#61

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

Guidance for Industry

This version of the guidance replaces the version made available May 2008.

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 the docket number FDA-1997-D-0444.

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 http://www.regulations.gov.

U.S. Department of Health and Human Services
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Center for Veterinary Medicine
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Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species

Guidance for Industry

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 the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance is intended to assist those interested in pursuing FDA approval of new animal drugs intended for minor uses in major species (minor use) or for use in minor species. It outlines the basic requirements and special considerations for these approvals and describes the incentives available to encourage the development of new animal drugs for minor uses and minor species (MUMS drugs).

Many of those seeking approval for MUMS drugs are new to the new animal drug approval process. To better assist those who may be unfamiliar with the approval process, topics are presented in the order in which they commonly arise in the development of a MUMS drug. Although FDA intends for this guidance to be generally useful for all parties that may pursue approval of a MUMS drug, some portions of this document contain information that applies specifically to applications for approval of MUMS drugs intended for use in aquatic species.

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.

Using This Guidance

This document includes citations to the applicable sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or to the implementing regulations in Title 21 of the Code of Federal Regulations (21 CFR), and references to related guidance documents.

Appendix 1 – Additional Resources lists all Guidance for Industry (GFI) documents referred to in this guidance and provides hyperlinks to these GFIs and other sources of information relevant to the topics included in this document.

Appendix 2 – Acronyms & Definitions provides a glossary of many terms and acronyms used in this document. These are included to provide a quick reference and may repeat some terms defined in the body of the document.

II. Definitions

There are many specialized terms and acronyms associated with the new animal drug approval process and the regulations related to MUMS drugs. Unless otherwise specified, the following definitions are found in FDA's regulations at 21 CFR 516.3. We provide examples or additional information to these definitions for clarity.

1. *Major Species* means cattle, horses, swine, chickens, turkeys, dogs, and cats.

2. *Minor Species* means animals, other than humans, that are not major species. Some examples of minor species are sheep, goats, bison, deer, finfish, shellfish, honeybees, rabbits, gamebirds, ferrets, laboratory rodents, pet birds, llamas, emus, and zoo animals.

3. *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. The term "indication," as used in this document, is the statement that appears on labeling to describe the intended use of the product, which includes the species of animal intended to be treated and the disease or condition or the structure or function of the body affected. Generally, this term is used when discussing the indication that is studied as the subject of a new animal drug application.

4. *Intended Use* means the intended treatment, control, or prevention of a disease or condition, or the intention to affect the structure or function of the body of animals within an identified species, subpopulation of a species, or collection of species.[1] In this guidance, the term "intended use" is used in the context of incentives for MUMS drugs.

5. *Sponsor (you)*, for purposes of this guidance, means the person requesting designation for a MUMS drug who must be the real party in interest of the development and the intended or actual production and sales of such drug (in this context, the sponsor may be an individual, partnership, organization, or association).[2] "Sponsor" also means the person responsible for an investigation of a new animal drug (in this context, the sponsor may be an individual, partnership, corporation, or government agency or may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of new animal drugs). "Sponsor" also means the person submitting or receiving approval for a new animal drug application (in this context, the sponsor may be an individual, partnership, organization, or association). In all contexts, the sponsor is

[1] 21 CFR 516.13

[2] 21 CFR 516.16

responsible for compliance with applicable provisions of the FD&C Act and regulations.

III. Background – The MUMS Act

The Minor Use and Minor Species Animal Health Act of 2004 (commonly referred to as the "MUMS" Act)[3] amended the FD&C Act to provide incentives to sponsors to develop new animal drugs for use in minor species or for use in major species afflicted with uncommon diseases or conditions (minor uses), while ensuring appropriate safeguards for animal and human health. Appendix 1 – Additional Resources provides a link to the MUMS Act.

Congress recognized that the markets for MUMS drugs are so small that there is little economic incentive for sponsors to pursue approval of conventional new animal drug applications. Congress also recognized that because some minor species populations are very small, and conditions of animal management may vary widely, it is often difficult to design and conduct studies to establish drug safety and effectiveness that meet the requirements of the traditional new animal drug approval process.

Significant provisions of the MUMS Act include the following:

1. *Conditional Approval* allows the marketing of a MUMS drug when all requirements for its approval have been met except the "substantial evidence" standard for effectiveness. Instead, conditional approval requires these MUMS drugs to meet a "reasonable expectation of effectiveness" standard. Conditional approval allows a sponsor to market the conditionally approved MUMS drug for up to 5 years while gathering the remaining data required to demonstrate substantial evidence of effectiveness and obtain a full approval. In 2018, Congress expanded the eligibility requirements for conditional approval beyond MUMS drugs to also allow for the possibility of conditional approval of new animal drugs intended for major uses in major species under certain limited circumstances. See further discussion of this expansion in section XXI.A. *Conditional Approval* below.

2. *Designation* provides incentives that encourage new animal drug sponsors to pursue approval or conditional approval for MUMS drugs. These incentives include competitive grants to support safety and effectiveness testing in connection with the development of designated drugs and 7 years of exclusive marketing rights beginning when the drug is approved or conditionally approved.

3. *The Index of Legally-Marketed Unapproved New Animal Drugs for Minor Species* (the Index) provides an alternative drug review process for the legal marketing of unapproved new animal drugs for use in certain minor species. Minor use drugs are not eligible for the Index. For further details about the Index, see GFI #201, "Small Entities Compliance Guide for The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species."

[3] (Pub. L. 108-282)

4. *Three-Year Exclusivity for Minor Use and Minor Species Approvals* allows for 3 years of market exclusivity (i.e., protection from generic copying) when sponsors conduct residue depletion studies for the approval of a MUMS drug.

5. The *Scope of Review for Minor Use and Minor Species Applications* directs FDA to use only the relevant information in an approved application to determine whether a supplemental application to add an intended use for a minor use in a major species or for use in a minor species can be approved.

6. *Office of Minor Use and Minor Species Animal Drug Development* (OMUMS). As mandated by the MUMS Act, FDA established the Office of Minor Use and Minor Species Animal Drug Development (OMUMS) within CVM. The Office is responsible for, among other things, making "minor use" assessments, designating qualified new animal drugs, and maintaining the Index.

IV. Things to Consider Before Pursuing Approval of a MUMS Drug

A. Jurisdiction

There are several Federal agencies involved in the regulation of products for animals. The first step to legally marketing a product for animal use is to find out which government agency has responsibility for regulating it.

In general, FDA regulates new animal drugs and medical devices for use in animals, the U.S. Department of Agriculture (USDA) regulates animal biologics (e.g., vaccines), and the Environmental Protection Agency (EPA) regulates pesticides. Contact CVM at AskCVM@fda.hhs.gov if you have questions about the jurisdiction of a specific product. CVM coordinates with the other Federal agencies on regulatory jurisdiction issues to help ensure consistency with applicable laws.

