OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

PROCEDURE FOR SPONSORS TO MAINTAIN CONDITIONALLY APPROVED PRODUCTS AND OBTAIN FULL APPROVAL

I. PURPOSE

The document explains to Office of New Animal Drug Evaluation (ONADE) reviewers:

- the content and timing requirements for a Conditional Approval (CA) renewal request;
- the review procedure for CA renewal requests;
- the content and timing requirements for an application for full approval after a CA;
- the procedure for reviewing an application for full approval after a CA; and
- what to do if a CA does not successfully proceed to a full approval.

This document discusses the process for a sponsor to progress from a CA to a full approval. The process is the same whether a product was determined to be eligible under the Minor Use and Minor Species[1] (MUMS) or Expanded Conditional Approval[2] (XCA) criteria. The available MUMS incentives do not impact technical section requirements or sponsor responsibilities.

A conditionally approved product is demonstrated to be safe and properly manufactured in accordance with the FDA approval standards for safety and manufacturing and is demonstrated to have a reasonable expectation of effectiveness (RXE) pending a full demonstration of effectiveness. The CA is valid for one year, and the sponsor may renew it annually for up to four additional 1-yr terms. The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that the application for full[3] approval be submitted no later than 180 days prior to the termination date of the last conditional approval period (~4.5 years from the date CA was granted).[4]

II. CA RENEWAL REQUEST

Sponsors must submit renewal requests each year in order to maintain their CA. The renewal request is submitted, using eSubmitter, as an N-G-OT submission. The CA

[1] See Guidance for Industry (GFI) #61.

[2] See GFI #261 and P&P 1243.2100.

[3] "Full" approval is used to distinguish a new animal drug approval from a CA.

[4] This timing requirement applies regardless of whether the sponsor is using the phased review process or the 180-day application process.

renewal request is a separate submission from the MUMS designation annual report. Prior to approval, sponsors of MUMS-designated products are required to submit designation annual reports to the Office of MUMS (OMUMS) that demonstrate due diligence to maintain a designation (see GFI #61). Once a MUMS-designated product is fully or conditionally approved, the designation annual reporting requirement to show due diligence ceases, so the sponsor no longer must submit designation annual reports. If a CA is withdrawn or not renewed, the sponsor must resume designation annual reporting to OMUMS until the product is fully approved, the designation is terminated, or the 7-yr period of exclusive marketing rights ends.

A. Deadline for Submission of Renewal Requests

To maintain the CA, the sponsor must submit their renewal request no later than 90 days from the end of each 1-yr period for which the original or renewed CA is effective.[5]

1. If a sponsor asks about submitting their renewal request early, we inform them that the only requirements are to demonstrate that they are making sufficient progress toward full approval and accurately reporting sales numbers. There is no restriction on a sponsor requesting a renewal early, but if the renewal request is submitted too early, the sponsor risks not being able to satisfy the requirements.

   The assigned project manager (PM) emails a reminder to sponsors 30 days before the due date of the renewal request each year. **Note:** While the PMs provide this email to the sponsor as a courtesy, it is the sponsor's responsibility to submit their renewal request on time. The PM uses the team template and documents the reminder email in the Submission Tracking and Reporting System (STARS) Drug Development Projects (DDP) module.

2. If the renewal request does not arrive on time or we have reason to believe that the request will not be timely, the PM convenes an internal meeting as described in Section V.

B. Content of a Renewal Request

A renewal request must demonstrate that:

1. the sponsor is making sufficient progress toward meeting the full approval requirements under Section 512(d)(1)(E) of FD&C Act (see examples in P&P 1243.5706);
2. the quantity of the drug distributed is consistent with the conditionally approved intended use and conditions of use; and
3. the same drug in the same dosage form for the same intended use has not received approval under Section 512 of the FD&C Act or, if such drug has been approved, the holder of the approved application is unable to assure the availability of sufficient quantities of the drug[6] to meet the needs for which the drug is intended.

[5] Refer to section 571(d)(1) of the FD&C Act for details on the requirement to submit annual renewal requests as well as the deadline.

[6] See Section 571(d)(2) of the FD&C Act

C. Review Process for a Renewal Request

We issue an acknowledgement letter informing the sponsor whether their CA was renewed within **90 days** of the received date, unless we grant ourselves a 90-day extension (see Item 7 below). Due to limitations in STARS, the STARS due date will show the standard N-G-OT timeframe of 180 days. When ONADE is able to assign a unique sub-class code to renewal requests, the submissions will reflect the appropriate 90-day timeframe. For now, these submissions will be differentiated in STARS from other G-OT submissions by the Purpose of Submission field.

