PROCESS FOR ELIGIBLE SPONSORS TO OBTAIN CONDITIONAL APPROVAL

I. PURPOSE

The purpose of this document is to explain to Office of New Animal Drug Evaluation (ONADE) members:

- The types of products that may be eligible for conditional approval (CA)
- The differences in information required to support a CA versus full approval
- The overall CA application procedure for new animal drug products/indications we have determined are eligible for the process

II. DEFINITION OF CONDITIONAL APPROVAL

Section 571 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), signed into law in 2004 and amended in 2018, provides for the CA of new animal drugs either for Minor Uses [in major species], or for use in Minor Species (referred to as MUMS CA[1]). It also provides for an expanded use of CA (referred to as Expanded Conditional Approval[2] (XCA)) if:

- The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND
- A demonstration of effectiveness would require a complex or particularly difficult study or studies.

This P&P document discusses how one obtains CA, regardless of through which criteria they were found eligible to pursue a conditional approval. The administrative process to obtain CA for products eligible under either MUMS or XCA criteria is the

[1] See CVM GFI #61 Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-61-special-considerations-incentives-and-programs-support-approval-new-animal-drugs-minor

[2] See XCA P&P 1243.2100 Eligibility for Conditional Approval Under the Expanded Conditional Approval (XCA) and draft CVM GFI #261 - Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs. ONADE reviewers can also reference SOP 1243.116.001 The Role of the Expanded Conditional Approval Eligibility Group (XCAEG) and How the Primary Reviewer Interacts with the Expanded Conditional Approval Eligibility Group During the Review of Expanded Conditional Approval Eligibility Requests

same once the product is determined to be eligible for CA. The available MUMS incentives do not impact technical section requirements.

CA allows potential applicants (referred to from this point as "sponsors") to make a new animal drug product commercially available after demonstrating the drug is safe and properly manufactured in accordance with the FDA approval standards for safety and manufacturing, but before they have demonstrated substantial evidence of effectiveness (SEE) of the conditionally approved product. To obtain CA, the sponsor instead needs to demonstrate reasonable expectation of effectiveness (RXE).

The CA is valid for one year and may be renewed annually for up to four additional one-year terms by showing active progress towards demonstrating SEE.[3] The FD&C Act requires that the application for full approval[4] be submitted no later than 180 days prior to the termination date of the last conditional approval period (approximately 4.5 years from the date CA was granted).[5] The CA will be terminated if SEE is not demonstrated within the time frame mandated.

III. INFORMATION REQUIRED TO SUPPORT A CONDITIONAL APPROVAL

As with all new animal drug products, a sponsor will decide whether to seek CA of a new animal drug through the phased review of data (P) submissions (the most commonly used approach) or by submitting all data at one time within the application. The process for receiving a CA is similar to the process for receiving full approval under section 512 of the FD&C Act, with variations noted below.

For more information related to the approval process or the CA pathway, ONADE can refer the sponsor to their assigned ONADE project manager (PM). Sponsors that have questions about the CA process and do not have a PM assigned to them may contact the PM teams by email using the mailbox CVM.ONADE.PM@fda.hhs.gov.

A. Review Process

1. Eligibility for CA

   Sponsors should be instructed to complete the determination step for any MUMS[6] or XCA[7] product before proceeding with their CA development plan, i.e., before submitting any H (supportive), E (protocol), or P (data)

[3] Section 571 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), provides for the conditional approval of new animal drugs for Minor Uses [in major species] or for use in Minor Species or for expanded use of conditional approval. For details on CA, please refer to Section 571 of the FD&C Act.

[4] From this point forward, the document will refer to the term "full approval" to distinguish an approval from a CA.

[5] The 4.5-year requirement applies regardless of whether the sponsor is using the phased review process or the 180-day application process.