B. U.S. Agent

Foreign sponsors must identify an authorized representative residing or maintaining a place of business in the U.S. to handle correspondence with the FDA. Such an authorized representative for a foreign sponsor is generally referred to as a U.S. agent. All submissions (correspondence, protocols, study reports, etc.) in support of new animal drug applications (pre- and post-approval) and any related information must be submitted through, and counter-signed by, a U.S. agent.[4]

C. Communication with CVM

Communication with CVM is important for all sponsors and is especially important for sponsors less familiar with the new animal drug approval process.

[4] 21 CFR 514.1(a)

The Office of New Animal Drug Evaluation (ONADE) project managers (PMs) serve as a central point of contact for drug sponsors and can provide information about the new animal drug review process and ONADE's regulatory procedures. If you have questions about the approval process and do not have an ONADE PM assigned to your company, you can contact the PM team using the CVM mailbox AskCVM@fda.hhs.gov.

You are encouraged to work with ONADE early in the drug development process. Early exchange of information between you and ONADE can help develop an approach to a product development plan (PDP) more efficiently. Your assigned PM can help you navigate the regulatory process and determine the most appropriate pathway to product approval.

NOTE: This document includes topics associated with the pre-approval evaluation of new animal drugs. Many of these topics are discussed in greater detail in other GFIs. To avoid redundancy, this guidance provides general coverage for those topics covered in other GFIs and provides detailed coverage for issues specific to Minor Use and Minor Species. All GFIs cited in this document are listed in Appendix 1 – Additional Resources, with hyperlinks to the documents.

V. User Fee Waivers and MUMS Status

A. Animal Drug User Fees

The FD&C Act authorizes FDA to assess and collect user fees for certain animal drug applications and supplements, products, establishments, and sponsors, and establishes criteria for FDA to grant a waiver from or a reduction of these fees in certain circumstances.[5]

FDA is authorized to collect four different types of user fees under the FD&C Act for animal drugs:

- An annual sponsor fee
- An annual establishment fee
- An annual animal drug product fee
- A one-time animal drug application fee

GFI #173, "Animal Drug Sponsor Fees Under the Animal Drug User Fee Act," and its appendix explain how to determine if you are an animal drug sponsor under the Animal Drug User Fee Act (ADUFA) provisions and thus subject to an annual sponsor fee. Note that animal drug sponsorship is not limited to pharmaceutical companies. Investigational files may belong to entities such as universities and State and Federal government agencies.

Once you are considered an animal drug sponsor under ADUFA, you are subject to an annual sponsor fee from the time you open an investigational new animal drug (INAD) file (see section VI.C. *Investigational New Animal Drug (INAD) File*), throughout the pre-approval process, and after approval of your new animal drug application. The two other annual fees (product and

[5] Section 740 of the FD&C Act

establishment) are assessed only after your application is approved and you are marketing your drug product.

The application fee is a one-time fee, assessed at the time of submission of certain animal drug applications or supplemental applications.

GFI #170, "Animal Drug User Fees and Fee Waivers and Reductions," describes ADUFA user fees and fee waivers/reductions available for animal drugs, including MUMS drugs, and the process for submitting a user fee waiver request.

You may qualify for a waiver or a reduction of some or all ADUFA user fees when your product is a MUMS drug. Eligibility for a waiver from user fees for a MUMS drug is clear when the intended use is for a *minor species*. A request for a waiver from user fees for a MUMS drug that is intended for a *minor use* in a major species should include evidence to establish eligibility for the waiver.

If you are a new sponsor of a MUMS drug and are not already paying an annual sponsor fee in connection with a non-MUMS animal drug, we encourage you to request a sponsor fee waiver *before* establishing the INAD file to ensure that you will not incur that fee.

Even if you are already paying annual user fees in connection with non-MUMS drugs, you can request a waiver from the one-time animal drug application fee for your MUMS drug when you are ready to submit the application.

Please note that waivers from annual user fees must be requested every year not later than 180 days after such fees are due.[6]

B. Minor Use Assessments

If your product is intended for a minor use in a major species, you should request a formal assessment of minor use status for your new animal drug. The responsibility for determining whether a proposed use of a new animal drug in a major species constitutes a minor use always rests with CVM's Office of Minor Use and Minor Species Animal Drug Development (OMUMS). Such requests are commonly submitted to CVM in the form of:

- A user fee waiver request;
- A request for "designation" of a new animal drug (designation is discussed in section IX. *Designation*);
- A stand-alone request for an assessment of minor use status to confirm that a product is eligible for conditional approval (conditional approval is discussed in section XXI.A. *Conditional Approval*); or

[6] Section 740(i) of the FD&C Act

- A stand-alone request for an assessment of minor use status to confirm that a product being developed directly for full approval is intended for a minor use.

Except for annual user fee waivers, which must be requested every year in order to continue to receive the waiver,[7] these assessments lock in minor use status as described below.

User fee waivers, designation, and conditional approval are independent incentives. You may take advantage of any or all of these incentives depending on the needs or status of your project. OMUMS uses the same criteria to establish a formal decision regarding "minor use" status for each of these incentives.[8] For that reason, once minor use status is in effect for purposes of one of these incentives, you can refer to that minor use status decision if you later request other MUMS incentives for the same project. For example, if you received minor use status in connection with a request for a waiver from user fees, there may be no need to demonstrate minor use status when requesting designation or conditional approval.

You can cite the earlier assessment of minor use status and, provided OMUMS determines that the previous finding is still valid, OMUMS intends to confirm the minor use assessment in the context of the designation or conditional approval process.

Most commonly, the minor use assessment is made in response to a sponsor's request for a waiver from user fees. That is an efficient way to obtain both a formal decision regarding minor use status for your new animal drug and a decision that the drug product is eligible for a user fee waiver at the beginning of the project.

1. Duration of a Minor Use Assessment

OMUMS confirms minor use assessments when annual user fee waiver requests are granted each year, both pre- and post-approval. If the product is designated, or determined to be eligible for conditional approval, or determined to be a minor use for purposes of the sponsor seeking full approval, that status can be cited to support the user fee waiver request. The length of time a minor use assessment remains valid differs depending upon how it was obtained.

CVM intends to consider minor use assessments obtained to establish a product's eligibility for conditional approval, or for products being developed directly for full approval, to remain in place throughout the course of the product development process, up through the full approval of the new animal drug application. Minor use assessments obtained for designated products remain in place from the date the product is designated through the 7 years of exclusive marketing rights following full approval or conditional approval, unless designation is otherwise terminated.[9]

[7] Section 740(i) of the FD&C Act

[8] 21 CFR 516.21

[9] 21 CFR 516.29

This means that even if there are changes in the occurrence of the disease or in the size of the population of the major species for which the drug is intended that could bring the eligible population above the small number threshold established for that species, FDA does not intend to revisit that specific decision. In such cases, the Agency plans to consider the minor use assessment as still valid as long as you show due diligence toward approval. In the event another sponsor later requests a minor use assessment for the same intended use, that sponsor's request could be denied if the size of the eligible population has changed to such an extent that it no longer meets the small number threshold for "minor use."

