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OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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**REFUSE TO FILE AND REFUSE TO REVIEW**

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**I. PURPOSE**

This document:

- Describes when we (ONADE) may “refuse to file” or “refuse to review” a submission, and
- Provides instructions for using the office letter templates to notify the sponsor (or applicant) of our decision.

**II. REFUSE TO FILE**

**A. Applicability**

We may refuse to file an original or supplemental new animal drug application (NADA) or an abbreviated NADA (ANADA).<sup>1</sup> Refuse to file only applies to applications. Therefore, we may not refuse to file a submission to a pioneer or generic investigational new animal drug file (INAD or JINAD).

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<sup>1</sup> See 21 CFR 514.110.

## B. Making the decision

The intent of refusing to file is to ensure that the sponsor provides complete and high-quality information. If any of the criteria below apply, you should consult with your team leader and division director on whether to refuse to file or to request an amendment to the application. If you decide to refuse to file, you should then seek concurrence from the Office Director. The Office Director signs Refuse to File letters

## C. Criteria

We will refuse to file an NADA or ANADA if any of the following criteria apply:<sup>2</sup>

- The application does not contain complete and accurate English translations of any pertinent part in a foreign language.
- The applicant submits fewer than three copies of the application.
- The application is incomplete on its face in that it is not properly organized and indexed.
- The information concerning the required matter is so inadequate that the application is clearly not approvable.
- The new animal drug is to be manufactured, prepared, propagated, compounded, or processed in whole or in part in any State in an establishment that has not been registered or exempted from registration under the provisions of section 510 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 USC 360.<sup>3</sup>
- The sponsor does not reside or maintain a place of business within the United States and the application has not been countersigned by an attorney, agent, or other representative of the applicant, which representative resides in the United States and has been duly authorized to

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<sup>2</sup> See 21 CFR 514.110(b) and the ADUFA Goals Letter found in P&P 1243.3022, Appendix 1.

<sup>3</sup> The Division of Surveillance assigns establishment numbers to each person who registers an establishment under section 510 of the Act. If you have questions regarding an establishment number, you should contact the Marketed Product Information Team.

act on behalf of the applicant and to receive communications on all matters pertaining to the application.

- The new animal drug is a drug subject to licensing under the Virus-Serum-Toxin Act (21 USC 151, et seq.).<sup>4</sup>
- The application fails to include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in 21 CFR Part 58, or, if the study was not conducted in compliance with such regulations, a brief statement of the reasons for the non-compliance.
- The applicant fails to submit a complete environmental assessment under 21 CFR 25.40 or fails to provide sufficient information to establish that the requested action is subject to the categorical exclusion under 21 CFR 25.30 or 21 CFR 25.33.

#### **D. Communicating the decision to the sponsor**

If we determine that an application is not acceptable for filing, we must notify the applicant of the reasons for our refusal within 30 days of receiving the application.<sup>5</sup> Although the regulations do not explicitly require that we provide this notification in writing, it is our policy to do so. We should also document the decision in a review.

Use the template provided on the C: drive of your computer to format the letter. You can find additional instructions for using this template in Section IV of this document.

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<sup>4</sup> Typically, the Office of Surveillance and Compliance in CVM assesses whether a product is subject to the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act before the filing of an NADA. As such, this criterion will seldom provide a basis for refusing to file a submission.

<sup>5</sup> See 21 CFR 514.110(c).

### **E. Filing over protest**

An applicant may file over protest if it disputes our decision that the application is not acceptable for filing.<sup>6</sup> The applicant must submit a written request that we file the application over protest. When we file an application over protest, the application will have its original due date in STARS. In this case, you should conduct a complete review that is as detailed as possible considering the quality and level of detail of the submission, and document the deficiencies in your review and letter to the sponsor.<sup>7</sup>

## **III. REFUSE TO REVIEW**

### **A. Applicability**

We may refuse to review any INAD or JINAD submission that is of insufficient quality.<sup>8</sup>

### **B. Making the decision**

The intent of refusing to review a submission is to ensure that the sponsor provides complete and high-quality information. You should not base your decision to refuse to review upon personal preference; use the criteria below. If you think we should refuse to review a submission, you should talk to your team leader and division director to get their concurrence. Division Directors and the Team Leaders of Generics and Environmental Safety sign Refuse to Review letters.

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<sup>6</sup> See 21 CFR 514.110(d).

<sup>7</sup> The regulations do not specify a timeframe in which a sponsor must file over protest. In most cases, we would expect the sponsor to file over protest in a relatively short timeframe. When a sponsor files over protest, we will file the application as of the day originally received. This means that the application will have the original due date. In the rare event that a sponsor files an application over protest such that you have a short time frame to review the application, you should notify your division director who will be responsible for notifying the Office Director. You will to conduct a complete review of the application. The Division Director and Office Director will discuss any ADUFA timeframe implications.

<sup>8</sup> See 21 CFR 514.110(b), the ADUFA Goals Letter found in Appendix 1 of P&P 1243.3022, and GFI #119.

### **C. Criteria**

In general, the criteria for refusing to review a submission are similar to those for refusing to file applications (see section II.C.). In addition, we may refuse to review submissions where the number and types of errors in the submission cause us to question the quality of the entire submission,<sup>8</sup> for example:

- Missing data sets or missing components in the submission,
- Lack of detail in a study protocol,
- Discrepancies between electronic data sets and the paper copy,
- Conflicting information between sections of the submission, and
- Absence of important information.

### **D. Communicating the decision to the sponsor**

When we decide to refuse to review a submission, we will notify the sponsor in writing within 60 days of our receipt of the submission.<sup>9</sup> Our letter should state that we did not accept the submission for review and summarize the reason(s) for our decision. We should also document the decision in a review.

Use the template provided on the C: drive of your computer to format the letter. You can find additional instructions for using this template in Section IV of this document.

## **IV. INSTRUCTIONS FOR OPENING AND USING THE LETTER TEMPLATES**

### **A. Opening the refuse to review and refuse to file letter templates**

#### 1. Finding the template

The templates are located on the hard drive (i.e., C:\ drive) of your office computer.

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<sup>9</sup> See GFI #119, and the ADUFA Goals Letter found in Appendix 1 of P&P 1243.3022.

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 recommend that you fill in 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 template 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 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 all the 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, go to File → Save, and save the file in the appropriate drive with the appropriate name.

## V. COMPLETING THE FINAL ACTION PACKAGE

You should prepare the final action package using procedures in P&P 1243.3030. P&P 1243.3033 includes the correct STARS action codes for refusing to file applications and refusing to review submissions. Do not use the STARS action code 063 (“Refuse Acc”, “Refuse to accept submission for filing; acct in arrears; letter sent”) for refuse to file or refuse to review actions. This code is only for use by ONADE’s ADUFA staff when we refuse to accept a submission because the sponsor is not current on the fees owed under the provisions of the Animal Drug User Fee Act (ADUFA) of 2003. You should route all Refuse to File final action packages through Quality Assurance (QA). QA will send them to the Office Director for signature.

## VI. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

§514.110, Refuse to file

CVM Guidance for Industry

GFI #119, “How the Center for Veterinary Medicine Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug.”

CVM Program Policy and Procedure Manual

1243.3010, Format and Style Conventions for Letters

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

1243.3030, Completing Final Action Packages for STARS Submissions

1243.3033, Permissible STARS Action Codes for STARS Submissions

## **VII. VERSION HISTORY**

December 13, 2005 – original version