OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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

I. Purpose 1
II. Background 1
III. Business rules 1
IV. Reviewing M submissions 5
V. References 7
VI. Version history 8

I. PURPOSE

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

II. BACKGROUND

An original or B1 supplemental new (or abbreviated new) animal drug application (A)NADA) is comprised of "major" and "minor" TSs, either in the application itself or by reference to content in other investigational (or generic investigational) new animal drug ((J)INAD) files or (A)NADAs.

- NADAs have five major TSs: Effectiveness, Target Animal Safety, Human Food Safety, Environmental Impact, and Chemistry, Manufacturing, and Controls (CMC); and two minor TSs: Labeling and All Other Information (AOI).

- ANADAs have five major TSs: Bioequivalence, Patent Certification and Marketing Exclusivities, Environmental Impact, Human Food Safety, and CMC; and one minor TS: Labeling. ANADAs do not have an AOI TS.

Sponsors may submit the information that will comprise the TSs within a single application or submit it separately to their (J)INAD) file using the phased review process for new animal drugs. As of October 2018, most 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 TSs or if we have already determined all major TSs are complete. Once we determine that all major and minor TSs are complete for a proposed new animal drug, the sponsor may submit their administrative (A)NADA.

III. BUSINESS RULES

The NADA target animal divisions (TADs), in consultation with impacted consulting reviewers and 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 project manager (PM) ensures that the M submissions are tied to the correct P submission in Submission Tracking and Reporting System (STARS). Also, the PM ensures that if the CVM due dates for the open P submission(s) are extended in STARS through resetting of the clock (see section E), the M submission due dates are extended as well (see P&P 1243.3051). 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 TSs for the applicable approval track. The M submissions' due dates can be impacted by when in the review process the M is submitted. If a sponsor submits their M submissions late (i.e., beyond our recommended submission date for that particular P submission) in the review of the last P submission or if we see the M submissions for the first time associated with a shortened review P submission, a 100-day target due date is established for the M submissions. Reviewers work to complete the M submission within this established 100-day review time frame recognizing that it is probable and acceptable for the submission to go overdue in STARS. Note: STARS will still show the CVM due date for the M to be the due date of the last P submission.

If the last P submission has a 180-day clock, the assigned PM encourages 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 a sponsor submits the M submissions after the recommended submission date, STARS still assigns the M the same CVM due date as the last open P submission. Then the TAD, in consultation with impacted consulting reviewers, and the PM, establishes a 100-day target due date and communicates the new target due dates to the PM and consulting reviewers.

If the last P submission has a 60-day clock, the assigned PM encourages the sponsor to submit the M submissions at the same time as that P submission. If we have reviewed the M submissions previously, the TAD, in consultation with the impacted consulting reviewers and the PM, discusses and determines if we can complete review of the M submissions by the CVM due date in STARS or establishes a new target due date. If we have not reviewed the M submissions previously, the TAD, in consultation with impacted consulting reviewers and the PM, establishes a 100-day target due date from the date it is received. Note: STARS will still show the due date for the M to be the due date of the last P submission.

When M submissions are submitted past the standard target date and new due dates are established, the PM contacts the sponsor to tell them these new target due dates.

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

A. Check Pending and Completed Submissions

Determine that pending P submission(s) plus the already completed TSs for the applicable approval track represent all major TSs or that all major TSs for that

[1] TADs 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.

approval track are already completed. This can be done by communication with the PM or in the End Game meeting.[2]

B. Confirm the Submission Code

1. LB for the Labeling TS

2. AO for the All Other Information TS

   If the submission was submitted electronically and was coded incorrectly, void the submission. You have 60 days from the received date to void the submission made to the investigational file.[3] If the submission was received in paper and coded incorrectly, the primary reviewer will email the EDSR Mailbox[4] to request recoding. The subject line should be STARS Correction Request.[5] The ONADE Business Informatics Team manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

C. Confirm the M Submissions 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 TSs 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 TS 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.[6]

[2] See P&P 1243.3051 Verifying Scope and Technical Section Status for Phased Review Investigational New Animal Drug Projects in the End Game
[3] See P&P 1243.3011 Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications.
[4] Internal information redacted.
[5] See P&P 1243.3002 Handling and Rejecting Paper Applications and Submissions.
[6] The process for review of original ADAA feed use combination NADAs within 60 days is described in P&P 1243.5730, "Review of 60 Day Original Animal Drug Availability Act of 1996 (ADAA) Feed Use Combination NADA.

4. Send an email to the EDSR Mailbox[7] if the M submissions reference the incorrect P or Z submission. The subject line should be STARS Correction Request. The ONADE Business Informatics Team manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

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

If the P submission referenced by the M is completed before other pending P submissions in the applicable approval track, no changes are made to the due date of the M submissions. The PM should contact the sponsor to make sure they understand the due dates for the remaining P submissions and M submissions.

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 (see P&P 1243.3026).