2. Demonstrating That an Intended Use is a Minor Use

If the proposed intended use for your product is already on the Designation List (found on the MUMS webpage of CVM's website), you may be able to use that designation listing to demonstrate that the intended use for your product is a minor use. This assumes that conditions have not changed since that designation was granted. Please consult with OMUMS to make sure that the intended use is still considered a minor use. If the intended use has not already been determined to be a minor use, you will need to provide information to support your claim that a particular intended use constitutes a minor use.[10]

3. Small Numbers and the Eligible Population

FDA has established by regulation[11] a "small number" threshold for minor use in each of the seven major species. The small number thresholds represent the largest number of animals of each major species that can be affected by a disease or condition over the course of a year and still have the use qualify as a minor use.

As of the date of this guidance, small number of animals means equal to or less than:

Horses – 50,000	Pigs – 1,450,000
Dogs – 80,000	Turkeys – 14,000,000
Cats – 150,000	Chickens – 72,000,000
Cattle – 310,000	

CVM periodically (on the order of every 5 years) reassesses the small number thresholds and publishes its findings in the Federal Register. The reassessment process is fully described in the preamble for the final rule, Defining Small Numbers of Animals for Minor Use Determination; Periodic Reassessment (87 FR 56583, September 15, 2022).

The "eligible population" is the total number of animals likely to be *afflicted* with the disease or condition on an annual basis based on the best available estimates. In the minor use status request, you must demonstrate that the eligible population of animals to which the MUMS drug

[10] 21 CFR 516.21

[11] 21 CFR 516.3

will be administered is equal to or less than the "small number" threshold for the major species of interest.[12]

Given the statistical degree of uncertainty typically associated with estimates of the rates of occurrence of uncommon animal diseases, the number of animals in the eligible population generally should be well below (usually, approximately 13% below) the published small number threshold. This statistical degree of uncertainty was anticipated by FDA when the small number thresholds were calculated; the small number thresholds were increased to account for this uncertainty.

Published literature, surveys, and veterinary hospital databases are possible sources of information that may be used to determine the number of animals in the eligible population. You may also want to look at the Freedom of Information Summaries for products that were conditionally approved to see how the minor use assessment was made. Such examples may be useful guides. OMUMS appreciates that the number of affected animals can be difficult to determine and encourages you to contact us to discuss approaches to gathering this information.

4. Reducing the Eligible Population

The eligible population may be reduced if there is a *medical* reason why it would be inappropriate to treat some portion of this population.[13] For example, in accordance with current veterinary practice, Grade I mast cell tumors are treated by surgical excision in dogs. A chemotherapy use could be limited to mast cell tumors other than Grade I as it would be considered medically inappropriate to treat Grade I tumors with chemotherapy. As a result, the eligible population of dogs with mast cell tumors would be reduced to dogs with mast cell tumors other than Grade I.

FDA does not intend to consider other factors, including the fact that some animals will not be treated, there are other medically appropriate treatments that could be used, or the use may be limited to specialty practices, as grounds for reducing the eligible population since these factors were already taken into account in establishing the small number thresholds.

5. Limiting the Eligible Population by Production Class

CVM does not generally consider specific production classes of a major species, such as lactating dairy cows or breeding turkeys, as an appropriate eligible population for purposes of an assessment of minor use—the entire species population should be considered. However, if the disease/condition only affects animals in a specific production class, then that production class may qualify as an eligible population.

For example, if a disease only occurs in breeding chickens, it may be appropriate to limit the eligible population to that production class. However, it is unlikely we would consider it

[12] 21 CFR 516.21

[13] 21 CFR 516.21(b)

appropriate to limit the eligible population to breeding chickens if the disease at issue could affect any chicken.

VI. New Animal Drug Files and Submissions

A. Electronic Submissions

Beginning October 1, 2018, all types of new animal drug applications (see section VI.B. *Types of New Animal Drug Applications*) and submissions supporting these applications must be created using the eSubmitter tool and submitted to the Agency through the Electronic Submissions Gateway.[14]

The eSubmitter tool provides sponsors with immediate electronic receipt confirmation, immediate electronic transmission of CVM's response, and includes templates for the various types of submissions to help sponsors ensure they include all necessary information. The FDA website has information about using eSubmitter, including GFI #108, "How to Register with the CVM Electronic Submission System."

B. Types of New Animal Drug Applications

Once you know that the proposed intended use of your drug product is for a minor use or a minor species, you can begin the process to get it approved or conditionally approved. The general requirements for new animal drug approval are the same for major and minor species.

There are three different types of new animal drug applications.

1. A *New Animal Drug Application* (NADA) is used to apply for FDA approval of a new animal drug.

2. An *Application for Conditional Approval of a New Animal Drug* (CNADA) is used to apply for FDA conditional approval of a new animal drug. A conditionally approved CNADA allows a sponsor to legally market a new animal drug after fulfilling the requirements for conditional approval. A conditionally approved CNADA has met all the requirements under section 512 of the FD&C Act to support full approval of the new animal drug except for a demonstration of "substantial evidence of effectiveness." For a CNADA, you only need to demonstrate a "reasonable expectation of effectiveness." A conditionally approved CNADA allows you to legally market a new animal drug for up to 5 years, provided FDA approves your required annual renewal requests, while you continue to collect the effectiveness data needed to meet the "substantial evidence" standard for full approval and prepare your NADA for submission.[15]

3. An *Abbreviated New Animal Drug Application* (ANADA) is used to apply for FDA approval of a generic new animal drug. A generic new animal drug is a copy of an

[14] Sections 512(b)(4) and 571(a)(4) of the FD&C Act

[15] Section 571 of the FD&C Act

approved new animal drug for which patents or other periods of exclusivity have expired. While MUMS drugs are eligible for generic approval under the same standards as other new animal drugs for which generic approval is sought, this guidance document focuses on NADA and CNADA requirements. Guidance documents addressing topics associated with generic new animal drug approval are available on CVM's website. You can also contact AskCVM@fda.hhs.gov if you have questions about the generic new animal drug approval process.

For any application you submit to be approved or conditionally approved, you should expect to provide scientific data. This could include information to support the product's safety, effectiveness, and quality.[16] CVM staff then review the submitted data to determine whether they meet established scientific and regulatory standards and are adequate to support FDA approval or conditional approval.

C. Investigational New Animal Drug (INAD) File

Data to support an NADA or CNADA are generally submitted by sponsors to an INAD file and reviewed by CVM during the investigational stage of drug development before they submit the completed NADA or CNADA. These data include the results from studies conducted under an investigational use exemption as described in 21 CFR 511.1(a) and (b). The exemption allows the shipment in interstate commerce of the unapproved investigational new animal drug so that it can be used in studies to generate the data needed to support approval of the sponsor's application.[17]

The INAD file includes all of a sponsor's submissions to CVM regarding the proposed new animal drug, e.g., study protocols, final reports including raw data, requests for meetings and other administrative actions. The INAD file also contains all of CVM's review documentation, including scientific reviews, meeting minutes, and correspondence between the sponsor and CVM.

