AMENDING STARS SUBMISSIONS

I. PURPOSE

This document:

- Defines "amendment,"
- Describes which amendments qualify as "minor" amendments,
- Describes the procedures the Office of New Animal Drug Evaluation (ONADE, we) will follow in processing and reviewing an amendment, and
- Describes the consequences that result from amending a submission.

II. WHAT IS AN AMENDMENT?

An amendment (or an amending submission) is **any** submission that corrects, or otherwise clarifies or revises, a **pending** submission. If we receive an amendment, we refer to the amended submission as the parent submission.

In our Submission Tracking and Retrieval System (STARS) database, the submission type code for an amendment is dependent on the submission being amended. The submission code for an amendment to:

- An original application ("A") is "M,"

- A reactivation of an original application ("E") is "T,"
- A supplemental application ("C") is "S,"
- A reactivation of an supplemental application ("R") is "U," and
- All other submissions is "T."

III. GENERAL CONSIDERATIONS FOR AMENDMENTS

A. Responsibility for review of an amendment

The division reviewing the parent submission (the review division) is responsible for evaluating the amendment and taking any necessary actions.

B. The need for a controlled amendment process

Sponsors are responsible for preparing complete and high quality submissions that will facilitate our complete and timely review. By their nature, amendments to a pending submission indicate a degree of incompleteness, lack of quality, or inadequate preparation, of the parent submission.

Sponsors may amend their pending submissions at any time. Their amendment may be the result of either our request (CVM-initiated) or their own initiative (sponsor-initiated). The programming of STARS links amendments with their parent submissions so that when we take actions, such as resetting the review clock or finaling out the parent submission, the actions automatically apply to both the parent submission and its amendments.

We should not allow or encourage a sponsor to circumvent existing queue procedures by submitting a poor quality submission as a placeholder in the review queue and then using the amendment process to 'rehabilitate' the parent submission.[1] We should minimize this potential for abuse by properly screening each submission as it arrives in the review division and then refusing to file or review any poor quality submission.[2]

[1] See P&P 1243.3020.
[2] See §514.110, GFI #119, and P&P 1243.2050.

While we generally discourage the submission of amendments, we recognize that there are circumstances in which a controlled amendment process can make the review of a submission more efficient. When used in a judicious manner, a controlled amendment process can reduce submission review cycles without compromising the responsibility of the sponsor to submit high quality submissions.

Because amendments are situation dependent, the determination of whether to request an amendment or to issue an incomplete letter will involve the judgment of the reviewer. The reviewer should keep the team leader informed regarding all requests for amendments so they can assure consistency across the Office.

C. How amendments can affect review due dates

All amendments assume the due date of the parent submission unless the amendment causes us to reset the review clock for the parent submission. When we reset the review clock of a parent submission, we consider the entire submission (parent submission and any amendments) as resubmitted on the received date of the last amendment that caused the "reset" action. If that received date occurs in the next fiscal (cohort) year, then we assign the entire submission to that new cohort year. For sentinel submissions, this change in cohort year may lead to shortened review times.[3]

IV. "MINOR" AMENDMENTS

A. Definition

A minor amendment, regardless of who initiates it, is an amendment that provides a relatively modest amount of specific information that corrects one or more deficiencies in the parent submission. The nature of a minor amendment should not cause us to alter our thinking significantly in the review of the parent submission.

[3] See P&P 1243.3022 for the definition of sentinel submission and cohort year, a description of the decreasing review times for sentinel submissions, and other discussions related to the implementation of the Animal Drug User Fee Act of 2003 (ADUFA).

B. Examples

The submission of the following types of information may individually qualify as a minor amendment. This list is not exhaustive. Other revisions similar in nature and scope may also qualify as a minor amendment. There may be instances in which a revision listed below does not qualify as a minor amendment because of its impact on our review of the submission or when viewed in the context of multiple other 'minor' amendments.

