OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

LABELING AND ALL OTHER INFORMATION TECHNICAL SECTIONS (MINOR TECHNICAL SECTON OR "M" SUBMISSIONS)

I. PURPOSE

This document describes the procedures for processing and reviewing Labeling and All Other Information technical sections.

II. BACKGROUND

An original or B1 supplemental new animal drug application (NADA) or an original abbreviated new animal drug application (ANADA) is comprised of "major" and "minor" technical sections, either in the application itself, or by reference to content in other investigational new animal drug [(J)INAD] or (A)NADA files. NADAs have five "major" technical sections (i.e., Effectiveness, Target Animal Safety, Human Food Safety, Environmental Impact, and Chemistry, Manufacturing, and Controls) and two "minor" technical sections (i.e., Labeling and All Other Information (AOI)). ANADAs have five "major" technical sections (i.e., Bioequivalence, Patent Certification and Marketing Exclusivities, Environmental Impact, Human Food Safety, and Chemistry, Manufacturing, and Controls) and one "minor" technical section (i.e., Labeling). ANADAs do not have an AOI technical section.

Sponsors may submit the information that will comprise the technical sections within a single application or submit it separately to their investigational new animal drug (INAD) file or the generic investigational new animal drug file (JINAD) using the phased review process for new animal drugs. As of October 2018, most of the submissions made to ONADE will be using eSubmitter. When sponsors use eSubmitter, they must select the correct submission type (M) along with the correct submission classification code before they are able to complete their submission. The sponsor must identify the last P submission when using eSubmitter. Sponsors may submit "M" submissions only if they submitted all the major technical sections, or we have already determined all major technical sections are complete. Once we determine that all major and minor technical sections are complete for a proposed new animal drug, the sponsor may submit their administrative NADA or ANADA.

III. BUSINESS RULES

The NADA target animal divisions (TAD), in consultation with the project management team, implement the business rules described in this section with respect to M submissions.[1] When the M submissions arrive, it is the responsibility of the project manager (PM) to ensure that the M submissions are tied to the correct P submission in Submission Tracking and Reporting System (STARS) when they arrive. Also, the PM should ensure that if the due dates for the open P submission(s) change, the M submission due dates change as well.[2] The generic animal drug reviewers confirm proper implementation the M submission business rules on their own.

Sponsors may submit their M submissions at any point after they submit all major technical sections for the applicable approval track. If the last P submission has a 180-day clock, the assigned PM will encourage the sponsor to submit the M submissions no later than 80 days into review of that P submission, to allow at least 100 days for review of the M submissions. If the last P submission has a 60-day clock, the assigned PM will encourage the sponsor to submit the M submissions at the same time as that P. If a sponsor submits the M submissions after the recommended submission date, the TAD will determine the target due date for completing review of the M submissions (which may or may not be consistent with the STARS due date driven by the pending P submission).

The following business rules apply for processing M submissions relative to the P submissions they reference.

A. Check Pending and Completed P Submissions

Determine that pending P submission(s) plus the already completed technical sections for the applicable approval track represent all major technical sections, or that all major technical sections for that approval track are already completed. This can be determined by communication with the PM or communicated in the End Game meeting. See P&P 1243.3051 for further questions about the End Game.

B. Confirm That the Submission Has Been Assigned the Correct Subclass Code:

1. LB for the Labeling Technical Section
2. AO for the All Other Information Technical Section

If the submission was submitted electronically and was coded incorrectly, void the submission. See P&P 1243.3011 for more detail. If the submission was received in paper and it was coded incorrectly, the primary reviewer can submit a STARS

[1] Target animal divisions are those that are responsible for effectiveness and target animal safety review or bioequivalence evaluation in the case of generic new animal drugs. Note: The Division of Generic Animal Drugs does not work with the ONADE Project Managers.
[2] See P&P 1243.3051, "Verifying Scope and Technical Section Status for Phased Review (INAD) Projects in the End Game."

Correction Request Form. See P&P 1243.3002 for handling and rejecting paper applications and submissions received after October 1, 2018.)

C. Confirm the M Submission References the Appropriate Submission

Confirm the M submission references the appropriate submission in the applicable approval track to assure assignment of the correct STARS due dates. All M submissions must reference either a P or Z submission for the applicable approval track. The referenced submission can be completed or under review.

1. If there are multiple pending P submissions, identify the P submission with the latest CVM due date. Confirm that the M submission references that P submission and that the consulting review and CVM due dates for the M submissions are the same as those for the referenced P submission.