In addition to protocols and data from studies, there are other submissions that are part of the investigational file. Some of the pertinent ones are described in the following sections.

1. Opening the INAD file

Requests to open an INAD file are usually directed to specific review divisions within CVM ONADE. You should choose the appropriate division from the drop-down menu in the eSubmitter tool. Generally, requests relating to drug products intended for use in food-producing animals go to the Division of Food Animal Drugs (HFV-130). Requests relating to companion animal drugs should be submitted to the Division of Companion Animal Drugs (HFV-110).

[16] Sections 512(b) and 571(a)(2) of the FD&C Act

[17] Sections 301(a), 501(a)(5), and 512(a) of the FD&C Act

All new animal drug products intended for use in aquaculture (for both ornamental and food-producing species), including drugs intended for production indications, such as spawning aids, are reviewed by the Aquaculture Drugs Team in HFV-130.

2. Disclosure Permission

Information in an INAD file is considered proprietary. CVM personnel are generally prohibited from confirming or denying even the existence of any particular INAD file unless it has been publicly disclosed or acknowledged by the sponsor.[18] To facilitate the process of new animal drug approval for some products, particularly when there are multiple entities involved, we encourage you to provide written disclosure permission. These permissions allow CVM to discuss either certain parts (e.g., specific technical sections or studies) or the entire INAD file with other individuals or groups specified in the permission. This makes it easier to share information among multiple research partners and other stakeholders.

3. Research Partners

Because some drug sponsors may not have the resources needed to conduct the studies to support approval for a MUMS drug, they often establish partnerships with other entities, either public or private. Federal, State, local, or tribal government agencies, non-profit organizations, universities, and others are possible partners. Such entities may conduct studies to support drug product approval. If data are generated in the public sector and provided in a submission to CVM, a summary of that information is generally made available in CVM-administered Public Master Files (PMFs) and posted on CVM's website. Sponsors seeking approval or conditional approval can refer to the data in these files to support their applications.

You should identify your research partner(s) in official correspondence submitted to the INAD file and provide written permission for FDA to discuss specific portions, or the entire file, with the partner(s). Identifying your research partner(s) makes it possible for a partner to apply for MUMS grants *provided the product is designated*. It also enables their work to be considered by FDA in determining whether there has been due diligence toward your approval or conditional approval, which you may use to maintain designation status.

Research partners generally establish their own separate INAD files for the submissions they generate. The INAD file for the sponsor who intends to file the complete application and market the new animal drug generally contains any proprietary data and information that will not be part of the public disclosure, such as information concerning the manufacturing process.

Since 1982, the USDA has had a public program that partners with sponsors of MUMS drugs to conduct research to support approvals of new animal drugs for minor species of agricultural importance. An OMUMS employee acts as the FDA liaison to this program to facilitate the progress of these research projects. This program was originally part of the USDA's IR-4

[18] 21 CFR 514.11 and 514.12

Program, then became known as the National Research Support Project #7 (NRSP-7), and is now known as the Minor Use Animal Drug Program (MUADP).

There are other public partners, including some that work on projects relating primarily to aquaculture. These include the U.S. Fish and Wildlife Service's Aquatic Animal Drug Approval Partnership (AADAP) as well as researchers in academia. Links to some websites can be found on the MUMS webpage and the work completed by research partners is acknowledged on the public master files webpage of CVM's website. See Appendix 1 – Additional Resources for links to associated web pages.

4. Additional Submissions

Once a sponsor receives a notification from FDA providing the assigned INAD file number, the sponsor may make additional submissions to the file. These include, but are not limited to, submissions of early information, requests for presubmission conferences or product development meetings, requests for food use authorizations, and a request for a categorical exclusion from the requirement to prepare an environmental assessment for studies conducted under the INAD file (see section XVI. *Environmental Impact*).

Sponsors are required to submit specific information to the INAD file before any shipment or other delivery of the drug intended for clinical investigational use. This is called a Notice of Claimed Investigational Exemption for a New Animal Drug (NCIE). The information required in an NCIE is described in 21 CFR 511.1(b)(4).

VII. Talk With CVM About the New Animal Drug Approval Requirements for Your Product – Presubmission Conference (PSC)

It is important for all sponsors, but especially important for sponsors of MUMS drugs, to discuss their plans for pursuing drug approval with CVM before they expend money and effort on activities that may not meet the requirements for approval. You should work with your ONADE PM to determine the most efficient path to obtain approval of your drug product.

After discussion with the PM, the next step may be to submit a request for a formal Presubmission Conference (PSC) with representatives from ONADE and OMUMS. The PSC is your opportunity to discuss the nature of the intended use and the studies that will eventually support the approval of the drug product. The purpose of the PSC is for CVM and the sponsor to reach agreement prior to the submission of an application or supplemental application about how the sponsor will meet the submission or investigational requirements for drug approval.[19]

You should invite all research partners to participate in the PSC so that everyone can discuss the studies and other information that will be gathered to support the drug approval. This may help to prevent misunderstandings and miscommunication later during the approval process. The sponsor

[19] 21 CFR 514.5(b)

of the INAD will receive a Memorandum of Conference (MOC) following the meeting that captures the discussion and agreements of the meeting.

In the meeting request, you should include an agenda that clearly outlines the scope, purpose, and objectives of the PSC and a list of names and positions of representatives who are expected to attend the PSC on your behalf. The PSC may be conducted in person at CVM, or remotely by teleconference or videoconference. In the event of an in-person meeting, any foreign nationals must be clearly identified in your request. You should also include a copy of any materials that you intend to present at the meeting, as well as copies of materials that you evaluated or referenced relative to the issues listed in the agenda. CVM must receive requests at least 30 calendar days in advance of the requested meeting date to give reviewers adequate time to prepare for the meeting.[20] You should include several possible dates for the meeting in the request.

At the PSC, you can discuss all technical sections of an NADA or CNADA with representatives of the divisions in ONADE that will eventually review your study protocols and study reports. This PSC provides the chance to have a conversation about how you can meet all the requirements for drug approval. ONADE will issue an MOC to you within 45 days of the meeting date.[21] If, later, you need to revise an understanding reached at the PSC, you should contact ONADE to determine the best path forward.

If you intend to request designation status for your MUMS drug, it is particularly important to have a PSC before you submit a designation request to OMUMS (see section IX. *Designation* below for more information). You should ensure that there is agreement with ONADE on the wording of the intended use for the drug product and that you have a clear understanding of the requirements for approval. The ONADE MOC from this meeting can serve as the required description of a product development plan (PDP) in a designation request.

Additional meetings to discuss the project can always occur as the project moves forward and new questions arise.[22]

VIII. Tests of Sameness

Tests of "sameness" are used to determine eligibility for designation status of MUMS drugs, conditional approval of MUMS drugs, and for the Index of Legally-marketed Unapproved New Animal Drugs for Minor Species (discussed briefly in section XXI.B. *The Index of Legally-Marketed Unapproved New Animal Drugs for Minor Species (the Index)* below. These definitions are specific to these programs and may be different in other contexts.