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 (see P&P 1243.3026). If the referenced P needs to be updated, the PM will email the EDSR Mailbox.[8] The subject line should be STARS Correction Request. The ONADE Business Informatics Team manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

F. When to Refuse to Review M Submission

Refuse to review (RTR) an M submission under the following circumstances:[9]

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 TS required for approval remains incomplete (i.e., we have not issued a “TS complete” (TSC) letter for that TS), or

7 Internal information redacted.

8 Internal information redacted.

9 See P&P 1243.2050 Refuse to Review and Guidance for Industry #119 How the Center for Veterinary Medicine intends to handle deficient submissions filed during the investigation of a new animal drug

b. at least one issued TSC letter is not currently valid or more information is going to be requested for a TS at the time the M is submitted.[10]

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 TS(s) not currently under review is incomplete or does not have a currently valid TSC letter at the time the M is submitted.

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 TSs are complete at the time the M is submitted.

4. The M submission is of inadequate quality.

   In each case, issue a RTR letter to the sponsor advising the sponsor submission of this information is premature and advise them 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, has the inappropriate subclass code, or has sent us a duplicate M submission. Follow the voiding submission workflow in the Appian User Guide.

IV. REVIEWING M SUBMISSIONS

Due to the nature of minor TSs, we expect sponsors to submit complete minor TSs 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 TSs.

Work to complete your review of a minor TS by the CVM due date in STARS or the target due date if one has been established. However, if there are issues you cannot resolve by the CVM due date in STARS or target due date, discuss with your team leader (TL) and/or division director (DD) if the submission should receive an incomplete letter or go overdue. Typically, when a project is in the end game and all scientific issues have been resolved, the general expectation is that you work toward completing the M submissions even if you need to establish new target due dates with your TL and allow the submission to go overdue, rather than sending an incomplete letter. For example, review of the M labeling submission may be dependent on information in the last P submission. If review of the last P submission takes the full or very close to the full review time, it may not be possible to incorporate the information from the P submission into the labeling by the due date. Talk with your TL and DD if additional review time is needed. Notify the PM if a new target due date is established.

As with the review of any submission, you may request amendments that are likely to help you complete the review of the submission (see P&P 1243.3026). You may also use informal communication means (e.g., email, telephone) 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 (see 21 CFR 10.70). The acceptance of amendments or the use of informal means of

[10] "Currently valid" means that we are not aware of any new scientific issues that would cause us to reconsider whether the data supporting a TS are adequate since we issued the TSC letter and that the caveats in the TSC letter have not voided any of the TSC letters.

communication generally should not result in resetting the review clock for the submission. Consult your TL and DD if you feel there is a need to reset the clock on an M submission.

For Labeling M submissions, all labeling (except representative (Blue Bird) labeling) of approved new animal drugs and generic new animal drugs must include the statement "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX", respectively, per Section 502(w)(3)[11] of the FD&C Act, or else the drug will be considered misbranded. Refer to the ONADE Policy "Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs" (on the ONADE Policy SharePoint) for additional information. If any labeling components included in the M submission other than Blue Bird labeling (and exemptions identified in the ONADE Policy) do not include the applicable labeling statement, the submission must be amended with updated labeling including the statement before the Labeling M TS can be complete.

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 TSs.

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 TS 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 the TSC letter 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 TSI 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 that communicates the following:

- indicate that we are issuing a TSI letter because the major TS remains incomplete and therefore, the M submission does not meet the conditions permitting its completion;
- include any findings from your review of the M submission commensurate with the information available at that time;

[11] 21 U.S.C. 352(w)(3)

- indicate that we will review the information when they submit a new M submission that meets the appropriate conditions for submission;
- indicate that CVM might make additional changes to the labeling when the labeling is reviewed as a whole; and
- ask the sponsor to include in the new M submission either an affirmation that the information in the new M submission remains the same as that previously submitted and is accurate, or the M submission contains amended information necessary to complete the minor TS.[12]

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 (GFI)

#119, How the Center for Veterinary Medicine intends to handle deficient submissions filed during the investigation of a new animal drug

CVM Program Policies and Procedure (P&P) Manual – ONADE Reviewer's Chapter

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 New Animal Drug Product Approval

1243.3051 - Verifying Scope and Technical Section Status for Phased Review Investigational New Animal Drug Projects in the End Game

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

[12] See section VIII.C. of P&P 1243.3060, "Implementing Shortened Review Times for New Animal Drug Application (NADA) Reactivations and Investigational New Animal Drug (INAD) File Resubmissions Using eSubmitter," for an example of the process when the last P is incomplete.

ONADE Office Policy Page

Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs

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.

January 27, 2020 – updated to clarify when new target due dates for M submissions can be established which may result in the M submissions going overdue in STARS.

June 26, 2020 - Updated all internal links for SharePoint sites because FDA has migrated this information to a new version of SharePoint.

August 25, 2020 – Updated to fix broken link in footnote number 8 for the Appian User Guide.

September 30, 2023 - Cyclical quality systems review completed, and minor formatting updated. Section IV. updated for changes associated with the law requiring the "Approved by FDA" labeling statement taking effect. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font. Section IV. updated for changes associated with the law requiring the "Approved by FDA" labeling statement taking effect.

December 7, 2023 – Updated section III. B., C., and E. to remove the STARS Change Request Form information. That form has been retired. The instructions are to now send an email request to the EDSR Mailbox to corrections made in STARS.