OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

ADMINISTRATIVE PATHWAYS FOR OBTAINING ADDITIONAL CHEMISTRY, MANUFACTURING, AND CONTROLS INFORMATION

I. PURPOSE

This document provides direction to Office of New Animal Drug Evaluation (ONADE) Chemistry, Manufacturing and Controls (CMC) reviewers in the Division of Manufacturing Technologies (DMT) as they decide which administrative pathway(s) to use to obtain additional information from sponsors when it is necessary to meet regulatory requirements. In addition, it describes the administrative actions to take when inspectional status is the only outstanding issue remaining before a technical section complete letter or approval letter can be issued. The information in this document will most commonly be used for CMC technical sections[1] and supplemental applications, but the concepts may also be applied to Minor Changes and Stability Reports (MCSRs) and master files where appropriate.

II. REQUESTING INFORMATION FROM SPONSORS TO MEET REGULATORY REQUIREMENTS

DMT reviewers assess the information submitted in the CMC technical section pre-approval and supplemental applications post-approval to determine if the submitted information meets the regulatory requirements for approval. The regulatory requirements for approval of CMC technical sections and supplemental approvals exist in relevant statutory provisions, regulations, guidance documents, and are incorporated in the eSubmitter templates.

It is critical that CMC reviewers understand the administrative options available to them when they determine that additional information must be submitted to meet regulatory requirements. The CMC reviewer should consider the extent of the missing information, remaining time left on the review clock, if there are outstanding inspectional issues, and how the submission under review fits into the overall project timeline when choosing one or more administrative pathway(s) to request additional information. The decision for which administrative pathway(s) to use is situation-dependent and involves the judgement of the CMC reviewer, in conjunction with the rest of the review team[2] including the CMC reviewer's quality control (QC) lead and/or supervisor. The administrative

[1] The term "CMC Technical section" includes submissions to investigational new animal drug files (INAD), generic investigational files (JINAD), original new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), and any associated resubmissions/reactivations to the file or of the application.

[2] For original new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs), DMT is the consulting review division. The decision as to which administrative path to use should be discussed with the target animal division and any other impacted divisions so that there is agreement across the review team.

pathway chosen should be the one that is most reasonable to allow the shortest time to approval while ensuring product quality. The available administrative pathways are described below.

A. Amendments[3] and Commitments

An amendment may be requested from a sponsor when additional information is needed to complete the review of the submission. In some cases, the CMC reviewer may identify additional information that is needed for regulatory approval but determines that the information can be submitted post-approval (e.g., in the first MCSR). In this case, the reviewer can also request an amendment to obtain the post-approval commitment. Major amendments are those that have a significant impact on our ability to review the information or make a regulatory decision within the remaining review time, causing us to reset the clock. This section only focuses on amendments that do not result in resetting the clock.

Considerations for making the decision to request an amendment are described in P&P 1243.3026 and include factors such as:

- the quality of the submission;
- if the requested information will allow the review team to complete the review of the submission; and
- if there is sufficient time to complete the review of the submission and amendment within the established review time.

If the submission meets the criteria for an amendment, this is the preferred administrative route for obtaining the missing information since it results in the shortest path for approval or technical section complete. If the amendment request does not meet these criteria, the DMT reviewer should use one of the administrative pathways described below.

B. Shortened Review Time (SRT)[4, 5] for CMC Technical Sections and Changes Being Effected in 30 Days (CBE-30) Reactivations for Prior Approval Supplements

SRT is an option that can be used when the information missing from the CMC technical section does not meet the criteria for an amendment, but also does not rise to the level of an incomplete letter with a full review clock for reactivation/resubmission. The criteria described in P&P 1243.3060 and 1243.3070 include factors such as:

- the quality of the submission;

[3] 1243.3026 Assessing Submission Quality and Amending and Resetting the Clock on Submissions.
[4] 1243.3060 Implementing Shortened Review Times for New Animal Drug Application (NADA) Reactivations and Investigational New Animal Drug (INAD) File Resubmissions Using eSubmitter
[5] 1243.3070 Implementing Shortened Review Times for Abbreviated New Animal Drug Application (ANADA) Reactivations and Generic Investigational New Animal Drug (JINAD) File Resubmissions

- if we can clearly identify and communicate to the sponsor the additional information that could reasonably be expected to complete the application or submission;

- and if we can complete review of the reactivation/resubmission and make a review decision within the shortened review time.

These are similar considerations as for requesting an amendment, but while the timeframe for review of an amendment is generally very short (days or weeks), the timeframe for SRT is longer, allowing for review of a wider range of issues than amendments. If the submission meets the criteria for SRT, we should use this administrative pathway since it offers a significantly shorter path to approval/technical section complete than an incomplete letter with a full review clock.

SRT is an administrative pathway that is only available for CMC technical sections. For prior approval supplements (PAS), if the missing information does not meet the criteria for an amendment, a possible administrative pathway to obtain the additional information needed to meet regulatory requirements is to incomplete the supplement and allow a resubmission of the PAS as a CBE-30. This pathway should be used when sufficient information has been submitted and reviewed in the PAS to reduce the risk of implementing the proposed supplemental change, but more information needs to be submitted to approve the supplement than is practical to be reviewed in an amendment.