[20] 21 CFR 514.5

[21] 21 CFR 514.5(f)

[22] See 21 CFR 514.5 for requirements regarding the PSC.

A. Same Drug

The term *same drug* means a MUMS drug for which designation, addition to the Index, or conditional approval is sought that is composed of small molecules and contains the same active moiety as a prior designated, conditionally approved, or approved MUMS drug. Even if the specific ester or salt is not the same, it is considered the same drug. However, if the first MUMS drug is conditionally approved or approved and the second MUMS drug is shown to be functionally superior to the conditionally approved or approved MUMS drug for the same intended use, it is *not* considered the same drug.[23]

B. Same Dosage Form

Same dosage form is based on the dosage form categories found in 21 CFR chapter I, subchapter E as follows:

21 CFR part 520 – Oral dosage form new animal drugs

21 CFR part 522 – Implantation dosage form new animal drugs

21 CFR part 522 – Injectable dosage form new animal drugs

21 CFR part 524 – Ophthalmic dosage form new animal drugs

21 CFR part 524 –Topical dosage form new animal drugs

21 CFR part 526 – Intramammary dosage form new animal drugs

21 CFR part 529 – Certain other dosage form new animal drugs

21 CFR part 558 – New animal drugs for use in animal feed

Any two dosage forms within the same category are considered to be the same dosage form (e.g., tablet and suspension are considered the same dosage form). Any two dosage forms in different categories are considered to be different dosage forms. Therefore, oral, implant, injectable, ophthalmic, topical, intramammary, other (e.g., inhalation anesthetics), and medicated animal feeds are considered different dosage forms for the purpose of this sameness test. Products that fall into the "Certain other dosage form new animal drugs" will be compared with others that are like the product in question. For example, if the product is administered by immersion, it will be tested for sameness against other immersion products in that category.

The dosage forms reflected on the approved product labeling for new animal drugs generally fall into one of the categories listed above. Specific dosage forms on approved product labeling may include, for example, capsule, cream, gel, powder, solution, sponge, spray, tablet, or Type A medicated article.

C. Same Intended Use

Same intended use in the context of MUMS drugs means an intended use of a MUMS drug for

[23] 21 CFR 516.3

which designation, addition to the Index, or conditional approval is sought, that is determined to be the same as a previously designated, conditionally approved, or approved intended use of a MUMS drug. Same intended use is determined by comparing the basic intent of two intended uses, not just by comparing the specific language used in labeling to state the intended use. Two intended uses are considered the same if one of the intended uses falls completely within the scope of the other.

For example, an intended use for "koi" would be within the scope of an intended use for "all ornamental finfish." Two intended uses of a drug are not considered the same if they involve different intended species or different definable production classes of a species.[24]

IX. Designation

A. General

Section 573 of the FD&C Act, as added by the MUMS Act, establishes a process for designating a new animal drug. The incentives associated with MUMS drug designation are modeled on some of those provided by the Orphan Drug Act for human drug products.

Designation makes the proposed intended use of a MUMS drug eligible for specific incentives supporting product approval or conditional approval. Absent such incentives, sponsors might not otherwise pursue approval due to the drug's limited market potential. **Products with designated MUMS indications cannot be legally marketed until they are approved or conditionally approved.[25] Please note that products that are pursuing addition to the Index are not eligible for designation and its incentives.**

In addition to the other incentives for MUMS drugs, designation provides the following incentives for approval or conditional approval of MUMS drugs:

> *Eligibility for grants and contracts* to defray the costs of qualified safety and effectiveness testing expenses incurred during the development of designated new animal drugs (this includes some manufacturing studies); and
>
> *Exclusive marketing rights* for a period of 7 years following approval or conditional approval to enable sponsors to recover costs of drug development without direct competition. The exclusive marketing rights for designated MUMS drugs provide protection from approval of another application for the same drug in the same dosage form for the same intended use and from generic copying of the designated drug.

B. Eligibility

Only MUMS drugs are eligible for designation under section 573 of the FD&C Act. However, a MUMS drug will not be eligible for designation if the same new animal drug in the same dosage

[24] 21 CFR 516.3

[25] Section 573(a) of the FD&C Act

form for the same intended use is already approved, conditionally approved, or designated at the time designation is requested. Each of the conditions of "sameness" (same drug, same dosage form, same intended use) is described in detail in FDA's regulations at 21 CFR part 516 and above in section VIII. *Tests of Sameness* of this document.

Designation needs to be requested by the sponsor, or their U.S. agent, that will ultimately file an application for approval or conditional approval.[26]

Investigators may apply for grants for studies supporting approval or conditional approval of the designated product if they have been acknowledged as research partners in the sponsor's INAD file.

C. Overview of the Designation Process

Designation requests are reviewed and either granted or denied by OMUMS. Requests for designation must be directed to the Director, Office of Minor Use and Minor Species Animal Drug Development.[27] These requests should be submitted electronically using eSubmitter.

1. What you need to provide

In your request for designation, you should indicate that the drug product for which you are seeking designation is a MUMS drug and state that the same drug in the same dosage form for the same intended use is not already approved, conditionally approved, or designated (described above in section IX.B. *Eligibility*).[28] In accordance with the regulations at 21 CFR 516.20(b), the following information must be included in support of the request:

- A request for designation that is specific (only one drug in one dosage form for a specified intended use);
- The name and address of the sponsor, the name of the contact person or U.S. agent, the established name and proprietary name (if any) of the active pharmaceutical ingredient of the drug, and the name and address of the source of the active pharmaceutical ingredient of the drug;
- A description of the proposed intended use;
- A description of the drug and dosage form;
- A discussion of the scientific rationale for the intended use of the drug;

[26] 21 CFR 516.16 and 516.20(b)(8)

[27] 21 CFR 516.14

[28] 21 CFR 516.20(a)

- A specific description of the PDP for the drug, its dosage form and its intended use;
- If the drug is intended for a minor use in a major species, documentation to demonstrate that the intended use is a minor use;
- A statement that the sponsor submitting the request is the real party in interest of the development of the drug; and
- A statement that the sponsor acknowledges that, upon granting a request for MUMS drug designation, FDA will make certain information regarding the designation publicly available as specified in 21 CFR 516.28.

2. Grounds for Refusal to Grant Designation

In accordance with 21 CFR 516.25, FDA will refuse to grant a request for MUMS drug designation if any of the following conditions apply:

- The drug is not intended for use in a minor species, or there is insufficient evidence to demonstrate that the use is intended for a minor use in a major species;
- An active designation already exists for the same drug in the same dosage form for the same intended use;
- The same drug in the same dosage form for the same intended use is already approved or conditionally approved (unless the drug for which designation is sought has been shown to be functionally superior); or
- The sponsor has failed to provide a credible scientific rationale in support of the intended use, an adequate PDP, or any other information required under 21 CFR 516.20.