[6] See CVM GFI #61 Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-61-special-considerations-incentives-and-programs-support-approval-new-animal-drugs-minor

[7] See XCA P&P 1243.2100 Process for Determination of Eligibility for Participation in the Expanded Conditional Approval (XCA) Program and draft CVM GFI #261 - Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs. ONADE reviewers can also reference SOP 1243.116.001 The Role of the Expanded Conditional Approval Eligibility Group (XCAEG) and How the Primary Reviewer Interacts with the Expanded Conditional Approval Eligibility Group During the Review of Expanded Conditional Approval Eligibility Requests

submissions to support the RXE technical section or Environmental Impact technical section as described below. After we have determined a product is eligible for CA, the sponsor may proceed with their development plan as discussed in a presubmission conference (PSC). For questions related to the determination step, please see the associated references or reach out to the appropriate ONADE PM.

2. PSC [8]

   We encourage sponsors to request PSC meeting(s) to discuss the requirements for each applicable technical section for the project.

3. Major Technical Sections[9]

   To support a CA, a sponsor will complete all technical sections with the exception of Effectiveness, for which they must instead complete the RXE technical section. Prior to conditionally approving a product, the major technical sections we will review are: the RXE, Target Animal Safety; Human Food Safety (for food-producing animal species); Chemistry, Manufacturing, and Controls; and Environmental Impact technical sections.[10] The text below highlights where there are differences between completing a technical section for a CA (which are the same for either MUMS CA and XCA) and a full approval.

   a. RXE

      With regard to the showing of effectiveness, in order for a product to receive CA, at a minimum, an RXE must be demonstrated. This means that the product is reasonably expected to provide the intended effect when used under the conditions of use described in the labeling. An RXE may be demonstrated based on evidence such as, but not limited to, pilot data in the target species or studies from published literature. The legal requirements for demonstrating RXE are found in section 571(a)(2)(B) of the FD&C Act.

      This is a lower standard than SEE required to support a full approval under section 512 of the FD&C Act. SEE means that the product has been shown, by substantial evidence, to provide the intended effect when used under the conditions of use described in the labeling. Although the standard to be met for RXE is not as rigorous as that for SEE, that does not alter the data quality expected in a submission. SEE must be demonstrated by one or more adequate and well-controlled studies that have been conducted to

[8] See 1243.3024 – Scheduling and Holding Meetings with Outside Parties for details on how to request and schedule a presubmission conference

[9] See 1243.3050 Determining Technical Section Requirements for New Animal Drug Product Approval or 21 CFR 514.1 for details on the technical section requirements.

[10] For details on the phased review process, refer to Guidance for Industry (GFI) 132 titled Administrative Applications and the Phased Review Process at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-132-administrative-applications-and-phased-review-process

demonstrate that the product will have the intended effect when used under the conditions of use described in the labeling.[11]

When sponsors submit an Effectiveness protocol (E) or data (P) submission, they will be prompted to select the appropriate Submission Classification Code (SCC) of "Effectiveness (EF)" or "Reasonable Expectation of Effectiveness (XE)" to identify whether the submission is intended to provide SEE or RXE. If a sponsor selects the XE sub-class code in eSubmitter, they are also prompted to select whether they are pursuing CA under XCA or MUMS. The review times are the same for the RXE and Effectiveness Technical Sections and protocols (180 days for data (P) submission and 50 days for protocol (E) submissions) as are the final action codes.

b. Environmental Impact

In accordance with the National Environmental Policy Act, federal agencies must evaluate the potential environmental impacts of their actions. At FDA, both a CA and full New Animal Drug Application (NADA) approval are considered actions [21 CFR 514.1(b)(14)] that require separate Environmental Impact technical sections (P submission). Therefore, a separate Environmental Impact technical section complete letter needs to be obtained prior to the CA, and again for the full approval.

It is always recommended sponsors wait on submitting the Environmental Impact technical section until they are confident that the dose, frequency, indication(s), species, and route of administration will not change prior to approval because the technical section should reflect the proposed drug approval conditions. Changes to the drug product may require further evaluations and/or additional submissions for the technical section.

