OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

ASSESSING SUBMISSION QUALITY AND AMENDING AND RESETTING THE CLOCK ON SUBMISSIONS

I. PURPOSE

This document:

- Provides an overview on how to assess submission quality,
- Defines amendments,
- Describes the decision process to determine when to request an amendment,
- Describes the process for how to request an amendment,
- Describes the procedures for processing and reviewing amendments,
- Describes the procedures to 'Reset the Clock' for submissions, and
- Describes the Appian closeout procedures for amendment reviews.

II. ASSESSING SUBMISSION QUALITY

When the Office of New Animal Drug Evaluation (ONADE) receives a submission, we assign it to a primary reviewer (PR). The PR requests various consults depending on the nature of the submission. The PR and the consulting reviewers (CR) should initially assess the submission for the purpose, content, and overall general quality.

For submissions containing data, the PR should either request a Refuse to Review/Refuse to File consult according to the Policy and Procedures (P&P) 1243.3100 "Refuse to Review (RTR) and Refuse to File (RTF) Assessment of Submissions and Applications That Contain Data" or perform a RTR/RTF assessment themselves as applicable. If we find the submission deficient, the PR should follow the procedures in Guidance for Industry (GFI) #119 "How the Center for Veterinary Medicine Intends to Handle Deficient Submission Filed During the Investigation of a New Animal Drug." If

we determine the submission is acceptable for review but is missing some information, we may need to request an amendment.

For submissions containing safety, effectiveness or bioequivalence data, the PR should also request a consult for a Quality Assurance Study Review (QASR) according to P&P 1243.3215 "Requesting a Quality Assurance Study Review from the Quality Assurance Team."

During the review of the submission, the PR and the CR(s) assess the submission and determine if we need additional information or data to complete the review of the submission.

III. AMENDMENTS THAT ALLOW US TO COMPLETE THE REVIEW OF THE SUBMISSION

An amendment is any submission that corrects, clarifies, or revises a current open submission. An amendment provides information that is expected to allow CVM to complete the review of the submission. If we receive an amendment, we call the original submission the parent submission. We can request amendments for various submission types and the submission type codes for amendments are based on what the parent submission type code is. See the parent codes and amendment codes in Appendix 1.

Amendments should assist the PR and CR in making critical decisions about the submitted information and should not significantly alter our assessment of the parent submission. Amendments may be either CVM-initiated or sponsor-initiated.

Submission of the following types of information may qualify as an amendment. This list is not exhaustive. Other revisions similar in nature and scope may also qualify as an amendment. There may be instances in which a revision listed here may qualify as a major amendment (see Section IV) because of its impact on our review of the submission or when viewed in the context of the need for multiple amendments.

1. Resubmission of a few pages because the pages in the parent submission were missing or unreadable (where it appears to be an error in assembling the submission and not indicative of an overall poor-quality submission);

2. Cited publications for a meeting request;[1]

3. Proper regulatory citations for the Environmental Impact technical section;

4. Revisions to a protocol that allow us to reach concurrence within the established review timeframe.

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

    - Discrete study records needed to complete our review (e.g., facility diagram, feed ration analysis)

[1] See P&P 1243.3024 Scheduling and Holding Meetings with Outside Sponsors

- A copy of a protocol used to conduct the study.

IV. MAJOR AMENDMENTS

A major amendment, which may be CVM- or sponsor-initiated, is an amendment that, due to the nature of its contents, has a significant impact on our ability to review the information or make a regulatory decision within the remaining review time. This may include an additional study, the raw data associated with a final study report, protocol revisions beyond the scope of what was requested, or new information that may significantly alter our assessment or interpretation of the information contained in the parent submission. Major amendments typically cause us to take some regulatory action such as resetting the clock (See Section VIII).

Before requesting a major amendment, the review team should determine the appropriate regulatory action. This may include requesting a major amendment and reviewing it under the normal review clock, requesting a major amendment and resetting the clock, or not requesting an amendment and instead issuing an incomplete or nonconcurrence letter.

V. MAKING THE DECISION TO REQUEST AN AMENDMENT

The purpose of requesting an amendment is to allow the sponsor to submit information in order for us to make a decision within the specified review time. When deciding to request an amendment, the review team should balance our responsibility to conduct quality reviews within the applicable statutory or ADUFA/AGDUFA timeframe and the sponsor's responsibility to submit complete and high-quality submissions.