3. Designation Does Not Change the Approval Process

MUMS drug products that are designated are evaluated for approval or conditional approval by ONADE in accordance with the same standards that are applied to non-designated drugs. Designation is an incentive program, not a different approval process.[29]

4. The Designation List

Designated MUMS drugs are listed on the FDA website. The listing includes the sponsor's name and address, the name(s) of the drug, dosage form, target species, intended use, and the date and status of the designation. No proprietary information is disclosed.[30]

[29] Section 573(a) of the FD&C Act

[30] 21 CFR 516.28

D. The Intended Use

The following definition of "intended use" is provided in FDA's regulations relating to the designation of MUMS drugs: "[*i]ntended use* means the intended treatment, control or prevention of a disease or condition, or the intention to affect the structure or function of the body of animals within an identified species, subpopulation of a species, or collection of species."[31] This definition is, however, substantially narrower than what is generally meant by "intended use" in other parts of FDA's regulations and the FD&C Act, and corresponds more closely to what is generally meant by "indication" – i.e., the *stated* purpose for which the drug is to be used and for which approval is sought.

For a designation to be granted, the proposed intended use of the MUMS drug needs to be clearly stated and there must be a description of the product development plan for the drug.[32] See section IX.F. *Production Development Plans (PDP)* below for more information regarding designation and product development plans.

You may request that the wording of a designated intended use be changed during the development process (prior to approval or conditional approval) if there is a valid scientific reason to do so. You should inform OMUMS of the need for such a change as soon as possible. A request to change the wording of a designated intended use may also be based on information stemming from ONADE or OMUMS recommendations, or other unforeseen developments.

In order for a sponsor's MUMS drug to be eligible for 7 years of exclusive marketing rights once it is approved or conditionally approved, the intended use that is designated must be consistent with the indication for use on the drug's labeling.[33] There is one exception to this requirement (see section IX.E. *Combining Designated Intended Uses* below).

As previously noted, the proposed designation must be for a MUMS drug, dosage form, and intended use that is not already approved, conditionally approved, or designated.[34] Because each entry on the MUMS drug Designation List is unique, it is important for sponsors to choose the wording of their designation requests carefully or their request may be refused (see).[35]

The four parameters to be considered when developing designation requests are the drug, the dosage form, and the two components of the intended use, which are: (1) the disease/condition or structure/function affected, and (2) the species to be treated. A change in any of these parameters would result in a different designation that is distinct from the original designation

[31] 21 CFR 516.13

[32] 21 CFR 516.20

[33] 21 CFR 516.31(a)

[34] 21 CFR 516.20

[35] 21 CFR 516.25

and would therefore be a separate designation listing. For example, the following changes would generally be considered separate designation listings:

Drug A **-** Type A medicated article for control of gapeworm in pheasants
(The original designation)

Drug B - Type A medicated article for control of gapeworm in pheasants
(The different drug makes this a separate designation listing)

Drug A **- water soluble powder** for control of gapeworm in pheasants
(The different dosage form makes this a separate designation listing)

Drug A - Type A medicated article for control of gapeworm in **quail**
(The different species makes this a separate designation listing)

Drug A - Type A medicated article for **control of cecal worm** in pheasants
(The different disease or condition makes this a separate designation listing)

E. Combining Designated Intended Uses

The intended use that is designated can be for a narrow or a broad label indication in accordance with your PDP. A narrow label indication might be to kill a specific parasite in channel catfish. A broad label indication might be to kill that parasite in all freshwater-reared finfish. If you ultimately want to have a broad label indication for many species of fish, there are two main ways to approach the designation and plan for approval(s).

Using the broad label indication example above, option one would be to obtain one designation for the broad intended use, conduct all the studies to support it, and file one NADA supporting the use in all freshwater-reared finfish. Option two would be to designate individual species or smaller groups separately, then do the studies and seek NADA approval for each species or group one at a time. Eventually, you should have approvals in enough species or groups to support a label indication for use in all freshwater-reared finfish.

The specific label indications you choose to pursue for approval will dictate how you should word your designation request(s). Keep in mind that designations must be unique and, therefore, there can be no overlap.[36] For example, you should not ask for one designation for channel catfish and another for freshwater-reared finfish because channel catfish are included in the freshwater-reared finfish group.

The wording of your designated intended use and the wording of your approved or conditionally approved label indication must be consistent in order to receive exclusive marketing rights for your MUMS-designated drug.[37] To continue with the previous example, if you designate "freshwater-reared finfish" and subsequently seek approval only for channel catfish, you would

[36] 21 CFR 516.20

[37] 21 CFR 516.31(a)

lose the designation incentive of exclusive marketing rights since the approval would not be for the designated use.[38] Using the same example, if you get the approval for channel catfish and still want to maintain the broader label indication for designation, the label indication for the designation would be changed to "freshwater-reared finfish *except* channel catfish." This is because you cannot obtain designation for an approved label indication.[39]

If during the product development process, you discover that you want to get a part (e.g., channel catfish, which is a freshwater-reared finfish) of your designated intended use (freshwater-reared finfish) approved in advance of the rest, you should contact ONADE for their assistance in making a modification to your existing designation (see discussion of this in section IX.J. *Amendment of a Designation* below). OMUMS can change a designation, but typically consults with ONADE to confirm that the change is acceptable. We encourage you to talk to both offices about how your official PDP will align with your designation(s).

Separate designated indications may be combined in the approved labeling. If you obtain approvals (or conditional approvals) over time for several indications that collectively could be combined into one, then ONADE may, if the data support it, agree to combine these individually approved indications into one labeled indication for the approved NADA or CNADA. While the collective approved label indication would not match the intended uses in the individual designations, this may be acceptable if ONADE agrees that the labeling for the one approved indication is equivalent to the aggregate labeling for the individual approvals (or conditional approvals). The individual designations would remain on the Designation List with their specific new animal drug application approval dates. The approval dates are the start dates for the exclusive marketing rights for the particular designated use.[40]

F. Product Development Plan (PDP)

Your request for designation must contain a description of the PDP for the MUMS drug.[41] We recommend that you discuss the development of your product with ONADE at a PSC before you request designation (see section VII. *Talk With CVM About the New Animal Drug Approval Requirements For Your Product—Presubmission Conference (PSC)*). When you submit a request for designation to OMUMS, you should attach ONADE's MOC from the PSC or reference the meeting ID number as a means to address the requirement for a description of the PDP.

While requesting designation without a PSC is discouraged, you may meet the PDP requirement by including a description of how you intend to fulfill (or have fulfilled) the technical sections required for a new animal drug approval. This description should be specific enough to demonstrate that you clearly understand the new animal drug approval process.