1. The resubmission of a **few** pages because the pages originally submitted were missing or unreadable (where it appears to be a machine error in the copying or assembling of the submission and not an ongoing pattern of recklessness in the preparation of submissions),

2. Providing a Form FDA 356v because the form is missing or incorrect,

3. Providing a more detailed agenda for a meeting request,

4. Providing the proper regulatory citation for the environmental technical section,

5. Providing simple revisions to a protocol that would easily allow us to reach concurrence on the adequacy of the protocol. For example:

    - Adding a data capture form,
    - Adding certain analytical test(s) to complete a list of the battery of necessary tests that will be run,
    - Modifying the observation schedule, or
    - Modifying the dose(s) administered,

6. For manufacturing chemistry related submissions:

    - Revising the specifications of the drug,
    - Providing additional stability data to support a proposed expiry date,

- Clarifying specifications that were inconsistent between the raw material supplier's Certificate of Analysis and the manufacturer's raw material specifications, or

- Clarifying different test results from a contract laboratory and the manufacturer,

7. Providing explanatory information about protocol deviations or amendments and their impact on the study results,

8. Clarifying adverse reactions,

9. For submissions containing technical section level data or studies:

    - Providing certain discrete study records (i.e., facility diagram, feed ration analysis),

    - Providing a copy of the electronic data or codes for use by the Biometrics Team,

    - Providing a copy of the protocol used to conduct the study, or

    - Providing additional information or clarification on some point(s) that would allow us to complete our review or make a decision.

10. Providing labeling or FOI language, or both, not submitted with P technical section, as needed.

V. PROCESSING CVM-INITIATED MINOR AMENDMENTS

A. When it is appropriate to ask for a minor amendment

We should exercise considered judgment in making decisions about what is a minor amendment so that we balance our responsibility to conduct quality reviews within STARS/ADUFA timeframes and the sponsor's responsibility to submit complete and high quality submissions. The purpose of requesting a minor amendment is to allow us to complete the review of a submission that has only minor deficiencies and avoid the need for another review cycle. We should not implement our "one cycle review" in a manner that circumvents our policy of

refusing to review or file poor quality submissions. Rather, "one cycle review" should be the goal only when we receive high quality submissions that require little or, ideally, no amending and it would be inefficient for a reviewer to have to re-review the entire submission later.

Generally, you (as a reviewer) should not request multiple CVM-initiated amendments for a pending submission. Instead, you should wait until you are nearing completion of your review and determine whether the information you would request, taken as a whole, meets the criteria of a minor amendment as described in this document. If your request would be too extensive to qualify as a minor amendment, do not ask for an amendment. You should complete your review of the submission as is and issue the sponsor a letter noting the deficiencies you found.

B. Criteria for requesting a minor amendment

Before you request a minor amendment, you need to be able to answer "YES" to all four questions below:

1. Being mindful of the sponsor's responsibility to submit high quality submissions and given the deficiencies you have identified, would you consider the current submission a high quality submission that merits being amended?

2. Will the information that you would be requesting likely allow you to complete a comprehensive review and reach a decision on the issue(s) presented in the submission?[4]

3. Is it likely that the sponsor could provide the information you would request by a date that would permit us to complete the review of the amended submission within the established review time?

4. If you were to request an amendment for the submission, would there still be sufficient time to complete the review of the amended submission within the established review time?

[4] For example, the completed review of the amended submission will support the decision to approve (or not approve) an application, to complete (or to incomplete) a technical section, to accept (or not accept) the results from the submitted study(ies), or to concur (or not concur) with a study protocol.

C. Information you should provide to the sponsor

When you request a minor amendment, you should tell the sponsor:

1. What specific information you need to complete your review of the submission,

2. The date by which we must receive the amendment to complete our review on time (the Amendment Receipt Date), and

3. How we will process the parent submission and amendment if we do not receive the amendment by the Amendment Receipt Date (see section VI.E. below).