2. If all major technical sections are complete (i.e., there are no pending P submissions) in the applicable approval track for this potential approval when we receive the M submissions, confirm that the M submissions reference the most recently completed P submission in STARS. For this situation, the due dates for consulting and primary reviews for the M submission(s) are 80 and 100 days, respectively, from the received date of the M submissions.

3. If no P submissions were required for review (as may be the case for some Animal Drug Availability Act of 1996 (ADAA) combinations intending to qualify for a 60-day review timeline), confirm that the M submission(s) references the Z submission in STARS in which agreements were made regarding each technical section requiring no further assessment. For this situation, the due dates for consulting and primary reviews for the M submission(s) are 80 and 100 days, respectively, from the received date of the M submissions. (Note: the process for review of original ADAA feed use combination NADAs within 60 days is described in P&P 1243.5730.)

4. Submit a STARS Correction Request Form if the M submissions reference the incorrect P or Z submission.

D. If the P Submission Referenced By the M Submissions is Completed Before Other Pending P Submissions

If the P submission referenced by the M is completed before other pending P submissions in the applicable approval track, submit a STARS Correction Request Form that requests the following changes:

1. Update all pending M submissions associated with the completed P submission in the applicable approval track to reference the pending P submission with the latest CVM due date in that approval track.

2. Confirm that the consulting and CVM due dates for the pending M submissions in that approval track are updated to the due dates of newly referenced P submission.

E. Amendments

1. Amendment to the referenced P submission

   If we receive an amendment (T submission) to the referenced P submission that causes us to reset the clock of the referenced P submission, the due dates of the M submissions are also set to the new due dates of the referenced P submission. Confirm that the due dates for the M submissions are the same as those for the amended P submission they reference.[3]

2. Amendments to P submissions not referenced by the M submissions

   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. [4] If the referenced P needs to be updated, the PM will submit a STARS Correction Request form.

F. When to Refuse to Review an M Submission

Refuse to review an M submission under the following circumstances:[5]

1. When there are no pending applicable P submissions in STARS in the applicable approval track at the time the M is submitted, and:

   a. at least one major technical section required for approval remains incomplete (i.e., we have not issued a "technical section complete" (TSC) letter for that technical section), or

   b. at least one issued TSC letter is not currently valid or more information is going to be requested for a technical section at the time the M is submitted.[6]

2. There are pending P submission(s) in the applicable approval track where it is likely to result in the issuance of a TSC letter, but at least one of the other major technical section(s) not currently under review is incomplete or does not have a currently valid TSC letter at the time the M is submitted.

[3] See P&P 1243.3026
[4] See footnote 3
[5] See P&P 1243.2050 and Guidance for Industry #119
[6] "Currently valid" means that we are not aware of any new scientific issues that would cause us to reconsider whether the data supporting a technical section are adequate since we issued the TSC letter and that the caveats in the TSC letter have not voided any of the TSC letters.

3. If we have no applicable P submissions in the applicable approval track that have been completed and/or none are currently under review and/or not all technical sections are complete at the time the M is submitted.

4. The M submission is of inadequate quality.[7]

In each of these cases, issue a refuse to review letter to the sponsor advising the sponsor submission of this information is premature. Advise the sponsor in a letter of the appropriate timing for them to send us their M submissions. This will close out the M submission.

G. When to Void an M Submission

An M submission may be voided in situations where the sponsor submitted the M by mistake or has sent us a duplicate M submission. Follow the voiding submission workflow in the Appian User Guide[8].

IV. REVIEWING M SUBMISSIONS

Due to the nature of minor technical sections, we expect sponsors to submit complete minor technical sections of adequate quality, i.e., submission of the entire labeling (facsimile or, if available, final printed) or all of the AOI information for the applicable technical sections. Work to complete your review of a minor technical section by the STARS due date. However, if there are issues you cannot resolve by the STARS due date, discuss with your team leader and/or division director if the submission should receive an incomplete letter or go overdue.

As with the review of any submission, you may request amendments that are likely to help you complete the review of the submission.[9] You may also use informal communication means (e.g., email, telephone, and facsimile) to reach agreements that would facilitate completion of the review of an M submission. Document the rationale, substance, and decisions relating to these informal communications in the administrative file.[10] The acceptance of amendments or the use of informal means of communication generally should not result in resetting the review clock for the submission. Consult your team leader and division director if you feel there is a need to reset the clock on an M submission.

