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Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs

Guidance for Industry

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2019-D-3361.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact AskCVM@fda.hhs.gov.

I. Introduction

This guidance is intended for sponsors and potential sponsors (you) who may be interested in pursuing conditional approval of new animal drug products (hereinafter referred to as "drugs") for certain major uses in major species under section 571 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 571 of the FD&C Act, as amended by the Animal Drug and Animal Generic Drug User Fee Amendments of 2018, now includes provisions which expand eligibility for conditional approval beyond minor uses in major species and use in minor species (MUMS) to also include certain major uses in major species in order to incentivize development of drugs for serious or life-threatening conditions or unmet animal or human health needs where a demonstration of effectiveness would require a complex or particularly difficult study or studies. Throughout this guidance, the Center for Veterinary Medicine (CVM or we) refers to the process for conditionally approving drugs that are not intended for MUMS indications as "expanded conditional approval." The term "expanded conditional approval" does not apply to applications for conditional approval involving drugs intended for MUMS indications (i.e., MUMS drugs).

The purpose of this guidance is to further clarify the statutory eligibility criteria for expanded conditional approval, specifically by defining the following terms that appear in section 571 of the FD&C Act:

- "serious or life-threatening disease or condition"
- "unmet animal or human health need," and
- "complex or particularly difficult study or studies"

CVM intends to describe the procedure for sponsors to use for requesting determinations of eligibility for expanded conditional approval in a separate guidance document.

Sponsors and potential sponsors interested in pursuing expanded conditional approval for a drug are encouraged to work with CVM's Office of New Animal Drug Evaluation

(ONADE) early in the drug development process and should contact ONADE for more information on this topic. You may contact AskCVM@fda.hhs.gov if you have questions about the expanded conditional approval process.

ONADE project managers (PMs) serve as a central point of contact for drug sponsors and potential sponsors and can provide information about the drug review process and ONADE's regulatory procedures. Sponsors or potential sponsors that have questions about the expanded conditional approval process and do not have an ONADE PM assigned to them may contact the PM team using the CVM mailbox CVM.ONADE.PM@fda.hhs.gov.

Throughout this guidance, the term "full approval" or "fully approved" is used when referring to an approval of an application submitted under section 512(b) of the FD&C Act. The term "conditional approval" or "conditionally approved" is used when referring to an application for conditional approval submitted under section 571 of the FD&C Act.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

In 2004, the Minor Use and Minor Species Animal Health Act (MUMS Act) was enacted and established section 571 of the FD&C Act (21 U.S.C. 360ccc), allowing for the conditional approval of drugs intended for use in minor species (those other than horses, dogs, cats, cattle, pigs, turkeys, and chickens) or for minor uses in major species (i.e., MUMS drugs).[1] For a drug intended for use in a major species to be eligible for conditional approval under the MUMS Act, the drug must be intended for a minor use (see section 571(a)(1)(A)(i) of the FD&C Act). The term "minor use" is defined in section 201(pp) of the FD&C Act.[2]

In 2013, in a goals letter FDA prepared in conjunction with the third authorization of its animal drug user fee program (ADUFA III),[3] FDA agreed to consider whether it would be appropriate to pursue possible statutory revisions to expand the concept of conditional

[1] In accordance with sections 201(nn) and (oo) of the FD&C Act (21 U.S.C. 321(nn) and (oo)), "major species" means cattle, horses, swine, chickens, turkeys, dogs, and cats; "minor species" means animals, other than humans, that are not major species.

[2] Section 201(pp) of the FD&C Act (21 U.S.C. 321(pp)) states, "[t]he term 'minor use' means the intended use of a drug in a major species for an indication that occurs infrequently and in only a small number of animals or in limited geographical areas and in only a small number of animals annually."

[3] The Animal Drug and Animal Generic Drug User Fee Reauthorization Act of 2013 was signed into law on June 13, 2013 and became Public Law 113-14.

approval in section 571 of the FD&C Act to other appropriate categories of drugs that would not be eligible for conditional approval under the MUMS provisions of the FD&C Act. Through a public process and working in concert with stakeholders, FDA explored the feasibility of the expansion of the conditional approval pathway.

