AMENDING STARS SUBMISSIONS

I. PURPOSE

This document:

- Defines “amendment”
- Distinguishes between “end review” amendments and “minor” amendments
- Describes which amendments qualify as “minor” amendments
- Describes the procedures the Office of New Animal Drug Evaluation (ONAIDE) follows in processing and reviewing a “minor” amendment

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 original, amended submission as the parent submission.

In the Submission Tracking and Reporting System (STARS) database, the submission type code for an amendment depends on the submission being amended. Amendment submission codes are assigned as follows:
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

Amendments to a pending submission may indicate a degree of incompleteness, lack of quality, or inadequate preparation of the parent submission. Alternatively,
an amendment is occasionally needed to provide additional information to address complex issues within submissions. Sponsors are responsible for preparing complete, high quality submissions that facilitate our complete and timely review.

Do 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. Minimize the 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.

A controlled amendment process, as described in this document, makes the review of a submission more efficient by reducing 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 a minor amendment and/or an end-review amendment or to issue an incomplete letter involves the judgment of the primary reviewer in conjunction with the consulting reviewers. As necessary, the primary reviewer keeps the team leaders, consulting reviewers, and project managers informed regarding all requests for amendments to assure consistency across the Office.

IV. END-REVIEW AMENDMENTS

An end-review amendment (ERA) is a specific type of CVM-initiated amendment that contains additional non-substantial data or information to allow for a complete review of an application or submission during the current review cycle of the parent application or submission. The Animal Drug User Fee Amendments of 2008 (ADUFA II) provides for use of the ERA process to enhance the review of INAD protocols (E) and study (P) submissions, and non-administrative, non-manufacturing NADA (A, E, C, and R) submissions. We allow only one ERA per review cycle of the parent submission. Use the ERA-specific procedures for reviewing and processing ERAs described in the following P&P documents:

P&P 1243.4070 – INAD E submissions

1 See P&P 1243.3020.
2 See §514.110, GFI #119, and P&P 1243.2050.
P&P 1243.4075 – INAD P submissions


Also refer to these P&P documents when you have concerns of possible timing overlap between minor amendment and the ERA processes.

V. “MINOR” AMENDMENTS

A. Definition

A minor amendment provides a relatively modest amount of specific information that corrects one or more deficiencies in the parent submission. The nature of a minor amendment does not alter our thinking significantly in the review of the parent submission, but may assist CVM in making critical decisions about the submitted information.

There are amendments that would not meet our definition of a minor amendment, and should not be treated as such. Examples may include the submission of: 1) 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 2) New information that significantly alters the characterization of the information contained in the parent submission or our interpretation of it.

Should we receive an amendment for a parent submission currently under review that does not meet the definition of a minor amendment, issue a “reset the clock” letter and reset the due date of the parent submission based on the receipt date of the amendment. If the final action package for the parent submission has cleared the review division, process the amendment as indicated in Section VI.E.3 below.3

B. How minor amendments affect review due dates

Sponsors may amend pending submissions with minor amendments at any time. Minor amendments may be either CVM-initiated or sponsor-initiated. The programming of STARS links amendments with their parent submissions so that actions, such as resetting the review clock or finalizing the parent submission, automatically apply to both the parent submission and its amendments.

3 “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.
Minor amendments assume the STARS due date of the parent submission. There are occasions when the amendment causes us to reset the review clock (i.e., if we receive the minor amendment after the amendment due date or if we receive a sponsor-initiated minor amendment late in the review process for the parent submission). The amendment due date is also known as the “Amendment Receipt Date” (see Section VI.C.2 below). If we must reset the clock, the entire submission (parent submission and any minor amendments) is considered as resubmitted. The new STARS due date is based on the date that we actually received the last minor amendment.

C. 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 carelessness in the preparation of submissions);

2. Providing a FORM FDA 356v because the form is missing or incorrect or not signed;

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

4. Providing the proper regulatory citation for the environmental impact technical section;

5. Providing simple revisions to correct errors in the original protocol that easily allow us to reach concurrence on the adequacy of the protocol.