1. Upon receipt of the renewal request from the sponsor, ONADE assigns the submission to a primary reviewer (PR) within the target animal division (TAD).

    a. Within **5 days** of the assignment of the renewal request, the PR consults CVM's Office of Surveillance and Compliance (OSC), Division of Pharmacovigilance and Surveillance (HFV-240) to ensure there are no outstanding adverse reporting issues that would impact the CA renewal; and to determine if any adverse drug experiences reported during the CA period should be considered for addition to the label, and to confirm that the sponsor has submitted appropriate pharmacovigilance data to CVM in compliance with the CA.

2. The PR uses the ONADE template "CA review timeline.xlsx" to calculate the appropriate due dates, including consulting due dates. The PR shares the populated timeline with individuals on their signature chain and consulting reviewers, to ensure all members of the review team are working toward the correct due dates.

3. The PR emails the appropriate team in ONADE's Division of Manufacturing Technologies (DMT) to confirm that there are no concerns regarding the manufacturing of the drug or the post-approval responsibilities (e.g., changes to stability times or storage conditions, sponsors are submitting their post-approval reporting including MCSRs, etc.).

4. The PR confirms whether the sponsor met the requirements necessary to renew the CA, using division SOPs as appropriate.

5. Optional Review Time Extension

    The timeframe for review can be extended from 90 days to 180 days in order to complete review of the renewal request; it cannot be extended for any other reason. Within 60 days of receipt of the submission, the PR determines whether they will extend the review time.

    If the PR determines that they will extend the review time, the PR creates a Q submission using Appian (Purpose of Submission will be "Other") by day 70 and issue a paper letter to the sponsor using the Renewal Request Extension (Q) Letter Template[7] by day 90.

[7] At this time, no non-final action functionality exists within N-G-OT submission types. Once we can program that functionality into the N-G-OT submission types, we will develop a non-final action letter, based on our template used for this Q submission, to reset the clock.

a. The letter informs the sponsor that we are extending the review time to 180 days, confirms that the CA remains in effect during this extension, and states that the extension does not change the anniversary date for purposes of the next renewal request deadline, nor does it change any of the responsibilities or requirements of the sponsor.

b. The division director (DD) will sign the letter; therefore, the Quality Assurance (QA) team is not required to be consulted.

c. The letter is sent to the sponsor no later than 90 days into the review, so that they receive an update on the status of their renewal request by the original 90-day deadline. Since the response will be a paper letter, the PM notifies the sponsor of the action and may provide a courtesy electronic copy of the letter to the sponsor.

6. The PR completes their review of the G submission and prepares the package for signature by the Office Director (OD). The PR will use the ONADE Review template for their review of the renewal request, and will use the ONADE CA Renewal Request Letter template to prepare the letter to the sponsor.

7. The PR issues a consult to the QA team (HFV-184) no later than day 80 (if following the standard 90-day review timeframe) or Day 170 (if following the extended 180-day review timeframe). The QA Team has 5 days from the date they are consulted to complete a single-pass review and return it to the PR. See P&P 1243.3210 for information on the process for requesting a QA Team consult.

8. The PR finalizes the package and routes it through Appian for OD signature.

9. If the PR determines that the CA will not be renewed, they alert the PM, and the PM will convene an internal meeting as described in Section V.

III. POST-CA SUPPLEMENTS

If a sponsor is interested in submitting any supplements to a CA product, ONADE will recommend that the sponsor discuss their proposal with us before making any submissions. We should determine whether the proposed change would impact the sponsor's ability to maintain the CA.

Note: Once a CA is established, the sponsor is unable to supplement the application to expand the indication or add indications; we may consider supplements to narrow the indication. If a sponsor wanted to pursue a new indication for an already conditionally approved product, they would need to submit an original application for conditional approval for that new indication. This precludes a sponsor from using indication changes to extend the life of a conditional approval.

IV. APPLICATION FOR FULL APPROVAL FOLLOWING A CA

A. Timing Considerations for the Application for Full Approval

A sponsor must submit their application for full approval no later than 180 days prior to the termination of the fifth one-year period or the CA is no longer in effect. If the sponsor does not submit the application for full approval by this deadline or if FDA

does not fully approve the drug within five years of the initial CA,[8] the sponsor must stop marketing (selling, promoting, or advertising) the drug, because in accordance with section 571(h) of the FD&C Act, it is considered to be unapproved.

B. Phased Review vs. 180-day NADA Approach[9]

While a sponsor can choose either a phased review or a 180-day NADA approach to work toward full approval, ONADE generally encourages them to file a 180-day NADA. This maximizes the amount of time a sponsor has to complete their study to support substantial evidence of effectiveness (SEE) while allowing them to submit an application for full approval by the deadline above.

