrence or a refuse to review letter, they may submit a revised protocol after addressing the deficiencies we identified and any recommendations we made. You should review the entire resubmitted protocol, but specifically focus on whether the sponsor addressed the comments we made on the previous submission. You should make sure 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, you should discuss with your team leader whether it is appropriate to inform the sponsor about them in response to the current review. You should 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, you should consider how these changes affect your evaluation of the protocol, and whether the sponsor should make additional revisions to the protocol.

2. Generally, when a sponsor resubmits a protocol, you should send consulting review requests through STARS to consulting reviewers who reviewed the original submission. In addition, you should request any additional consulting reviews on the revised protocol for sections of the protocol that were not included in the previous version. You should discuss the best approach for reviewing the resubmitted protocol with all consulting reviewers (See section V. C. 4.).

E. Writing the review

In writing a review for a protocol submission there are certain standards of consistency that we need to sustain across ONADE. This section describes the standards that we expect you to meet. 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

   You should follow the ONADE general review format adding secondary or subordinate headings as necessary for clarity.[11]

   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 doing this 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. This 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

   You should 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, you should include responses to any specific issues or questions raised by the sponsor in relation to the protocol in its cover letter. The reviewer should provide comments on any supporting information the sponsor submits with the protocol. Supporting information may include, but is not limited to, published literature, pilot study data, or method validation information. 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.

[11] See P&P 1243.3030 for format information.

b. An assessment as to whether the element is acceptable based on your knowledge of the area the element addresses, its consistency with designs for 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 (team leader, 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. If an element of the protocol is unacceptable, you should state the reasons and suggest how the sponsor could make the element acceptable. In all cases, the review should be a complete review of the entire protocol.

In making suggestions and recommendations for making a protocol acceptable, you should avoid rewriting the protocol for the sponsor. The sponsor will have to make the necessary changes in the context of how they can conduct the study.

Additionally, you should 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.

Occasionally sponsors will include minor issues or questions in the cover letter that do not directly pertain to the protocol. You should address those items in the review section as well.

3. Conclusions

The "Conclusions" section of your review should clearly state whether the protocol is acceptable as the sponsor submitted it. You have a choice of two conclusions:

a. Protocol concurrence[12]

If the protocol is acceptable as the sponsor submitted it, you should send the sponsor a protocol concurrence letter (see Section VI. A.).

b. Protocol non-concurrence.

If the protocol is incomplete or otherwise not acceptable, you should send the sponsor a protocol non-concurrence letter (see Section VI. B.).

4. Transmit to sponsor

The Transmit to Sponsor section should include your transmit to sponsor information, and incorporate the transmit to sponsor information the consulting reviewer(s) prepared without modification except to direct the comments to the sponsor (i.e., use "you," not "they" or "the sponsor"). If changes or clarification to a consulting reviewer's transmit to sponsor language are necessary, you should obtain concurrence from the consulting reviewer(s) regarding the modifications. If you and the consulting reviewer cannot agree, then you should consult appropriate managers. When you do not use the consulting reviewer's original transmit to sponsor language, you should document in the final review the actual language that the letter will use, and how we made that decision. You should 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 that need revision, and should tell the sponsor if we need any additional information. Comments should refer to the sponsor's numbered sections of the protocol when possible.

[12] 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. Sponsors should be advised to formally submit a protocol for our review if they wish to get our concurrence.

5. Recommendation(s)

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

VI. HOW TO PREPARE THE LETTER TO THE SPONSOR

We will issue either a protocol concurrence or protocol non-concurrence letter. The letter should clearly and concisely state whether we agree, disagree, or lack sufficient information to reach a decision that the protocol design, execution plans, and data analyses are adequate to achieve the objectives of the study. You should include the title and the protocol number in the letter.