D. Actions you should take related to requesting a minor amendment

1. You should select an Amendment Receipt Date that will allow you (and other reviewers of the submission, if any) to complete the review of the amended submission within the assigned review time, and

2. You must document in the administrative file the basis for the request for the amendment, the Amendment Receipt Date established, and the description of the amendment requested.[5]

E. How you should process the amendment when we receive it

1. If we receive the amendment by the Amendment Receipt Date (i.e., the stamp date (or received date) for the amendment is on or before the Amendment Receipt Date), you should review the parent submission and the amendment together and complete the review on time.

2. If we receive the amendment after the designated Amendment Receipt Date, but **before** the final action package has cleared the review division, you should issue a "reset the clock" letter and reset the due date for the amended submission based on the date we receive the amendment.[6]

[5] See §10.70(b).
[6] "Cleared the review division" means the review is complete and the final action package has been forwarded for signature outside the division or to DCU for final processing.

3. If we receive the requested amendment **after** the final action package has cleared the review division, you must return the amendment to the Document Control Unit (DCU) and instruct them to assign this new submission the same submission type code as the submission that it was intended to amend. You should prepare a letter indicating that this newly classified submission is unacceptable for review (STARS action code 065) because it is incomplete on its face.[7] This letter should also indicate that:

    - Review of the new submission would require a written request by the sponsor to review this new submission in conjunction with the submission it was intended to amend, and

    - The sponsor should include with their request any information addressing other issues identified (if any) in our letter responding to the previous submission (the submission the sponsor was originally attempting to amend).

4. If we do not receive the amendment, or the amendment received by the Amendment Receipt Date does not contain the information requested or needed, you should complete the review of the pending submission and issue a letter that describes the deficiencies of the submission within the assigned review time.

VI. PROCESSING SPONSOR-INITIATED MINOR AMENDMENTS

We will not reset the review clock for a pending submission when the sponsor submits a sponsor-initiated amendment if we determine that the sponsor-initiated amendment:

- Meets the definition of a minor amendment,

- Meets the criteria we would have used to request this amendment (see section V.B.), and

- Has been submitted in time to lead to a comprehensive review and decision within the assigned review time.[8]

[7] See P&P 1243.2050 for details on how to "refuse to review" a submission.
[8] "Submitted in time" means received by a date equivalent to the Amendment Receipt Date that the review division would have set had they requested the amendment.

If we receive a sponsor-initiated amendment that is a minor amendment and it meets our criteria for requesting an amendment, but it was not submitted in time or is not likely to make the parent submission complete, we will reset the review clock for the pending (now parent) submission unless the final action package for the pending submission has cleared the review division. In that case, you should process the amendment as indicated in section V.E.3.

VII. AMENDMENTS THAT ARE NOT MINOR

Clearly, there are amendments that would not meet our definition of a minor amendment. Examples include the submission of:

- A final study report for a study that was intended to be reviewed collectively with the results of other similar studies in the submission, or
- New information that significantly alters the characterization of the information contained in the parent submission or our interpretation of it.

You should never request this type of an amendment from a sponsor because the sponsor has failed to meet its responsibility to submit quality submissions. If a sponsor does submit this type of an amendment, you should issue a "reset the clock" letter and reset the due date of the parent submission based on the date we received the amendment unless the final action package for the pending submission has cleared the review division. In that case, you should process the amendment as indicated in section V.E.3.

VIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 10 – Administrative Practices and Procedures

§10.70, Documentation of significant decisions in the administrative file

Part 514 – New Animal Drug Applications

§514.110, Reasons for refusing to file applications

CVM Guidance for Industry

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 Procedures Manual

1243.2050, Refuse to file and refuse to review

1243.3020, Managing the review of submissions in the STARS queue

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

IX. VERSION HISTORY

May 16, 2006 – original version

December 8, 2006 – incorporate changes identified at ONADE council