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[38] 21 CFR 516.31(a)

[39] 21 CFR 516.25(a)(3)

[40] 21 CFR 516.31

[41] 21 CFR 516.20(b)(6)

Clarity regarding the drug, dosage form, intended use, and PDP is important to designation for MUMS drugs because there must be *only one* designation for a particular drug, dosage form, and intended use.[42] Because a sponsor granted a designation by CVM could block designation of the same drug in the same dosage form for the same intended use by another sponsor, CVM may terminate that designation if the sponsor is not actively pursuing approval of the drug with due diligence.[43]

G. Timing the Request for Designation

Section 573(a)(1) of the FD&C Act requires that sponsors who intend to seek designation status for their MUMS drugs submit such requests before they submit an NADA or CNADA. It may be to your advantage to request designation early in the drug development process as designation affords you the opportunity to apply for grant money to support drug development. However, because MUMS drug designations are made public shortly after being granted, some sponsors may wish to delay the request for designation and the public notice that a designation has been granted until shortly before submission of an application for approval or conditional approval.

H. Competing Sponsors

On rare occasions, two or more sponsors may simultaneously choose to pursue designation of the same drug, in the same dosage form, for the same intended use. Because only one sponsor can be granted designation for a specific drug, dosage form, and intended use, the first sponsor to provide a complete and acceptable request will be granted the designation.[44] The second sponsor will be sent a denial of designation letter on the basis that the same drug, in the same dosage form, for the same intended use has already been designated.[45]

In the event that the sponsor granted designation has the designation terminated, the termination will be made public through a change in the status on the Designation List.[46] In that event, the second sponsor may again request that designation.

Failure to achieve designation due to competition with another sponsor does not prevent you from taking advantage of other MUMS incentives should you decide to continue to pursue approval or conditional approval for that product. You can continue to seek approval for the same drug/dosage form/intended use at the risk of being denied the ability to market your product if the designated sponsor's product is approved first and thus has exclusive marketing rights for 7 years.

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[42] 21 CFR 516.20(a)

[43] 21 CFR 516.29(d)

[44] 21 CFR 516.20(a)

[45] 21 CFR 516.25(a)

[46] 21 CFR 516.28

However, if you complete the approval or conditional approval before the designated sponsor, that designation would be terminated.[47] At that point, neither of the sponsors would have designation status, and neither sponsor would receive MUMS-drug exclusive marketing rights.

I. Designation Annual Reports

In accordance with 21 CFR 516.29(d) and 516.30, sponsors are required to pursue approval of designated products with due diligence to keep the designation status.

To show due diligence, sponsors of MUMS drugs must submit a brief progress report to the Director of OMUMS annually. The annual report documents the work you have done during the reporting period to advance the designated MUMS drug toward approval or conditional approval. The first annual report is due within 14 months of the date that designation is granted, and subsequent reports are due annually on the anniversary of the first report's due date until the drug is approved or conditionally approved.[48]

In accordance with FDA's regulations at 21 CFR 516.30, the reports must include:

- A short account of the progress of drug development, including a description of studies initiated, ongoing, and completed, and a short summary of the status or results of such studies;
- A description of the investigational plan for the coming year, as well as any anticipated difficulties in development, testing, or marketing; and
- A brief discussion of any changes that may affect the MUMS-designated drug status of the product; for example, a situation in which testing data demonstrate that the proposed intended use is inappropriate due to unexpected issues of safety or effectiveness.

The short account of progress in the annual report should describe information provided by all research partners and should identify the INAD file number and submission number under which the studies were submitted to CVM. Any changes that may affect the MUMS-designated drug status of the product as discussed in the annual report could result in the need to amend the designation or, in some cases, could even lead to the end of the project.

Designation and the associated incentives remain in place so long as the sponsor shows due diligence toward approval.[49] We recommend that you follow the advice from ONADE and OMUMS as to how to demonstrate due diligence. As stated previously, the annual reports provide an opportunity to show your progress and document that you are actively pursuing

[47] 21 CFR 516.29(f)(4)

[48] 21 CFR 516.30

[49] 21 CFR 516.29(d)

approval with due diligence in accordance with section 573(a)(3)(B) of the FD&C Act. Sponsors that are not actively pursuing approval may have their designations terminated.[50]

J. Amendment of a Designation

You may seek to amend a designation at any time prior to approval or conditional approval. You may apply for an amendment to the designated intended use if the proposed change is due to new and unexpected findings while performing research on the drug, information arising from FDA recommendations, or other unforeseen developments.[51]

If, for example, while pursuing an intended use for a species group, studies show that the drug is not safe in a particular species in that group, then the designation listing should be changed to only include species for which the drug is safe. As product development proceeds, it is important for you to communicate with both ONADE and OMUMS to ensure that acceptable changes to the intended use are reflected in the wording of the designation listing. The Designation List can be accessed through the MUMS webpage of CVM's website.

K. Exclusive Marketing Rights

The period of exclusive marketing rights for designated MUMS drugs begins on the date of approval or conditional approval and continues for 7 years. These exclusive marketing rights protect the designated intended use from generic copying and from FDA approving or conditionally approving another sponsor's application for the same drug in the same dosage form for the same intended use during that 7-year period.[52]

The Agency sends the NADA or CNADA sponsor, or the sponsor's U.S. agent, written notice of the initiation of exclusive marketing rights in the designated product's approval or conditional approval letter and makes this information publicly available.[53]

Although the period of exclusive marketing rights of designated MUMS drugs is separate from the period of marketing exclusivity associated with the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, their effects overlap.

The generic animal drug provisions of the FD&C Act afford sponsors of so-called pioneer applications protection from having these products and/or intended uses copied by sponsors of generic drug applications. These provisions provide 5 years of marketing exclusivity for those applications providing for the first-time approval for animal use of a new chemical entity, or 3

[50] 21 CFR 516.29(d)

[51] 21 CFR 516.26(a)

[52] 21 CFR 516.31(a)

[53] 21 CFR 516.34

years of marketing exclusivity for those applications providing for new intended uses or if the chemical entity has already been approved in another application.[54]

Once they go into effect, designated MUMS-drug exclusive marketing rights and GADPTRA marketing exclusivity run concurrently, *not* sequentially. However, GADPTRA marketing exclusivity begins upon the date of full NADA approval, *not* conditional approval. Thus, if a designated MUMS drug product involving a new chemical entity initially reaches the market by means of a full approval (rather than a conditional approval), both the designated MUMS-drug exclusive marketing rights and the GADPTRA marketing exclusivity begin running on the date of approval. In this scenario, the 7 years of designated MUMS-drug exclusive marketing rights would simply subsume the 5 years of GADPTRA marketing exclusivity.

On the other hand, if a designated MUMS drug product involving a new chemical entity initially reaches the market by means of a conditional approval (rather than a full approval), the 7 years of designated MUMS-drug exclusive marketing rights begins running on the date of conditional approval and carries over to the full approval—which must be obtained within 5 years of the conditional approval.[55] The 5 years of GADPTRA marketing exclusivity does not begin until the date of the *full* approval and runs concurrently with the remaining 2 years of the designated MUMS-drug exclusive marketing rights carried over from the conditional approval. Therefore, it is possible that, if a conditional approval exists for the maximum permissible 5 years before full approval is achieved, the full approval is protected by the remaining 2 years of designated MUMS-drug exclusive marketing rights, followed by the remaining years of GADPTRA marketing exclusivity (3 more years for a new chemical entity or 1 more year for an approval providing for a new intended use).