A. The protocol concurrence letter

If we concur with the protocol, you should send a protocol concurrence letter. Concurrence is a fundamental agreement between ONADE and the sponsor that we agree with the design, execution, and analyses proposed in the protocol we reviewed under this process, 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.[13,14] 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. If you have significant comments, in number or substance, or suggestions for future protocol submissions, you should issue a protocol non-concurrence letter. If the Biometrics Team recommends it, you should include a description of how sponsors typically format data when they submit data and their statistical program code to us. We have included a boilerplate paragraph in the protocol concurrence letter template, for you to use or delete as appropriate.

[13] See P&P Manual 1243.3022 Implementing the Animal Drug User Fee Act of 2003 (ADUFA) for a copy of the ADUFA goals letter.
[14] Concurrence does not mean that we concur with the dose interval or withdrawal times that the sponsor proposes.

Our letter should include a caveat explaining that while we agree with the design, execution plans, and data analyses, there is no guarantee that the results of the study will support a particular finding or approval of the new animal drug.[15] Also our letter should also caution the sponsor that if they make any changes to the protocol after receiving concurrence, our concurrence does not extend to the modified protocol. Finally, our letter should inform the sponsor that if they have other questions or requests, not related to the protocol, they should send those to us separately.

B. The non-concurrence letter

If you do not concur with a protocol, you should send 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, we should number our comments in the letter and reference the particular section of the protocol they address. If we did not subject the protocol to, for example, a statistical review include a comment in the letter explaining why we did not perform such specific review(s), but that we may perform such review(s), as necessary, when the sponsor resubmits the revised protocol. Our letter should also address any specific protocol-related questions or issues the sponsor included in their cover letter.

[15] For example: You should not interpret our comments as prior endorsement of the data you ultimately generate. Specifically, we can make no commitment that the data you obtain from this protocol will support approval.

C. Templates

We expect you to use the office templates for the protocol concurrence and protocol non-concurrence letters on the C: drive of your computer.

1. Finding the template.

   The templates are located on the hard drive (i.e., C:\ drive) of your office and work at home computers.

2. Opening the template

   Open Microsoft Word, go to **File → New → General Templates**, and select the appropriate template. The template will open as a "Read Only" Word document.

3. Making sure the template is protected

   When you first open the template, you will see that the form is protected or locked. The template form has fill in fields and drop down lists (all in gray areas within the template). We recommended that you fill in these all the gray areas and select from the drop down lists first ***before*** you unprotect the form to add or delete any text. To move from one gray fill in area to the next just hit the tab key. While the form is protected, you will be able to look at the bottom of your screen for additional instructions. You will also find instructions in comment boxes in the margin of the form.

4. Unprotecting the template

   After you have completed those all the gray areas and deleted instructions that are in the gray areas, you should unprotect the form by going to **Tools → Unprotect**. You can then insert the reasons for refusing to file the application or refusing to review the submission. This will come from the Transmit to Sponsor section of your review and any consulting reviews. If your division does not provide alternative contact information, delete this from the letter. If you add so much text that you have moved the closing paragraph to the second page of the letter, to maintain the headers on all the pages after page one of the letter you will need to insert a section break on page one.

5. Before saving the document

   When you have completed filling in the template, you should delete any comment boxes in the margin by selecting the **Reject Change/Delete Comment** (in the "Reviewing" toolbar) → select **Delete All Comments in Document.** Make certain you have made any formatting adjustments (adding multiple principal identifier information to headers, adding returns or page breaks etc), so that you comply with P&P 1243.3010.

6. Saving the document

   To save the document you have created, go to **File → Save,** and save the file in the appropriate drive with the appropriate name.

VII. COMPLETING THE FINAL ACTION PACKAGE

You should follow the procedures in the P&P 1243.3030, when you complete the final action package.

If the sponsor submitted an "E" or "F" submission electronically, you are to process it in accordance with procedures we established for electronic submissions.

