OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

PROCESS FOR ELIGIBLE SPONSORS TO OBTAIN CONDITIONAL APPROVAL

I. PURPOSE

This document explains 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; and
- 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 (XCA)[2]) 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.

As described in the FD&C Act, a person may not file an application for conditional approval of a new animal drug product if any of the following conditions apply:

- It is contained in or is a product of a transgenic animal. See section 571(a)(3)(A)(i) of the FD&C Act.
- The sponsor has previously filed an application for conditional approval of a product with the same active ingredient, dosage form, and intended use - whether or not it was subsequently conditionally approved. See section 571(a)(3)(A)(ii) of the FD&C Act.

[1] See Guidance for Industry (GFI) #61
[2] See P&P 1243.2100 draft CVM GFI #261. ONADE reviewers can also reference Standard Operating Procedure (SOP) 1243.116.001.

- The sponsor obtained the application, or any data or other information contained therein, directly or indirectly, from a person who previously filed an application for conditional approval of the same drug, in the same dosage form, for the same intended use, whether or not subsequently conditionally approved. See section 571(a)(3)(A)(iii) of the FD&C Act.

A person may not file an application for conditional approval of a new animal drug product under the XCA pathway if:

- The product contains an antimicrobial active ingredient. See section 571(a)(3)(B) of the FD&C Act.

An application for conditional approval of a new animal drug product will be denied if another product with the same drug, dosage form, and intended use has been approved under section 512 of the FD&C Act, unless the applicant for conditional approval can show that the sponsor of the approved product is unable to assure the availability of sufficient quantities of the drug product to meet the needs for which it is intended. See section 571(c)(3).[3]

This 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 same once the product is determined to be eligible for CA. The available MUMS incentives do not impact technical section (TS) 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 1 year terms by showing active progress towards demonstrating SEE.[4] The FD&C Act requires that the application for full approval[5] 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).[6] 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 seeks 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.

[3] An application for conditional approval of a new animal drug product will also be denied if any of the conditions described in section 512(d)(1)(A) through (D), or (F) through (I) apply. See section 571(c)(1) through (c)(3) for additional criteria.
[4] Section 571 of the FD&C Act provides for MUMS CA or XCA. For details, refer to Section 571 of the FD&C Act.
[5] From this point forward, the document will refer to the term "full approval" to distinguish an approval from a CA.
[6] The 4.5-year requirement applies regardless of whether the sponsor is using the phased review process or the 180-day application process.

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[7] or XCA[8] product before proceeding with their CA development plan, i.e., before submitting any H (supportive), E (protocol), or P (data) submissions to support the RXE TS or Environmental Impact TS 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, see the associated references or the appropriate ONADE PM.

2. PSC[9]

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

3. Major Technical Sections[10]

   To support a CA, a sponsor will complete all TSs with the exception of Effectiveness, for which they must instead complete the RXE TS. Prior to conditionally approving a product, the major TSs we will review are: the RXE, Target Animal Safety; Human Food Safety (for food-producing animal species); Chemistry, Manufacturing, and Controls; and Environmental Impact TSs.[11] The text below highlights the differences between completing a TS 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

[7] See GFI #61
[8] See P&P 1243.2100 and draft CVM GFI #261. ONADE reviewers can also reference SOP 1243.116.001
[9] See P&P 1243.3024.
[10] See 1243.3050.
[11] 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

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 demonstrate that the product will have the intended effect when used under the conditions of use described in the labeling.[12]

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 the conditional approval eligibility criteria under which they qualify, either MUMS or XCA. The review times are the same for the RXE and Effectiveness TSs 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 TSs (P submissions). Therefore, a separate Environmental Impact TS 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 TS until they are confident that the dose, frequency, indication(s), species, and route of administration will not change prior to approval because the TS 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 TS. 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 ONADE, the Office of

[12] See 21 CFR 514.4 for details on substantial evidence.

Surveillance and Compliance (OSC) and the Office of Minor Use and Minor Species (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 Policy and Procedure (P&P) 1243.5706.

IV. CONDITIONAL APPROVAL APPLICATION PROCEDURE

When the sponsor submits the application for CA, it is assigned an application number specific to the CA. Once the CA period has ended, no further submissions may be made to the CA application number as that CA is no longer in effect. The subsequent application for full approval is 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 (see Guidance for Industry (GFI) #170).

When a sponsor submits their application for CA, they will pay their 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.

Note that there is no exclusivity granted for a conditional approval. There are exclusive marketing rights available only for MUMS-designated products,[13] which start on the date of initial approval (CA or full approval) and provide for a 7-year period where FDA/CVM will not approve or conditionally approve the same drug (pioneer or generic), in the same dosage form, for the same intended use except in certain limited circumstances.[14] No exclusivity is available for the conditional approval for non-designated MUMS products and for XCA products. Upon approval of the drug product under section 512 of the FD&C Act, they would be eligible to receive the 5 or 3 years of marketing exclusivity (protection from generic copies) provided for in section 512(c)(2)(F) if the relevant criteria are met. That exclusivity period starts on the date of full approval. But in practical terms, a conditionally approved product does not face the generic competition that exclusivity would protect against because FDA/CVM can only approve generic copies of new animal drug products that have been previously approved under Section 512 of the FD&C Act. And so, even though non-designated CA products do not receive any explicit protection from generics, it is

[13] Additional details can be found in CVM GFI #61, titled Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species.

[14] The limited circumstances are that either the sponsor of the designated product cannot assure sufficient quantities of the drug to satisfy the need, or that the sponsor of the designated product consents in writing to the approval or conditional approval of the product that would otherwise be barred by the designation exclusivity.

not possible to obtain a generic approval based on a conditionally approved product. That is, a conditionally approved drug product may not be used as a reference-listed new animal drug. For language to include in the approval letter, refer to P&P 1243.5780 Exclusivity and Exclusive Marketing Rights Boilerplate Language for Use in the Following Documents - MRA, Letter to Applicant, and FOI Summary.

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 #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 Policies and Procedures 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

1243.5780 Exclusivity and Exclusive Marketing Rights Boilerplate Language for Use in the Following Documents - MRA, Letter to Applicant, and FOI Summary

ONADE Standard Operating Procedure

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

July 13, 2022 – Quality systems review for minor formatting updates.

May 16, 2023 – Quality systems review with minor modification to clarify that MUMS and XCA describe different CA criteria, not different pathways. 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.

September 11, 2023 – Revised section IV. A. paragraph two to change the wording from "…will pay their full application user fee…" to "…will pay their application user fee…" to encompass all fee standards.

April 15, 2024- Revised section II. to explain under what circumstances a product is not eligible for conditional approval. Also revised section IV. B. to add information about exclusivity and exclusive marketing rights language. Added a reference to P&P 1243.5780 Exclusivity and Exclusive Marketing Rights Boilerplate Language for use in the Following Documents - MRA, Letter to Applicant, and FOI Summary.