OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

ELIGIBILITY FOR CONDITIONAL APPROVAL UNDER THE EXPANDED CONDITIONAL APPROVAL (XCA) CRITERIA

I. PURPOSE

This purpose of this document is to explain:

- What Expanded Conditional Approval (XCA) is,
- How to advise a sponsor interested in XCA about how to initiate contact with Office of New Animal Drug Evaluation (ONADE),
- The types of meetings we use for a sponsor request to discuss XCA, and
- How to advise a sponsor about requesting a determination of eligibility for XCA.

II. DEFINITION OF EXPANDED CONTITIONAL APPROVAL

Conditional Approval (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)[1] of the conditionally approved product. Under conditional approval, the sponsor needs to demonstrate reasonable expectation of effectiveness (RXE). A drug sponsor can then market a conditionally approved product for up to five years, through annual renewals, while collecting substantial evidence of effectiveness data required to support an approval.

Section 571 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), signed into law as the Minor Use and Minor Species Animal Health (MUMS) Act on August 2, 2004, provides for the conditional approval of new animal drugs for Minor Uses (in major species) or for use in Minor Species.

On August 14, 2018, the Animal Drug User Fee Amendments of 2018 (ADUFA IV) were signed into law to reauthorize the Animal Drug User Fee Act (ADUFA) for another five years. This legislation amended section 571 of the FD&C Act to include provisions for an expanded use of conditional approval. Under the revised legislation certain new animal

[1] For details on the requirements for demonstrating substantial evidence of effectiveness see 512(d)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and 21 CFR524.4 at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=514.4

drugs for major species, that do not qualify for minor use,[2] may qualify for expanded conditional approval (XCA) if the following two criteria are met.

1. 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

2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

If a sponsor's product meets the criteria for expanded conditional approval, they would be able to market their conditionally approved product for up to five years, through annual renewals while collecting substantial evidence of effectiveness.

III. MEETINGS TO DISCUSS ELIGIBLITY FOR XCA

If a sponsor wants to discuss potential eligibility for XCA, we should recommend that the sponsor request a meeting with ONADE. Although we prefer sponsors meet with us first, sponsors can proceed directly to submitting a G submission (see Section IV.A).

If a sponsor has questions related to the determination process, or what to include in their request for determination of eligibility for XCA, ONADE should direct sponsors to an ONADE project manager (PM). If the sponsor has questions related to the justification before they submit their request for determination of eligibility, they may request a meeting with ONADE. ONADE may advise sponsors who have not been assigned an ONADE PM to contact CVM.ONADE.PM@fda.hhs.gov.

The following is information ONADE staff can use to advise sponsors on the process for having a meeting to discuss XCA.

A. Types of Meetings

Sponsors who are not currently paying an annual sponsor fee and do not have any open investigational new animal drug (INAD) files may meet with CVM before establishing or opening an INAD, because opening an INAD may trigger the annual sponsor fee. We would meet with sponsors who do not have an INAD under a pre-INAD Meeting, as described below.

1. Pre-INAD Meetings

   a. Sponsors may request a pre-INAD meeting under a General Correspondence (GC) file to discuss XCA.

   b. If the sponsor has a GC file, they should submit their meeting request to that GC file. If the sponsor does not have an existing GC file, advise the sponsor to establish one. The initial submission to establish a new file is coded as A-0000.

[2] A product that qualifies for MUMS cannot quality for XCA.

c. Once the sponsor has created the GC file, or has a GC file to reference, then they can submit a meeting request (Z submission). The Z submission will have the OO meeting type indicator code.[3]

d. Pre-INAD meetings may be assigned to a member of a review division or to a PM depending on the content of the meeting request.[4] The assigned primary reviewer for the meeting request is responsible for arranging and facilitating the meeting.

e. Typically, no documentation is sent to the sponsor after a pre-INAD meeting. The reviewer will document key aspects of the GC meeting for the CVM administrative record in an internal memo to file.