For a sponsor considering the phased review approach, ONADE will remind them that they would need to submit the final P submission(s) no later than 360 days prior to the termination of the fifth one-year period. This is because they need to account for at least a 180-day timeframe for review of the final P submission(s) while still submitting the administrative NADA no later than 180 days prior to the termination of the fifth one-year period. The shorter review timeframe for an administrative NADA does not change the deadline by which the application for full approval must be received.

ONADE will also advise the sponsor to consider their ability to submit the application by the deadline above if any P submission receives an incomplete.

C. Content of the Application

1. Technical Section (TS) Information

   To support a full approval, the sponsor must submit all the information necessary to support a complete NADA in accordance with section 512(b)(1) of the FD&C Act. In most cases, the sponsor can attach the TS complete letters used to support the CA for:

   - Target Animal Safety
   - Human Food Safety (when applicable)
   - Chemistry, Manufacturing, and Controls (CMC), along with a reference to any CMC supplements approved under the CA

   The sponsor will always submit:

   - Effectiveness TS to demonstrate SEE
   - Environmental Impact TS
   - Updated Labeling TS
   - Updated All Other Information TS

2. NADA Number

[8] The only exception is that CVM may extend the time by 180 days if necessary to complete the review of the timely and complete application, as described later.

[9] Refer to GFI #132.

The application for full approval is assigned a different NADA number than that of the CA. This is either a new NADA number or an existing NADA number if the application for full approval is filed as a Category II (B1) supplement. Once the product is fully approved, no additional submissions should be made to the CA file except in circumstances where ownership changes, as the CA file, including all records, should be transferred along with the INAD and full approval NADA files and records to the new sponsor.

3. User Fee Cover Sheet

The application for full approval requires a new user fee cover sheet.[10] For products where a sponsor has an approved and active CA and they are submitting their application for full approval on time, under Section 3.2 of the cover sheet, the sponsor should select "Previously Granted Conditional Approval." This is the same selection whether the sponsor is submitting an original application or a supplement. Once that option is selected, several things will appear differently on the cover sheet.

a. This selection will generate a "zero dollar" cover sheet, since this status allows a sponsor to circumvent any potential user fees, if applicable.

b. A new field will appear (Section 3.3) where the sponsor will include their application number for the original CA.

c. Section 3.4 (NADA-ADAA combinations) will be automatically selected as "No" and Section 4. (user fee waiver selections) will gray out so that it cannot be selected.

Note: If the sponsor's CA is not currently in effect,[11] they are not eligible to select "Previously Granted Conditional Approval" and instead would select "Original Application" or "Supplemental Application." They also need to pay the appropriate application fee or select the appropriate fee waiver. Sponsors who are eligible to receive a waiver need to request a new waiver; they are not able to reuse a waiver previously granted for the CA application.

D. Review Process for the Application

1. ADUFA Fees Evaluation

If the sponsor indicates on the user fee cover sheet that no application fee is being paid because the application for full approval follows a previously granted CA, the Business Informatics (BI) Team contacts the sponsor's assigned PM[12] to ask whether the CA is still in effect and if the application was received by the deadline (no later than 180 days prior to the end of the CA period).

a. The PM checks the project record in STARS DDP to confirm whether the CA is still in effect, and if so, uses the project timeline to verify whether the application was received no later than 180 days prior to the end of the CA period.

[10] The Food and Drug Administration User Fee Cover Sheet is OMB Form No. 0910-0540

[11] Either through a previous action or because the application for full approval was submitted late

[12] PM/Sponsor assignment list can be found in SharePoint: Internal information redacted

b. If the PM confirms the CA is still in effect and the application was received on time, then the BI team processes and releases the application to the appropriate TAD review team.

c. If the PM confirms the CA is no longer in effect or the application is late, the BI team informs the sponsor that they need to amend with a new user fee cover sheet reflecting either an application fee waiver (if applicable) or payment of the application fee before the application will be released for review.

2. Application Review

The PR reviews the application following office policy and procedures (refer to P&P 1243.3800). If the application for full approval has not been approved by the CA termination date, then the CA issued is no longer in effect unless the sponsor has been granted an extension of an additional 180-day period.

a. Optional Review Time Extension

CVM may extend the timeframe for review by an additional 180 days (for a total of 360 days) in circumstances where extra time is necessary to complete our review of the application by the final action date (CA termination date). If the PR determines that they will extend the review time, the PR creates a Q submission using Appian (Purpose of Submission will be "Other") and issues a paper letter to the sponsor.[13]

i. The letter informs the sponsor that we are extending the review time to 360 days, confirms that the CA remains in effect during this extension, and states that the extension does not change any of the responsibilities or requirements of the sponsor.