The following questions may aid the review team in making a decision to request an amendment:

1. Is the current submission a quality submission?

   We should not use amendments to correct major submission quality issues with the parent submission. Sponsors are responsible for preparing complete, quality submissions that facilitate our complete and timely review. Occasionally there may be missing information, points that are not clear to us, or recommended modifications in an otherwise quality submission that can be addressed through an amendment.

2. Has any member of the review team determined that the submission will be incomplete or a non-concurrence?

   If the identified deficiencies are extensive or if the submission has been determined to be incomplete by one or more members of the review team, we should not request an amendment. For data submissions, incomplete in this context refers to the submission (final action of: study not acceptable, incomplete submission) and not the technical section. The review team should determine if the data submission will be incomplete before requesting an amendment.

3. Will the requested information allow the review team to complete a comprehensive review and reach a decision on the submission? Is the information necessary to make the regulatory decision?

   The PR and CR(s) should determine that there are no other known issues at that time except those identified for the amendment request.

   Reviewers should consider whether we have other resources to obtain the necessary information (e.g., literature search, consultation with colleagues), or if we can make the regulatory decision without the information we plan to request (i.e., can we make a risk-based decision in the absence of the information?). This information is not a substitute for the sponsor providing a justification or other data to support some critical aspect of the protocol or submission but helps support the review and regulatory decision.

4. If we receive an amendment by the date specified, will there be sufficient time to complete the review of the parent and amending submissions within the established primary and consulting review timelines?

   Reviewers should only request amendments from sponsors if there is enough time remaining to allow all assigned reviewers to complete their reviews within their individual STARS due dates. We can decide we need to amend a submission at any time up to the STARS due date; however, reviewers should consider issuing an incomplete or nonconcurrence letter with a Shortened Review Time (SRT) upon reactivation, if applicable, or resetting the clock, if there is limited review time remaining.

   If it is determined that there is not enough time for the reviewers to meet consulting and STARS due dates, the regulatory actions described under Section IV may be more appropriate. Because there may be exceptions to this, talk with your team leader (TL) or division director (DD) as appropriate

VI. REQUESTING AN AMENDMENT

A. Who May Request an Amendment?

Both the PR and CR(s) may identify the need for an amendment from sponsors. If a member of the review team (consisting of the PR, CRs, TL, and/or project manager (PM), as appropriate) determines the need for an amendment, they should communicate with the rest of the review team to determine if an amendment request is appropriate or if another member of the review team also has an amendment request. To avoid multiple amendment requests when possible, the PR, in conjunction with the CR(s), should compile amendment items into the same request.

If a sponsor submits an unsolicited amendment (i.e., sponsor-initiated) without a prior conversation with CVM, the review team should determine if the information submitted is minor in nature and if there is sufficient time to complete the review of the parent and amended submissions within the established primary and consulting review timelines. If both criteria are met, review the unsolicited amendment with the parent submission. If both criteria are not met, see Section

VIII for information on resetting the STARS clock[2] or issuing an incomplete or nonconcurrence letter.

B. How to Request an Amendment

1. The requestor(s) should prepare an email to the sponsor's Responsible Official identified in eSubmitter. The email should contain the following information:

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

    b. The amendment due date, which is the date we request to receive the amendment to complete the review on time,

    Select an amendment due date that allows the PR and CR(s) to complete their reviews of the amended submission by their respective due dates.

    c. That the requested amendment is necessary for us to finish our review but does not guarantee concurrence or acceptance of the submission.

2. The PR (or if applicable, the CR) should document in their review the basis for the request for the amendment, the requested amendment due date, and the description of the amendment requested. Include a copy of the emailed amendment request (and any additional email communications with the sponsor) as an appendix to the review.

VII. PROCESSING AMENDMENTS

Amendments have the same STARS due date of the parent submission. 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. STARS automatically assigns amendments to the PR of the parent submission when we receive them, but STARS does not automatically assigned amendments to the CR(s).