For Labeling M submissions, we are now requesting the addition of an "Approved by FDA" labeling statement based on the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (H.R. 5554). These amendments added a section to the Federal Food, Drug, and Cosmetic Act (FD&C Act) that requires the addition of the statement "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA #

[7] See P&P 1243.2050 and Guidance for Industry #119.
[8] See Appian User Guide for information regarding voiding submissions:
Internal information redacted.
[9] See P&P 1243.3026
[10] See 21 CFR 10.70

XXX-XXX" to labeling (except representative [Blue Bird] labeling) of approved new animal drugs and generic new animal drugs, respectively, by September 30, 2023. We are requesting the addition of the labeling statement to all approved and marketed labeling components of these products. We are also encouraging the addition of the statement to Blue Bird labeling to clearly identify that the medicated feed was manufactured in accordance with FDA-approved Blue Bird labeling. If the labeling included in the M submission does not include the applicable labeling statement, refer to the ONADE Policy 'Initial Recommendations for the Addition of Approved by FDA Statements to Labeling' found on the ONADE Policy SharePoint page for information on when and how to ask the sponsor to add the statement to the labeling.[11] The Technical Section Complete letter template also includes language to request addition of the statement to the labeling included in the sponsor's administrative A/NADA if there is there isn't adequate time for the draft labeling to be amended under the labeling M submission.

Do not close the submission (i.e., send the sponsor a letter) for an M submission until you determine the final status of all major technical sections.

The following are actions we may take upon receiving an M submission and determining it is acceptable for review:

A. If the TSC Letters for All Major Technical Sections Are Currently Valid

Complete the review of the M submission and send the sponsor a letter (TSC or technical section incomplete (TSI)), as appropriate).

B. If There are P Submission(s) Pending, and Our Review of All Pending P Submissions Results in TSC Letters

Complete the review of the M submission and send the sponsor a letter (TSC or TSI, as appropriate) for the M submission after that for the referenced P submission. Ideally, all M submissions and the Q submission for the Freedom of Information (FOI) should be closed out on the same day.

C. If There are P Submission(s) Pending, and Our Review of At Least One Pending P Submission Does Not Result in a TSC Letter

Review the M submission to the fullest extent possible and issue a technical section incomplete letter. The final action code should be "Technical Section Incomplete; Submitted Information Not Acceptable; Letter Sent."

Document the extent and substance of your review efforts for the M submission. Send a TSI letter to the sponsor. Indicate in the letter that we are issuing a TSI letter because the major technical section remains incomplete and therefore, the

[11] Link to ONADE Policy on "Approved by FDA…" labeling statements
Internal information redacted.

M submission no longer meets the conditions permitting its completion. Include in the letter any findings from your review of the M submission commensurate with the information available at that time. Indicate in the letter that we will review the information when they submit a new M submission that meets the appropriate conditions for submission. Also, indicate in the Labeling incomplete letter that CVM might make additional changes to the labeling when the labeling is reviewed as a whole. Ask the sponsor to include in the new M submission either an affirmation that the information in the previous M submission remains current and accurate, or the M submission contains amended information necessary to complete the minor technical section. See P&P 1243.3060 section V.D. for an example of the process when the last P is incomplete.

V. REFERENCES

Code of Federal Regulations (Title 21)

Part 10 – Administrative Practices and Procedures

§10.70, Documentation of significant decisions in administrative file

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

1243.3002 – Handling and Rejecting Paper Applications and Submissions

1243.3011 - Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications

1243.3026 - Amending and Resetting the Clock on Submission Tracking and Reporting System (STARS) Submissions

1243.3050 - Identifying and Documenting Technical Section Requirements for Approval

1243.3051 – Verifying Scope and Technical Section Status for Phased Review INAD Projects in the End Game

1243.3060 – Implementing Shortened Review Times for NADA Reactivations and INAD Resubmissions using eSubmitter

1243.4085 - All Other Information

1243.5730 – Review of 60-day Original Animal Drug Availability Act of 1996 (ADAA) Feed Use Combination New Animal Drug Applications (NADAs)

ONADE Office Policy Page

Initial Recommendations for the Addition of Approved by FDA Statements to Labeling

VI. VERSION HISTORY

March 29, 2011 – original version

April 12, 2012 – update original version to incorporate our electronic based submission process (eSubmitter) and update P&P numbers

December 1, 2015 – updated to remove references to the ERA process, added shortened resubmission information, and clarify business rules.

June 17, 2016 – update format and redacted internal information.

July 5, 2018 – Updated to incorporate changes in processes associated with the review of original ADAA combination medicated feed combination NADA applications within 60 days.

October 1, 2018 - This document has been updated to incorporate changes introduced as a result of the ADUFA IV Goal of reviewing original Animal Drug Availability Act of 1996 (ADAA) feed use combination NADA applications within 60-days. The new processes associated with these submission types are to be implemented as of October 1, 2018.

April 4, 2019 – updated to add instructions on when and how to ask for addition of "Approved by FDA…" statements to labeling. Updated to include information about accepting and rejecting paper submissions and applications.