ii. During the extension period, the sponsor will not be asked to submit additional data, but may be asked to submit a minor amendment.

iii. Note: An extension will not be granted if the sponsor is late in filing their application, or needs more time to gather information. Rather, the extension is only to allow extra time to complete our review of an application.

iv. The DD signs the letter; therefore, the QA team is not required to be consulted.

v. The letter will be sent to the sponsor no later than 180 days into the review of the application for full approval. Since the response will be a paper letter, the PM will notify the sponsor of the action and may provide a courtesy electronic copy of the letter to the sponsor.

b. If the application will not be approved, the PR alerts the PM as soon as the PR confirms that the application will not be approved. The PM's next step will depend on the timing of the application. If the CA period is in its fifth year (i.e., no further renewals are possible), the PM convenes an internal meeting as

[13] At this time, no non-final action functionality exists within N-A-OT or N-C-B1 submission types to reset the clock in this manner. Once we can program this functionality into these submission types, we will develop a non-final action letter in order to reset the clock.

described below in Section V. If the CA period is within its first four years (i.e., further renewals are possible), CVM determines whether to renew the CA, considering the reason for the incomplete application and the sponsor's ability to submit a successful application for full approval no later than 180 days before the end of the CA period.

V. UNSUCCESSFUL TRANSITION FROM CA TO FULL APPROVAL

If a CA ends for any reason before full approval is granted, the product is considered unapproved. The PM creates a Q submission under the CA NADA and convenes an internal meeting to discuss next steps and the appropriate course of action. Meeting attendees will typically include the CVM Policy & Regulations Staff; ONADE TAD PR and TL; representatives from the ONADE Policy Team; the product manager and safety reviewer from the Division of Pharmacovigilance and Surveillance in OSC; and representatives from OMUMS if the CA is for a minor use minor species product. It is important to note that we don't have to wait until the CA deadline has passed to start having these discussions if we anticipate a problem with the CA or its successful transition to a full approval.

The PM will include the reason for the unsuccessful transition in the meeting invitation (most likely, but not limited to, one of the following):

- The sponsor withdrew or plans to withdraw the CA.
- CVM will not renew the CA.
- The sponsor did not request to renew the CA by the anniversary date, so the CA is no longer in effect.
- The sponsor did not submit an application for full approval by the deadline (180 days prior to the end of the CA period), so the CA is no longer in effect.
- CVM will not approve the application for full approval, and the CA period is in its fifth year (i.e., no further renewals are possible).

Meeting attendees determine the appropriate course of action and next steps, including necessary correspondence with the sponsor and communication with the public. If additional meetings are needed, attendees determine who will schedule and facilitate those meetings (PM or another representative). If additional correspondence or meetings occur, Q submissions are created as determined by the participants. The PM documents the outcome of the meeting discussion in the Q submission and obtains attendee concurrence before closing out the Q submission with FNR/MEMO.

In order to update the document status in STARS, the PM emails the ONADE BI Team Internal information redacted when a CA document needs to be withdrawn. The BI Team submits an Employee Resources and Information Center (ERIC) ticket to request an update to the document status in STARS to reflect a withdrawn status for the CA NADA. The records for the CA remain in the system under the CA NADA number per records retention schedules as an inactive file. Any additional development work towards an approval is conducted under the corresponding INAD.

VI. REFERENCES

The Federal Food, Drug and Cosmetic Act

Section 512(d)(1)(E)

Section 571(a)(1)(A)(ii)

Code of Federal Regulations

21 CFR 514.1 for details on the technical section requirements

21 CFR 514.4 for details on Substantial Evidence of Effectiveness (SEE)

Guidance for Industry Document

CVM GFI #61 - Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species

CVM GFI #261 - Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs

CVM Program Policies and Procedure Manual – ONADE Reviewer's Chapter

1243.2100 - Eligibility for Conditional Approval Under Expanded Conditional Approval (XCA)

1243.3210 – Requesting a Quality Control Review from the Quality Assurance Team for Final Action Packages Signed by the Office or Center Director

1243.3800 - Reviewing, Preparing, and Routing Approval Packages for Certain Abbreviated and New Animal Drug Applications

1243.5706 - Meeting to Discuss Post-Approval Responsibilities for Sponsors of Conditional Approvals

VII. VERSION HISTORY

December 21, 2021 – Original version.

July 13, 2022 – Quality system review to make minor formatting updates. Updates to OSC references to reflect 2022 reorganization.

February 2, 2023 – Revised Section II.C.8. to point to the P&P on the process for requesting a consulting review from the QA Team.

May 16, 2023 – Updated sections II C and V to reflect the OSC reorganization and include information on the Division of Pharmacovigilance and Surveillance. 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.