In 2018, Congress enacted legislation reauthorizing FDA's animal drug user fee program for an additional 5 years.[4] This legislation also amended section 571 of the FD&C Act to include provisions for expanded conditional approval (i.e., conditional approval for certain non-MUMS drugs) and directed the FDA to issue guidance or regulations to further clarify the eligibility criteria for expanded conditional approval.[5] In developing the definitions CVM is providing in this guidance for the terms "serious or life-threatening disease or condition" and "unmet animal or human health need," CVM considered the definitions for "serious disease or condition" and "unmet medical need" provided in the Guidance For Industry (GFI) entitled, "Expedited Programs for Serious Conditions – Drugs and Biologics" that was issued by FDA's Center for Drug Evaluation and Research and its Center for Biologics Evaluation and Research in May 2014.[6]

Conditional approval for MUMS or non-MUMS drugs allows a sponsor to legally market a drug after demonstrating the drug is safe and manufactured in accordance with the full approval standards, and that there is a reasonable expectation of effectiveness. The sponsor may be able to market the conditionally approved MUMS or non-MUMS drug for up to 5 years while gathering the remaining data required to demonstrate substantial evidence of effectiveness. The statute requires annual renewal of the conditional approval in order for the conditional approval to remain in effect (see section 571(d) of the FD&C Act). To obtain renewal, the sponsor of the conditionally approved MUMS or non-MUMS drug needs to be making sufficient progress toward meeting the effectiveness standard for full approval (see section 571(d)(2) of the FD&C Act).

The eligibility criteria for expanded conditional approval are discussed below.

III. Eligibility for Expanded Conditional Approval

A. Statutory Criteria

Section 304 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 amended section 571 of the FD&C Act expanding the conditional approval pathway to allow certain non-MUMS drugs to become eligible for conditional approval. As stated above, for purposes of this guidance, CVM refers to the process for conditionally approving non-MUMS drugs as "expanded conditional approval." To be eligible for

[4] The Animal Drug and Animal Generic Drug User Fee Amendments of 2018 was signed into law on August 14, 2018 and became Public Law 115-234.

[5] See section 304 of Public Law 115-234.

[6] https://www.fda.gov/media/119293/download

expanded conditional approval, section 571(a)(1)(A)(ii) of the FD&C Act requires the non-MUMS drug to meet the following two criteria:

1. The 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.

Section 571(a)(3)(A) of the FD&C Act states that the conditional approval pathway cannot be used for transgenic animals. A "transgenic animal" is defined in section 571(j) of the FD&C Act as "an animal whose genome contains a nucleotide sequence that has been intentionally modified in vitro, and the progeny of such an animal; Provided that the term 'transgenic animal' does not include an animal of which the nucleotide sequence of the genome has been modified solely by selective breeding." We note that intentional genomic alterations (IGAs) in animals include those that are "transgenic," as defined in section 571 of the FD&C Act. However, "IGA" is a broader term than "transgenic" and may include types of alterations (e.g., deletions) that would not meet the above-cited definition. Therefore, IGAs in animals may be eligible for conditional approval. In addition, FDA does not consider an animal containing non-heritable alterations to be a "transgenic animal" within the meaning of section 571(j) of the FD&C Act. For IGAs and other novel technologies, we encourage you to contact CVM to discuss whether your product may be eligible for conditional approval.

Section 571(a)(3)(B) of the FD&C Act states that drugs containing an antimicrobial active ingredient are not eligible for expanded conditional approval.

Section 571(a)(1)(B) of the FD&C Act directs FDA to further clarify the criteria specified in section 571 of the FD&C Act for expanded conditional approval. In accordance with this directive, in section III.B. *Definitions* below, we are providing clarifications of the following terms for the purpose of implementing the expanded conditional approval provisions of section 571 of the FD&C Act:

- "serious or life-threatening disease or condition,"
- "unmet animal or human health need," and
- "complex or particularly difficult study or studies"

B. Definitions

1. *Serious or life-threatening disease or condition*

FDA interprets "serious or life-threatening disease or condition" to mean a disease or condition that is associated with morbidity that has substantial impact on day-to-day functioning or is associated with mortality in the target animal. Short-lived and self-limiting morbidity will usually not be sufficient, unless the disease or condition is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or

the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. A disease or condition may be considered serious based on the magnitude of its effect on the target animals that would receive the drug, its potential to affect humans if they were to contract the disease or condition from an affected target animal, or its potential to adversely impact the food supply.

The following are considered serious or life-threatening diseases or conditions:

- A disease or condition associated with mortality or morbidity that has substantial impact on day-to-day functioning in the target animal; or
- A disease or condition in animals that is zoonotic[7] and that presents a risk of a serious or life-threatening disease or condition to human beings, whether or not it also presents a risk of harm to the target animal receiving the drug; or
- A disease or condition that causes wide-spread morbidity in food-producing animals that presents a risk of regional or national disruption to food production, even if the effect of the disease or condition on an individual-animal basis is minor.