In eSubmitter, sponsors are prompted to select the applicable type of action when submitting the P submission for the Environmental Impact technical section. For a P submission intended to support a CA, sponsors will select "Conditional NADA (CNADA)."

B. Recommended Additional Steps

1. ONADE will recommend that sponsors begin working on their SEE study(ies) before obtaining their CA, because the sponsor may require longer than the duration of the CA period to complete the study(ies) and prepare their data and information to support SEE. We should encourage sponsors pursuing CA to begin planning the study(ies) to support SEE and request a presubmission conference to discuss this study(ies) before the product is conditionally approved.

2. ONADE recommends that sponsors request a meeting to discuss the sponsor's responsibilities post-CA. This meeting is intended to provide answers to any sponsor questions as well as provide an opportunity for

[11] See 21 CFR 514.4 for details on substantial evidence

ONADE, the Office of Surveillance and Compliance (OSC) and the Office of Minor Use and Minor Species Animal Drug Development (OMUMS) (if applicable), to clarify the obligations for sponsors of a CA product. The PM will follow up with the sponsor about requesting this meeting as described in ONADE P&P 1243.5706.

IV. CONDITIONAL APPROVAL APPLICATION PROCEDURE

When the sponsor submits the application for CA, it will be assigned an application number specific to the CA. Once the CA period has ended, no further submissions may be made to the application number associated with the CA as that CA is no longer in effect. The subsequent application for full approval will be made under a different NADA number.

A. Application Fee

For MUMS products, the sponsor will be advised to request a MUMS waiver of the application fee before submitting the application for CA. For XCA products, there is not a waiver specific to XCA products. However, a sponsor may request a waiver of the application fee if they believe they qualify for any of the available waivers.[12]

When a sponsor submits their application for CA, they will pay their full application user fee. If the CA is granted, the sponsor will work toward full approval. If a sponsor successfully transitions from a CA to a full approval, the sponsor will not need to pay another application fee. If the CA is not maintained, and a sponsor does not successfully transition to a full approval, any future attempt to obtain a full approval will require a new application fee.

B. Approval package

ONADE will follow the procedures outlined in P&P 1243.3800, and the associated P&Ps and templates to prepare the approval package and finalize the approval as applicable for a CA.

V. REFERENCES

Federal Food Drug and Cosmetic Act (FD&C Act)

Section 512(d)(1)(E) of the FD&C Act

Section 571(a)(1)(A)(ii) of the FD&C Act

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)

CVM Guidance for Industry Document (GFI)

[12] Refer to CVM GFI #170 titled Animal Drug User Fees and Fee Waivers and Reductions and GFI #173, Animal Drug Sponsor Fees Under the Animal Drug User Fee Act (ADUFA)

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

GFI #132 Administrative Applications and the Phased Review Process

GFI #170 Animal Drug User Fees and Fee Waivers and Reductions

GFI #173 Animal Drug Sponsor Fees Under the Animal Drug User Fee Act (ADUFA)

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 the Expanded Conditional Approval (XCA) Criteria

1243.3024 – Scheduling and Holding Meetings with Outside Parties

1243.3050 – Determining Technical Section Requirements for New Animal Drug Product Approval

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

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

1243.5706 - Meeting to Discuss Sponsor Responsibilities following Conditional Approval

ONADE Standard Operating Procedure

SOP 1243.116.001 - The Role of the Expanded Conditional Approval Eligibility Group (XCAEG) and How the Primary Reviewer Interacts with the Expanded Conditional Approval Eligibility Group During the Review of Expanded Conditional Approval Eligibility Requests

Website

https://www.fda.gov/animal-veterinary/development-approval-process/minor-useminor-species

VI. VERSION HISTORY

January 11, 2021 – Original version

February 1, 2021 – Updated to fix a typo and the name of the P&P referenced in footnote 2. Updated to include reference to new P&P 1243.5706 Meeting to Discuss Sponsor Responsibilities following Conditional Approval