A. CVM-Initiated Amendments

1. When we receive the amendment on or before the CVM requested amendment due date, the PR should notify any CRs, as the information in the amendment may be important for the consulting review(s). If the CR needs to review the information contained in the amendment, the PR should formally issue a consult in Appian to the CR for the amendment using the Appian workflow 'ONADE consult request' according to the procedures in P&P 1243.3200. The PR should also evaluate the amendment to determine if any

[2] Generally, CVM will not reset the STARS review clock for unsolicited amendments that contain additional stability data to support the drug product expiry period or amendments made to similar pending generic applications or submissions per the criteria listed in the AGDUFA II goals letter ("Amending Similar Applications and Submissions").

additional consulting review requests are needed and issue them, as applicable. The PR and any CRs should review the parent submission and the amendment (as applicable) together and complete their reviews on time.

2. If the sponsor proposes a change in the CVM requested amendment due date or we receive an amendment after the CVM requested amendment due date, the review team should consider whether the amendment is acceptable and if the PR and CRs can complete their reviews within the remaining review clock time or if another action should be taken. This may include issuing a reset the clock letter, an incomplete or non-concurrence with a shortened review time, as appropriate, or acknowledgement letter with a comment that we did not review the information in the amendment because we did not receive it by the amendment due date.

   If we decide to reset the clock, use the ONADE template and reset the due date for the amended submission as described under Section VIII. The PR should notify the CR(s) and the PM that the review clock has been reset.

3. If the sponsor is unable to submit the requested amendment due to time constraints or does not submit the requested amendment by the time we must make a regulatory decision, the reviewer will issue an incomplete, non-concurrence, with a shortened review time, as appropriate, or acknowledgement letter, as applicable.

4. If we receive the amendment, but it contains information beyond the scope of what was requested, then the PR should discuss with their TL and the review team 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. It may be appropriate to offer a shortened review time upon resubmission or reactivation of the submission, if applicable.

B. Sponsor-Initiated Amendments

Sponsors may amend pending submissions at any time. The reviewer should consider the amount of information being submitted (see Section III) and the remaining review timeline to determine if review of the amendment and parent submission can be completed within the assigned review time.

If the review team determines that the information submitted qualifies as a major amendment, see section VII.C below for the possible actions we can take.

C. Major Amendments

If we receive a CVM requested major amendment, we will process the amendment based on our determination described in Section IV.

If we receive a sponsor-initiated amendment that contains a large amount of information or if a CVM-initiated amendment contains a large amount of information beyond what was in our amendment request, we may handle the amendment by resetting the review clock (see section VIII) or by issuing an incomplete, non-concurrence, or acknowledgement letter. If an incomplete, non-

concurrence, or acknowledgement letter is issued, it should contain a request to the sponsor to submit the information in a new submission. If the review team determines that resetting the clock is appropriate, the PR should discuss the decision with their TL or DD.

VIII. RESET THE CLOCK

If we receive a major amendment or an unsolicited amendment that cannot be reviewed in the statutory timeline for the parent submission, as described above, we may choose to reset the clock. If we reset the clock, the entire submission (i.e., the parent submission and any amendments) is considered resubmitted and a new STARS due date is assigned based on the date we received the amendment (triggering the reset). We reset the clock using the Appian workflow described below.

A. How to Reset the Clock

Resetting the clock is performed through Appian under the Actions Tab using the ONADE Reset The Clock workflow.

- A non-final action (NFA) letter is issued to the sponsor as part of the reset the clock process. The letter (found on the ONADE template page) informs the sponsor that the clock has been reset on their submission and indicates the new submission due date. The new due date for the submission is based upon the receipt date of the amendment.
- The PR's TL or DD signs the NFA letter
- The NFA letter is issued though Appian to the sponsor.
- The PR should notify the CR(s) and the PM and tell them they have reset the review clock. Although STARS will automatically update the submission and CR due dates, the PR should also provide an updated timeline (found on the ONADE template page) to the CRs with the revised reviewer due dates.

You can find additional information on the Appian workflow in the CVM ONADE Appian User Guide.

B. Resetting the Clock for Minor Technical Sections (M Submissions)

If resetting the clock of a major technical section (P submission) impacts the review clock for the linked minor technical sections, please refer to P&P 1243.4080 for information on how this impacts the M submissions and appropriate actions to take.[3] If a Q submission is open, the PR should consider changing the due date of the Q submission to match the M submissions.