2. Meetings under an INAD file:

If a sponsor has an INAD file and has questions related to the justification for XCA before submitting the determination of eligibility submission, inform them they can request a meeting with ONADE. The sponsor may request an Other ONADE (OO) meeting type (I-Z-OM (OO)), or a presubmission conference (PS) meeting type (I- Z-OM (PS)).[5]

a. A meeting to discuss the overall development plan which includes questions about XCA should be submitted as meeting type PS.

b. A meeting to discuss XCA questions and/or the approach for a future G-DE submission should be submitted as meeting type OO.

c. A meeting to discuss XCA questions and the proposed Effectiveness (RXE and/or substantial evidence) development plan should be submitted as meeting type PS.

i. Although an INAD PS meeting may document agreements (21 CFR 514.5(f)(1)(i)), no formal or informal agreements of eligibility can be reached with regard to XCA.

ii. As with all PS or OO meetings, CVM will send a memorandum of conference 45 days after the meeting date.[6]

B. Purpose and Outcome of Meetings

1. The XCA meeting materials (or XCA portion of the meeting materials) provided by the sponsor should include a high-level justification of eligibility for XCA to allow for ONADE to provide useful feedback during the meeting. Additionally, the meeting materials should outline the challenges with the study and why the proposed study design is necessary for the evaluation of effectiveness.

a. The meeting should be used to discuss whether the drug, proposed indication, and proposed effectiveness study design(s) may qualify for XCA. ONADE

[3] In some circumstances, a paper submission may be accepted under a GC file. If a sponsor is interested in submitting a paper submission to their GC file, please work with your ONADE PM for clarification.
[4] See P&P 1243.3024 section IV for information on meetings before an investigational file (INAD) is established that take place under a general correspondence (GC) file.
[5] Refer to P&P 1243.3024 for scheduling and holding meetings with outside parties for details on the appropriate meeting type.
[6] Refer to P&P 1243,3025 on preparing meeting documentation.

should provide feedback regarding the sponsor's proposal on what areas of concern and what information ONADE would like included in the XCA eligibility determination request the sponsor will submit. It may also be helpful to discuss the timing considerations for the Effectiveness technical section during the meeting, because the sponsor may need longer than the conditional approval period to demonstrate effectiveness. If the study design is likely to be long, it may be worthwhile to discuss in the meeting, so the sponsor understands the timing limitations of the XCA program.

b. The outcome of the meeting with regard to XCA will be non-decisional, because our process is that we provide a formal determination of eligibility after we receive and have reviewed a sponsor's request for determination submission under the INAD file (see Section IV. below).

c. With regard to meetings, we do not need to consult with The Expanded Conditional Approval Eligibility Group (XCAEG), which provides feedback to the primary reviewer under the determination of eligibility submission regarding eligibility to ensure consistency in ONADE's interpretation of eligibility across divisions (see section IV. below)

d. If at the meeting we conclude that the product may be eligible, we will advise the sponsor to submit their complete justification under the determination of eligibility submission.

e. ONADE should identify any potential concerns regarding the eligibility justification during the meeting and ask the sponsor to address the items in the submission if they choose to move forward.

Note: The meeting discussion does not influence the formal determination of eligibility nor guarantee that a sponsor will have an accepted determination of eligibility

IV. XCA ELIGIBILITY

A. Review of the Submission for Determination of Eligibility for XCA

1. Sponsors who elect to pursue XCA must submit a request for determination of eligibility to ONADE (sometimes referred to as determination of eligibility and has a submission code of I-G-DE) as a G submission to the INAD file.

2. The submission should contain adequate information to justify a determination of eligibility based on the criteria described in Guidance for Industry (GFI) #261 "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs".[7]

3. The sponsor should specify in the submission which criteria they think their proposed product meets that makes the product eligible for XCA.

   a. For example, the justification regarding the evaluation of effectiveness requiring a particularly difficult study or studies should specify which criteria in the GFI is applicable to their drug.