2. *Unmet animal or human health need*

FDA interprets "unmet animal or human health need" to mean a disease or condition whose treatment, control, or prevention is not adequately addressed by available therapy. This is a disease or condition that affects individual or defined groups of animals or humans, or a condition that more broadly affects animal or human health (e.g., antimicrobial resistance).

For the purpose of this guidance, a disease or condition is one for which treatment, control, or prevention is "not adequately addressed" by available therapy when: 1) available therapy does not exist for the same intended use proposed for the drug, or 2) available therapy does exist for the same intended use but the drug for which expanded conditional approval is sought is reasonably expected to provide a meaningful advantage over available therapy.

For the purpose of this guidance, "available therapy" means a product that is approved under section 512 of the FD&C Act, licensed by the U.S. Department of Agriculture, or registered by the Environmental Protection Agency, and is currently being marketed in the United States, for the same intended use in the same species as the proposed drug for which expanded conditional approval is sought.

It should be noted that extralabel use of an approved animal or human drug does not qualify as an "available therapy" because safety and substantial evidence of effectiveness have not been established for the extralabel use. In addition,

[7] Zoonotic diseases (also known as zoonoses) are caused by infections that are shared between animals and people.

conditionally approved drugs are not considered "available therapy" because substantial evidence of effectiveness has not been demonstrated.[8]

For the purpose of this guidance, "meaningful advantage" means that the drug for which expanded conditional approval is sought is reasonably expected to provide one or more of the following advantages over available therapy. Such a product would:

a. provide clinically relevant improved effectiveness on an outcome of the involved disease or condition when compared to the available therapy;

b. provide a clinically relevant beneficial effect on the disease or condition that is not provided by available therapy for that disease or condition;

c. provide comparable effectiveness on an outcome of the involved disease or condition in animals that cannot tolerate the available therapy;

d. provide effectiveness comparable to available therapy, while improving safety. For example: (i) avoiding serious toxicity that occurs with available therapy, (ii) avoiding less serious toxicity that is common and causes discontinuation of treatment for a serious disease or condition, (iii) reducing the potential for harmful drug interactions;

e. provide for safe administration with other therapies that are necessary for an improved beneficial effect on an outcome of the involved disease or condition when available therapy cannot.

3. *Complex or particularly difficult study or studies*

CVM intends to determine whether a study or studies is complex or particularly difficult on a case-by-case basis by considering the extent to which one or more of the following factors apply to demonstrating substantial evidence of effectiveness:

a. the nature of the disease or condition makes it unusually time consuming or difficult to enroll sufficient numbers of eligible animals to provide substantial evidence of effectiveness. Among other possible factors, CVM intends to consider the degree to which the following factors apply in making this determination: the sporadic occurrence of the disease or the condition, the unpredictability of the occurrence or outcome of the disease or condition, the difficulty in diagnosing the disease or condition, and the lack of feasible alternatives such as induced disease model studies. In determining whether it is unusually time consuming or difficult to enroll sufficient numbers of eligible animals based upon the nature of the disease or condition, other factors limiting enrollment that are not based upon the nature of the disease or condition (e.g., owner reluctance to enroll animals, safety concerns related to the drug that cause stringent inclusion criteria) will not be considered.

[8] As with conditionally approved new animal drugs, other conditionally available products (e.g., conditionally licensed animal biologics) also are not considered to be available therapy.

b. the demonstration of effectiveness is unusually difficult or complex due to logistical challenges, such as needing an unusually large number of animals in the study or studies or the need for use of advanced or complicated tests.

c. it is necessary to develop and qualify effectiveness endpoints (e.g., clinical endpoints, biomarkers) to conduct the study or studies.

d. it is necessary to develop and validate or qualify novel methods to adequately evaluate effectiveness outcomes (e.g., complex animal models, technologies, or diagnostic tests).

e. the endpoint being evaluated is a delay in progression of a chronically progressive disease or condition where evaluation of effectiveness for an individual animal will likely take an extended period of time (typically a year or more). CVM intends to take into consideration the frequency and complexity (including logistical or technical difficulty) of monitoring the disease or condition during the study when considering this factor.

f. there is a need to evaluate the treatment of a disease or condition over an extended period of drug administration where evaluation of effectiveness for an individual animal will likely take an extended period of time (typically a year or more). CVM intends to take into consideration the frequency and complexity (including logistical or technical difficulty) of monitoring the disease or condition during the study when considering this factor.

g. the drug will be indicated for mitigating transmission of a zoonotic disease from animals to humans and it is necessary to conduct a study(ies) to evaluate the human aspect of effectiveness.