[3] P&P 1243.4800 Labeling and All Other Information Technical Sections (Minor Technical Sections or M Submissions)

C. Resetting the Clock and Changing the Review Time for Shortened Review Time Submissions

If we receive an amendment with new or unrequested information for a submission with a shortened review time (SRT), the submission may no longer qualify for SRT. See P&P 1243.3060 and 1243.3070 for more information on the SRT process.

If we determine that the amendment contains more information than we can review in the SRT timeline and the submission no longer qualifies for the SRT process, we can reset the clock or change the review time.

1. Review Time Change: If we determine that the submission no longer qualifies for SRT, we can convert the submission from SRT to the normal review time for that submission type through the review time change process in Appian. STARS will utilize the original received date of the parent submission to calculate the new due date.

   For example, if the submission type in question is a technical section (P submission), the submission due date would be changed from the shortened review timeframe to the normal review timeframe and the new due date would be 180 days from the original received date of the parent submission.

   You can find additional information on the Appian workflow in the CVM ONADE Appian User Guide.

2. Resetting the Clock: If we receive an unsolicited amendment, an amendment that contains unrequested information, or a major amendment, we may reset the clock on that submission, as described above. Resetting the clock on an SRT submission will convert the submission from a shortened review time to the normal review time for that submission type (as described above for review time change) AND reset the clock based on the date the of the amendment.

   For example, if the submission type in question is a technical section (P submission), the submission due date would be changed from the shortened review timeframe to the normal review timeframe of 180 days. The new due date would be 180 days from the received date of the amendment for the submission.

IX. APPIAN CLOSEOUT PROCEDURES

When a CR returns consulting reviews in Appian, it is important to know they must return the consult for the parent submission and consults for any amendments separately.[4]

The PR is responsible for ensuring all consulting reviews and corresponding amendments have been returned through Appian before closing out a submission. When the PR closes out the parent submission, all the amendments will automatically close out in Appian. Unlike the CR close out process outlined in P&P 1243.3030, the

[4] See P&P 1243.3029 Closing Out a Consulting Review for STARS Submissions

PR only needs to initiate final action on the original submission. If we have to reset the clock during the review of the submission, a copy of the 'reset the clock' letter will be automatically placed in Corporate Document Management System (CDMS) when the parent submission is closed.

X. 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 – ONADE Reviewer's Chapter

1243.2050 - Refuse to File and Refuse to Review

1243.3020 - Managing the Review of Submissions in the Submission Tracking and Reporting System (STARS) Queue

1243.3024 - Scheduling and Holding Meetings with Outside Parties

1243.3029 - Closing Out a Consulting Review for Submission Tracking and Reporting System (STARS) Submissions

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

1243.3060 Implementing Shortened Review Times for New Animal Drug Application (NADA) Reactivations and Investigational New Animal Drug (INAD) File Resubmissions Using eSubmitter

1243.3100 – ONADE Refuse to Review (RTR) and Refuse to File (RTF) Assessments of Submissions and Applications that Contain Data

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

1243.3070 - Implementing Shortened Review Times for Abbreviated New Animal Drug Applications (ANADA) Reactivations and Generic Investigational New Animal Drug (JINAD) Resubmission

1243.4800 - Labeling and All Other Information Technical Sections (Minor Technical Sections or M Submissions)

Appian User Guide: Internal information redacted

XI. 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. Information on resetting the clock was added.

December 9, 2020 – updated to reflect current procedures for assessing submissions for quality and update amendment process. The title was changed from Amending and Resetting the Clock on Submission Tracking and Reporting System (STARS) Submissions to Assessing Submission Quality and Amending and Resetting the Clock on Submissions

December 17, 2020 – updated to fix a typo and fix a broken link

March 3, 2021 – Updated to unbold the Appendix in the table of content.

March 5, 2021 – Updated to fix a couple of typos

March 15, 2021 – Updated to fix a few typos and update the TOC. Updated to add the "the applicable statutory or ADUFA/AGDUFA timeframe" to Section V.

APPENDIX 1: AMENDMENT SUBMISSION CODES

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 as follows:

Parent Submission Types, Submission Codes and Amendment Submission Codes:

Parent Submission Type[5]	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

If a sponsor attempts to amend a submission after CVM has closed out the parent submission, CVM's ESS (Electronic Submission System) will reject the amendment.

[5] (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