
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

AMENDING AND RESETTING THE CLOCK ON SUBMISSION TRACKING AND REPORTING SYSTEM (STARS) SUBMISSIONS

| | |
|--|---|
| I. Purpose | 1 |
| II. What is an amendment? | 1 |
| III. General consideration for amendments | 2 |
| IV. Minor amendments..... | 3 |
| V. Processing CVM-initiated minor amendments | 6 |
| VI. Processing sponsor-initiated amendments | 8 |
| VII. Appian Closeout procedures..... | 8 |
| VIII. References | 9 |
| IX. Version history..... | 9 |

I. PURPOSE

This document:

- Defines "amendment,"
- Describes which amendments qualify as "minor" amendments,
- Describes the procedures the Office of New Animal Drug Evaluation (ONADE) follows in processing and reviewing "minor" amendments, and
- Describes the procedures to 'Reset the Clock' for submissions.

II. WHAT IS AN AMENDMENT?

An amendment (i.e., 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 submission as the parent submission. Amendments can be made to various submissions identified in the table below.

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:

| Parent Submission Type ¹ | Parent Submission Code | Amendment Submission Code |
|---|----------------------------------|---------------------------|
| Original (A)NADA | A | M |
| Reactivation of (A)NADA | E | T |
| Supplemental (A)NADA | C | S |
| Minor changes and stability report- (A)NADA | B | S |
| Reactivation of a supplemental (A)NADA | R | U |
| Reactivation of minor changes and stability report – (A)NADA | F | U |
| All other submissions to (A)NADAs not listed above in this table | All other submission codes | T |
| All submissions to (J)INAD, VMF and GC files | All submission types | T |

III. GENERAL CONSIDERATION FOR AMENDMENTS

A. Origin of an amendment

An amendment to a submission is typically CVM-initiated and is the result of our requesting the sponsor submit missing or additional information to facilitate the review of a submission or application. Sponsor's will sometimes submit unsolicited amendments while a submission is under review. These sponsor-initiated amendments are typically minor amendments.

B. Responsibility for review of an amendment

The reviewer assigned the parent submission is responsible for evaluating the amendment and taking any necessary actions, which include making sure the appropriate consulting reviewers examine the amendment or if additional consulting review requests are needed (see P&P 1243.3200).

¹ (A)NADA refers to abbreviated new animal drug applications (ANADA) and new animal drug applications (NADA); (J)INAD refers to generic investigational new animal drug (JINAD) files and investigational new animal drug (INAD) files; VMF refers to veterinary master files; GC refers to general correspondence files

C. The need for a controlled amendment process

Amendments to a pending submission may be needed to address incompleteness, lack of quality, or inadequate preparation of the parent submission. Alternatively, an amendment is occasionally needed to provide additional information to further explain 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.²

A controlled amendment process, as described in this document, allows for an efficient review process without compromising the expectation that the sponsor submit high quality submissions.

Because amendments are situation-dependent, the determination of whether to request an amendment or to issue an incomplete letter involves the judgment of the primary reviewer in conjunction with the consulting reviewers and their supervisor. The primary reviewer should keep the team leaders, consulting reviewers, and project managers informed regarding all requests for amendments.

IV. MINOR AMENDMENTS

A. Definition

An amendment is defined as minor if it 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 significantly alter our assessment of the parent submission, but may assist CVM in making critical decisions about the submitted information. Minor amendments may be either CVM-initiated or sponsor-initiated.

There are amendments which contain information that exceeds our definition of a minor amendment. 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 may significantly alter our assessment of the information contained in the parent submission or our interpretation of it. A list of examples of minor amendments are provided in Section IV.C. below.

² See §514.110, GFI #119, P&P 1243.3100 and P&P 1243.2050.

B. How amendments affect STARS due dates

The STARS programming will automatically link an amendment with its parent submission. This allows certain actions, such as resetting the review clock, or finalizing the parent submission, to automatically apply to both the parent submission and its amendments.

Minor amendments assume the STARS due date of the parent submission. There are occasions when an amendment causes us to reset the review clock (i.e., if we receive the minor amendment after the requested amendment due date, if we receive a sponsor-initiated minor amendment late in the review process, or the amendment does not qualify as a minor amendment). If we must reset the clock, the entire submission (i.e., parent submission and any minor amendments) is considered as resubmitted and a new STARS due date is assigned based on the date the amendment is received using the Appian workflow (see Section IV.D below).

C. Examples of minor amendments

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 more detailed agenda for a meeting request³;
3. Providing the proper regulatory citation for the environmental impact technical section;
4. Providing simple revisions to correct errors in the original protocol that easily allow us to reach concurrence on the adequacy of the protocol.
5. 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

³ See P&P 1243.3024

-
- Clarifying different test results from a contract laboratory and the manufacturer.
6. Providing explanatory information about protocol deviations or amendments and their impact on the study results,
 7. Clarifying adverse reactions,
 8. 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 or pharmacokinetic 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.
 9. Providing labeling⁴ or Freedom of Information Summary language if not submitted with the applicable major technical section, as needed.

D. Resetting the Review Clock

If we receive an amendment for a parent submission currently under review that does not meet the definition of a minor amendment, the primary reviewer may choose to “reset the clock” for the submission. This means the STARS due date for the parent submission and amendments associated with it will change. If you believe resetting the clock is appropriate, discuss it with your team leader to make sure there is agreement.