VIII. 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 Safety of Compounds Used in Food-Producing Animals

#33, Target Animal Safety Guidelines for New Animal Drugs

#85, Good Clinical Practices

#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

CVM Program Policy and Procedures Manual

1243.2610, Movement Procedures of Electronic Submissions (Submitted by E-Mail)

1243.3020, Managing the Review of Submissions in the Stars Queue

1243.3022, Implementing the Animal Drug User Fee Act of 2003 (ADUFA)

1243.3030, Completing Final Action Packages for STARS Submissions

IX. VERSION HISTORY

October 24, 2005 – original version

APPENDIX A: DECISION MATRICES

<table>
<tr><th colspan="3">When ONADE determines a protocol is pivotal:</th></tr>
<tr><th colspan="2">And the sponsor :</th><th>ONADE will:</th></tr>
<tr><td rowspan="2">Requested a review of:</td><td>a protocol they think is pivotal

OR

a protocol without stating whether it is pivotal or not</td><td>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” and issue either a “protocol concurrence” letter (final action code 045) or a “protocol non-concurrence” letter (final action code 046) within the STARS time frame.</td></tr>
<tr><td>a protocol they think is non-pivotal</td><td>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.</td></tr>
<tr><td rowspan="2">Did not specify whether or not to review

OR

Asked us to file (without review):</td><td>a protocol they think is pivotal

OR

a protocol without stating whether it is pivotal or not</td><td>Inform the sponsor that we will review the protocol, and then follow the steps in the first cell in this column.</td></tr>
<tr><td>a protocol they think is non-pivotal</td><td>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.</td></tr>
</table>

When ONADE determines a protocol is non-pivotal:		
And the sponsor :		ONADE will:
Requested review of OR Did not specify whether to review:	a protocol they think is pivotal OR 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.
	a protocol 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.
Asked us to file (no review):	a protocol they think is pivotal	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.
	a protocol without stating whether it is pivotal or not OR a protocol they think 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 B: REGULATIONS THAT RELATE TO SAFETY AND EFFECTIVENESS PROTOCOLS

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).[16] 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.[17] Substantial evidence consists of one or more "adequate and well-controlled studies."[18] 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.[19] 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

[16] 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)).
[17] See 21 CFR §514.1(b)(8)(ii).
[18] See 21 CFR §514.4(a).
[19] See 21 CFR §514.4 (b)(3)(ii)

literature as substantial evidence of effectiveness, if we have access to necessary documentation.[20]

C. Bioequivalence protocols for generic 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.

[20] See GFI #106.

APPENDIX C: 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:[21]

    - 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, substrain, 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;[22]

[21] 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.

[22] 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 is unclear whether the protocol provides adequate methods for controlling bias, you should discuss it with your team leader or division director.

- 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;[23]

- 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:

      - Guidance #33: Target Animal Safety Studies for New Animal Drugs.

[23] 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).

b. For human food safety studies:

- GFI #3: General Principals for Evaluating the Safety of Compounds 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,
- GFI # 115: Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Studies – VICH GL22,
- GFI # 116: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing – VICH GL23,
- GFI # 141: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing - VICH GL28,
- GFI# 147: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing – VICH GL31,
- GFI# 148: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing – VICH GL32,
- GFI# 149: Studies to Evaluate the Safety of the Residues of Veterinary Drugs in Human Food: General Approach to Testing - VICH GL33,
- GFI# 159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI – VICH GL36, and

- GFI# 160: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing -VICH GL37.

You should 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:[24]

   - a clear statement of the study objectives;
   - a statement acknowledging the applicability of, and intention to follow, a standard of conduct acceptable to FDA;[25]
   - 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;
   - 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;[26]
   - a description of method of selecting animals for the study;[27]
   - 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;

[24] See 21 CFR §514.117

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

[26] 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).

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

- an explanation of the methods of observation and recording of the animal response variables,[28] 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.

    You should consult with your team leader if you need further instruction.

C. Bioequivalence Studies for Generic Products

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

[28] 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.

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 the Safety of Compounds Used in Food-Producing Animals. See also section A 2., human food safety studies, above.

You should 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. You should 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:

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

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

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

d. 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.[29]

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