[7] GFI 261 can be found at the following link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-261-eligibility-criteria-expanded-conditional-approval-new-animal-drugs

4. In eSubmitter, the sponsor should have affirmed or denied each of the following and may have also attached supporting documentation in order to justify that their product is eligible for XCA:

    a. Does the drug treat a serious or life threating disease or condition?

    b. Does the drug meet an unmet human or animal health need?

    c. Does the evaluation of effectiveness require a particularly difficult study or studies?

        i. Note that c. is required, **and** either a. **or** b. are required to be eligible for expanded conditional approval.

5. The determination of eligibility submission is assigned to the appropriate target animal division (TAD) in ONADE. The Submission Tracking and Reporting System (STARS) review timeframe is 100 days from the date of receipt.

6. The primary reviewer will review the submission and work with the XCAEG as described in the ONADE SOP entitled: "The Role of the Expanded Conditional Approval Eligibility Group (XCAEG) During Eligibility Determination Reviews for Expanded Conditional Approval." The purpose of this SOP is to ensure ONADE is consistent in their interpretation of criteria across teams and divisions. The primary reviewer assigned the submission still makes the ultimate determination on whether the drug qualifies for XCA.

7. The TAD will issue a letter informing the sponsor whether the drug qualifies for XCA.[8] The division director is the signing authority for the letter. The PR will select one of the following final actions (FA) in Appian:

    a. Product Eligible; Letter Sent (FA 213, PROD ELG)

    b. Product Ineligible; Letter Sent (FA 214, PROD INELG)

    c. Eligibility Determination Incomplete; Letter Sent (FA 215, DET INC)

8. Once a sponsor has a product that has been determined to be eligible for XCA, they should proceed with their development plan as discussed in a presubmission conference. For more information related to the Conditional Approval pathway, refer the sponsor to their assigned PM.

V. TIMING CONSIDERATION FOR XCA DETERMINATION AND MEETINGS

The outcome of a formal determination of eligibility informs a new or may change an existing development plan. Therefore, the order in which a sponsor submits a meeting request and the determination for eligibility of XCA and the timing between the two submissions can be critical. ONADE suggests that sponsors contact their PM to figure out the best order, timing, and overall submission strategy to minimize time to approval. A few items for the sponsor's consideration are below:

1. If a sponsor obtains a determination of eligibility after they have an agreed upon development plan with ONADE based on a substantial evidence of effectiveness

[8] Refer to P&P 1243.3010 Format and Style Conventions for Letters.

(SEE), then the sponsor is encouraged to request a meeting with ONADE to discuss RXE.

2. If a meeting is held while a determination of eligibility submission is under review, ONADE will not discuss the eligibility determination during that meeting.

VI. REFERENCES

The 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 (CFR)

21 CFR 514.4

Guidance for Industry Document

GFI #261 “Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs”

CVM Program Policies and Procedure Manual-ONADE Reviewer’s Chapter

1243.3024 Scheduling and Holding Meetings with Outside Parties

1243.3025 Preparing Meeting Documentation (i.e., Memorandum of Conference, Acknowledgement Letter, Other Review Documentation)

1243.3010 Format and Style Conventions for Letters

ONADE Standard Operating Procedure

1243.116.001 - The Role of the Expanded Conditional Approval Eligibility Group (XCAEG) During Eligibility Determination Reviews for Expanded Conditional Approval

VII. VERSION HISTORY

April 10, 2020 – Original version.

June 24, 2020 – Updated all internal links for SharePoint sites because FDA has migrated this information to a new version of SharePoint.

January 14, 2021 – Updated section A.2.a Meetings under an INAD file to reflect additional meeting type PS if a sponsor includes potential agreements in the meeting request. Updated the name of the title.

October 24, 2023 – Revised to move wording that explains the sponsor submits a request for determination of eligibility for expanded conditional use is sometimes referred to as determination of eligibility for expanded conditional use and that the submission code for this request is I-G-DE from section III to section IV.A.1. Also, updated reference information on meetings that happen under a GC file before an INAD is established. That information is now included in P&P 1243.3024. 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. The document was also put into the most recent template version.

February 1, 2024 – Updated to remove the word draft from Section IV and from the reference section.