After discussing with your team leader, prepare a Reset the Clock letter using the ONADE template following your division’s document concurrence procedures. After the letter is ready, use the Appian ‘ONADE Reset the Clock’ workflow. Select the amendment for which you would like to reset the clock of the parent submission. The new STARS due date will be calculated based on the date received for the selected minor amendment. Next, Appian will instruct you to select the initiator role, clearance chain, and upload the Reset the Clock letter. Once all the individuals in the clearance chain have concurred on the package, you will receive an email confirmation that the change has been applied. The email will contain a link to the letter. A copy of the letter will be automatically placed in CDMS when the parent submission is closed. The primary reviewer should notify the consulting reviewer(s) and the project manager that the review clock has been reset.

For the labeling and AOI minor technical sections: If we receive an amendment to the referenced P submission that causes us to reset the clock of the referenced P submission, the due dates of the M submissions we have received are also set to

⁴ See P&P 1243.4080

the new due dates of the referenced P submission. Resetting the clock of pending P submissions not referenced by the M submissions in an applicable approval track may necessitate changing the referenced P submission because the newly-amended P submission may have a later due date than the referenced P submission. Anytime the clock is reset for a P submission in the end game, the entire review team should be notified to ensure the M submissions reference the correct P submission, see P&P 1243.4080 for more information.

V. PROCESSING CVM-INITIATED MINOR AMENDMENTS

A. When it is appropriate to request 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.

The reviewer should try to avoid requesting multiple minor amendments for a pending submission. The review team, which may consist of the 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. The reviewer should indicate in the letter to the sponsor the deficiencies that need to be addressed in a subsequent submission.

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? The selected date that the amendment is due to CVM from the sponsor is also known as the "Amendment Due Date".
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 requested Amendment Due Date), and
3. How we will process the parent submission and amendment if we do not receive the amendment by the requested Amendment Due Date (see Section V.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 Due 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 requested Amendment Due Date, and the description of the amendment requested.

E. How you should process a minor amendment when received

The amendment is automatically assigned to the primary reviewer when received. The primary reviewer should create any necessary consulting reviews for the amendment using the Appian workflow 'ONADE consult request' according to the procedures in P&P 1243.3200.

1. If we receive the amendment on or before the requested Amendment Due 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 Amendment Due Date, but before the final action package has been closed in Appian, issue a "reset the clock" letter using the ONADE template and reset the due date for the amended submission based on the date we receive the amendment using the Appian 'ONADE Reset the Clock' workflow. The primary reviewer should notify the consulting reviewer(s) and the project manager that the review clock has been reset.
3. If we receive the amendment by the designated Amendment Due 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.
4. If we receive the amendment, but it contains information beyond what was requested, then the primary reviewer should discuss with their

supervisor and decide to either: 1) review the new information within the current submission timeline, 2) reset the clock, or 3) inform the sponsor in the letter that the new information was not reviewed and to resubmit it in a new submission.

VI. PROCESSING SPONSOR-INITIATED AMENDMENTS

Sponsors may amend pending submissions with minor amendments at any time. If we determine that a sponsor-initiated minor amendment:

- Meets the definition of a minor amendment (see Section IV.A.),
- Was submitted in time to lead to a comprehensive review and decision within the assigned review time,⁵

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

The amendment is automatically assigned to the primary reviewer when received. The primary reviewer should create any necessary consulting reviews for the amendment using the Appian workflow 'ONADE consult request' according to the procedures in P&P 1243.3200.

If 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 using the ONADE template and reset the due date of the parent submission based on the receipt date of the amendment using the Appian 'ONADE Reset the Clock' workflow described above in Section IV.D. The primary reviewer should notify any consulting reviewers and the project manager that the review clock has been reset. Alternatively, you may decide to issue an incomplete letter and request the sponsor submit the information in a new submission.

VII. APPIAN CLOSEOUT PROCEDURES

When a consulting reviewer is returning consulting review packages in Appian, the consult to the parent submission and consults to any amendments to the parent submission must be returned separately, see P&P 1243.3029.

The primary reviewer is responsible for ensuring all consulting reviews and corresponding amendments have been returned through Appian before closing out a submission. When the primary reviewer closes out the parent submission, all the amendments will automatically close out in Appian. Unlike the consulting reviewer close out process, the primary reviewer needs only to initiate final action on the original submission. See P&P 1243.3030 for more information. If the clock has been reset during the review of the submission, a copy of the 'reset the clock' letter will be automatically placed in CDMS when the parent submission is closed.

⁵ "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.

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

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

1243.3024 - Scheduling and Holding Meetings with Outside Parties

1243.3029 - Closing Out a Consulting Review for STARS Submissions

1243.3030 - Completing Final Action Packages for Submission Tracking and Reporting System (STARS) Submissions

1243.3100 – Refuse to Review (RTR) and Refuse to File (RTF) Assessments of Submissions and Applications

1243.3200 - Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

1243.4080 - Labeling and All Other Information Technical Sections (Minor Technical Sections or M Submissions)

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

January 16, 2019 – updated to reflect current procedures and remove end review amendment information.