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 Biostatistics Team or pharmacokinetics reviewers,
   • Providing a copy of the protocol used to conduct the study, or
   • Providing additional information or clarification on some point(s) that allows us to complete our review or make a decision.

10. Providing labeling or Freedom of Information Summary language if not submitted with the applicable major technical section, as needed.

VI. PROCESSING CVM-INITIATED MINOR AMENDMENTS

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

When deciding to request an amendment, balance our responsibility to conduct quality reviews within our required 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.
Avoid requesting multiple CVM-initiated minor amendments for a pending submission. The review team (consisting of primary reviewer, consulting reviewers, team leaders, or project manager, as appropriate) communicates during the review process to determine if a minor amendment is appropriate for the submission and to coordinate the request into a single amendment. If the request is too extensive to qualify as a minor amendment or there is not enough time for the reviewers to meet consulting and CVM final action due dates, do not ask for a minor amendment.

B. Criteria for requesting a minor amendment

Before requesting a minor amendment, you need to be able to answer “YES” to all four questions below:

1. Is the current submission a high quality submission that merits a minor amendment?

2. Will the requested information allow you to complete a comprehensive review and reach a decision on the submission?

3. Is it likely that the sponsor can provide the information by the date you specify?

4. If you receive an amendment by the date specified, is there sufficient time to complete the review of the amended submission within the established primary and consulting review timelines?

C. Information to provide to the sponsor

When requesting a minor amendment, tell the sponsor:

1. The specific information needed to complete the review of the submission,

2. The date by which we must receive the amendment to complete the 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).
4. The requested amendment is necessary for us to finish our review, and does not guarantee concurrence or acceptance of the submission.

D. Actions to take when requesting a minor amendment

1. Select an Amendment Receipt Date that allows primary and consulting reviewers to complete their reviews of the amended submission by their respective due dates, and

2. Document in your review the basis for the request for the amendment, the Amendment Receipt Date established, and the description of the amendment requested.

E. How you should process a minor 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 and any consulting reviewers 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, issue a “reset the clock” letter and reset the due date for the amended submission based on the date we receive the amendment.¹

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. Prepare a letter indicating that this newly classified submission is unacceptable for review (STARS action code 065) because it is incomplete on its face.² This letter indicates that:

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

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¹ “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.
² See P&P 1243.2050 for details on how to “refuse to review” a submission.
• 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 by the Amendment Receipt Date, or we receive the amendment by the Amendment Receipt Date but it does not contain the information requested or needed, complete the review of the pending submission and issue a letter that describes the deficiencies of the submission within the assigned review time.

VII. PROCESSING SPONSOR-INITIATED MINOR AMENDMENTS

If we determine that a sponsor-initiated minor amendment:

• Meets the definition of a minor amendment (see Section V. A),

• Was submitted in time to lead to a comprehensive review and decision within the assigned review time,6

Review the minor amendment and parent submission to complete the final action within the assigned review time.

Should we receive a sponsor-initiated amendment for a parent submission currently under review that does not meet the definition of a minor amendment, issue a “reset the clock” letter and reset the due date of the parent submission based on the receipt date of the amendment. If the final action package for the parent submission has cleared the review division, process the amendment as indicated in Section VI.E.3 above.

VIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 10 – Administrative Practices and Procedures

§10.70, Documentation of significant decisions in the administrative file

6 “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.
Part 514 – New Animal Drug Applications

§514.110, Reasons for refusing to file applications

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 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)

1243.4070, Integrating an End-Review Amendment (ERA) into the Investigational New Animal Drug Protocol (E) Submission Review Process

1243.4075, Integrating an End-Review Amendment (ERA) into the Investigational New Animal Drug Data (P) Submission Review Process

1243.5730, Integrating an End-Review Amendment (ERA) into the New Animal Drug Application Review Process

IX. VERSION HISTORY

May 16, 2006 – original version

December 8, 2006 – incorporate changes identified at ONADE council

June 18, 2010 – updated to acknowledge end-review amendment process