C. Overdue Submission

In certain situations, the reviewer, with their supervisor, should consider if allowing the submission to go overdue is the appropriate administrative action. The two most common situations where we may choose to go overdue are:

1. If the submission meets all criteria for an amendment request except for time left on the review clock, and the CMC technical section is the last technical section before project approval (i.e., “end game”), the review team should consider requesting the amendment and allowing the submission to go overdue.

2. The only remaining issue before approval/technical section complete is waiting for the outcome of a scheduled inspection (see section III).

In all cases, before making the final decision to go overdue on a submission, the DMT supervisor for the review team should inform the division director of the proposed decision to go overdue so that they can work with ONADE’s Senior Project Manager to determine that the decision will not impact ONADE’s ability to meet the overall ADUFA or AGDUFA goals for that submission type. Once ONADE’s Senior Project manager confirms the acceptability of the decision to go overdue, the supervisor for the review team should email the sponsor to inform them that the submission will be overdue and provide an expected completion date for the submission.

D. Information Acceptable, Technical Section Incomplete

If the only substantial remaining issue for a technical section is the current Good Manufacturing Practice (CGMP) status and/or an open pre-approval inspection (PAI), the reviewer should request an amendment to resolve any outstanding minor issues and issue an “information acceptable, technical section incomplete” letter, where

appropriate (see section III for additional details). The comment issued should indicate that the sponsor should reactivate/resubmit the response once the CGMP status is acceptable, the PAI, including review of the firm's responses to any 483s has been closed, and/or the facility is ready for inspection/reinspection, as applicable.

E. Incomplete Letter

The reviewer should incomplete the technical section or application when 1) the missing information is of a magnitude that indicates a poor-quality submission, 2) if it is unclear that the requested information will allow the review team to complete the application or submission (e.g., review outcome is dependent on the review of additional studies), or 3) if the information that would be requested cannot be reviewed in the timeframe allotted for an amendment or SRT.

III. IMPACT ON DECISION WHEN INSPECTIONAL STATUS IS THE ONLY REMAINING ISSUE

Before a technical section complete for a new animal drug approval or approval of supplemental changes involving new facilities or major changes involving existing facilities can be recommended, not only must the submitted regulatory information for approval be acceptable but the facilities cited in the submission must be CGMP compliant and ready for commercial manufacturing. If the regulatory information for approval is acceptable and a PAI was conducted and resulted in a final APPROVE recommendation, the reviewer should approve the application or issue a technical section complete letter. If the regulatory information for approval is acceptable but the inspectional status is unacceptable or pending, the following actions may be taken:

A. If a PAI was conducted and resulted in a final WITHHOLD recommendation, the reviewer should issue an "information acceptable, technical section incomplete letter" for (J)INAD files or an incomplete letter for applications. However, if CVM believes the initial withhold recommendation may be downgraded to approve after further review of the firm's responses and/or the establishment inspection report (e.g., based on additional information obtained through inspection involvement), on rare occasions CVM may decide to allow the submission to go overdue so that the CGMP status can be efficiently determined.

B. If a PAI request was issued, but the inspection did not occur due to the facility informing FDA that they are not available for inspection, not ready for inspection, or not ready for commercial manufacturing, the reviewer should issue an "information acceptable, technical section incomplete letter" or an incomplete letter for applications. Any open PAI requests will be cancelled and reissued, as necessary, upon reactivation.

C. If the file/application due date is approaching, a PAI request was issued, but the inspection is not scheduled, DMT will request a major amendment from the sponsor, where appropriate, to reset the clock on the submission, unless the PAI cannot reasonably be scheduled (e.g., due to travel restrictions). If CVM knows the PAI cannot reasonably be scheduled (e.g., due to travel restrictions), the reviewer should issue an "information acceptable, technical section incomplete letter" to a (J)INAD or an incomplete letter for an application. Any open PAI requests will be cancelled and reissued, as necessary, upon reactivation.

D. If the file/application due date is approaching, a PAI request was issued, and the inspection is scheduled but is beyond the due date, DMT will allow the submission to go overdue or request a major amendment from the sponsor, where appropriate, to reset the clock on the submission so that the CGMP status can be efficiently determined.

IV. REVIEWING A SUBMISSION OUT OF THE QUEUE (ADMINISTRATIVE REVIEW)

For submissions where the only remaining issue before a technical section complete or application approval is the inspectional status, the DMT reviewer should perform an "administrative review" of the application once an inspection is closed with a satisfactory outcome and the sponsor reactivates/resubmits their response to the incomplete letter. Administrative review is a situation where there is no additional technical information, including significant information contained in referenced master files, to review. After obtaining supervisory concurrence, the reviewer should close the submission out of the queue so we can process the technical section complete or approval letter as soon as is practical.[6]

V. REFERENCES

CVM Policies and Procedures Manual – ONADE Reviewer's Chapter

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

1243.3026 - Assessing Submission Quality and Amending and Resetting the Clock on Submissions

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

1243.3070 - Implementing Shortened Review Times for Abbreviated New Animal Drug Application (ANADA) Reactivations and Generic Investigational New Animal Drug (JINAD) File Resubmissions

VI. VERSION HISTORY

March 22, 2024– Original version.

[6] 1243.3020 Review of Submissions in the Submission Tracking and Reporting System (STARS) Queue