Designated MUMS-drug exclusive marketing rights will be terminated in accordance with 21 CFR 516.31 if:

- the designation is terminated; or
- FDA withdraws the approval or conditional approval for any reason.

Designated MUMS-drug exclusive marketing rights may also be terminated in accordance with 21 CFR 516.31 if the sponsor:

- provides written consent for FDA to approve or conditionally approve another application before the expiration of 7 years; or
- fails to provide sufficient quantities of the drug.

L. Grants for Designated New Animal Drugs

[54] Section 512(c)(2)(F) of the FD&C Act

[55] Section 571(d) of the FD&C Act

Section 573(b) of the FD&C Act authorizes FDA to make grants to help support the development of designated MUMS drugs.

Sums anticipated to be awarded as grants in each fiscal year are announced as part of a request for applications on CVM's website and on the grants.gov website (http://www.grants.gov). Several fiscal years are included in one announcement and the funds to be awarded are dependent on actual appropriations. Grants are intended to help defray the costs to sponsors of safety, effectiveness, and certain manufacturing studies in support of new animal drug approval or conditional approval for designated MUMS drugs.

You must have the designation in place to complete the grant application process.[56] In addition, you must have protocol concurrence from ONADE for each study to be supported by the grant. The grant application process includes several registrations, and it is recommended that you allow sufficient time for completion. A description of the application process and other information are periodically announced on the grants.gov website and on the OMUMS webpages.

M. Termination of Designation

In accordance with 21 CFR 516.29, the designation of a MUMS drug *must* be terminated:

- Upon notification to FDA by a sponsor of the decision to discontinue active pursuit of approval or conditional approval;
- Upon notification to FDA by a sponsor of its decision to discontinue manufacture of an approved or conditionally approved drug;
- Upon the expiration of any applicable period of exclusive marketing rights.

In addition, the designation of a MUMS drug *may* be terminated:

- If FDA independently determines that the sponsor is not actively pursuing approval or conditional approval with due diligence;
- If FDA determines that a sponsor is unable to provide sufficient quantities of an approved or conditionally approved drug to meet the needs for which it is designated;
- If FDA finds that the request for designation contained an untrue statement of material fact;
- If FDA finds that the request for designation omitted material information;

[56] Section 573(b) of the FD&C Act

- If FDA finds that the drug, in fact, was not eligible for MUMS-drug designation at the time of submission of the request;

- If the same drug in the same dosage form for the same intended use becomes approved or conditionally approved for another sponsor; or

- If FDA withdraws the approval or conditional approval of the application for the drug.

For an approved or conditionally approved drug, termination of MUMS-drug designation terminates the sponsor's exclusive marketing rights but does not withdraw the approval or conditional approval of the application for the drug.[57] When a designation is terminated, the FDA will notify the sponsor in writing and give public notice of the termination through a change in the status on the Designation List on the MUMS webpage on the CVM website.[58]

N. Re-designation

If a sponsor's MUMS drug designation has been terminated, FDA intends to grant a request to re-designate the same (or a part of the same) intended use by that same sponsor only under limited circumstances. For example, if a sponsor has financial or logistical difficulties which prevent the sponsor from obtaining approval, the sponsor may voluntarily terminate a designation without prejudice. The sponsor may subsequently request the same designation so long as no other sponsor has been granted designation, approval, or conditional approval for the same drug in the same dosage form for the same intended use.[59]

As discussed in the previous section, designations can be terminated by FDA due to a finding of a lack of due diligence, or for other reasons as specified in 21 CFR 516.29. FDA does not intend to consider a request from the original sponsor for re-designation of all or part of the terminated designation for a period of 120 days following the date of publication of the termination. During this time, other sponsors may request all or part of the terminated designation.

O. Appeal Process

The FD&C Act and its implementing regulations do not provide for an appeal process specific to requests for designation. Therefore, CVM intends to apply the appeal procedures described in CVM's GFI #79, "Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine."

X. Protocol Development and Next Steps

Protocol review by CVM is not required to obtain approval of your MUMS drug but is strongly recommended for any study intended to support an NADA or CNADA. However, if you intend

[57] 21 CFR 516.29(g)

[58] 21 CFR 516.29(i)

[59] 21 CFR 516.20(a)

to apply for a grant for your designated MUMS drug product, protocol concurrence from ONADE is needed for each study to be supported by a grant. See above, section IX.L. *Grants for Designated New Animal Drugs*.

Obtaining CVM concurrence for a protocol helps prevent you from conducting a study that may not be acceptable to us. You are encouraged to discuss specific questions about study design in early communications with us. Any contract research organization or collaborating institution should communicate with us through the INAD holder. We recommend that you submit pilot data and/or literature that informed your proposed study design early in drug development, prior to submission of a study protocol. This information represents basic knowledge about the drug we may need to evaluate a proposed study design and can facilitate the protocol review process. Your assigned PM can advise you how and when this information should be submitted.

Studies should be conducted in accordance with the appropriate standard of conduct. For nonclinical laboratory studies (e.g., safety studies), you must follow the good laboratory practices (GLP) regulations.[60] For effectiveness studies, you should follow the good clinical practices found in GFI# 85, "Good Clinical Practice." If you have concerns about your ability to follow the standards, you should contact the appropriate division in ONADE.

XI. New Animal Drug Applications

Additional guidance dealing with all aspects of new animal drug applications (NADA, CNADA) and the drug approval process can be found on the Guidance for Industry page of CVM's website. Appendix 1 – Additional Resources includes a link to a list of these guidance documents.

A. General

New animal drugs are approved for specific indications and dosages via submission of an NADA. The application may be an original application or a supplement to an existing NADA. For a conditional approval, you submit a CNADA and for a generic approval, you submit an ANADA. While MUMS drugs are eligible for generic approval under the same standards as other new animal drugs for which generic approval is sought, this guidance document focuses solely on NADA and CNADA requirements.

The next sections of this document give a general overview of the new animal drug approval process with more detailed information provided about aspects of that process that may apply specifically to minor species, particularly for aquatic species. Other guidance documents are available that discuss different aspects of the drug approval process that are specifically applicable to terrestrial species. This document provides more information to sponsors seeking approval for aquaculture products. However, when there are opportunities for extrapolation or special considerations for terrestrial minor species, that information is also included.

[60] 21 CFR part 58; 21 CFR 514.1(b)(12)(iii)

B. Parts of the Application

Please refer to GFI #132, "Administrative Applications and the Phased Review Process," for more details on the review process, including which review divisions within ONADE are responsible for the review of protocols and data supporting each technical section.

Each application is divided into technical sections as follows:

- EFFECTIVENESS
- TARGET ANIMAL SAFETY
- HUMAN FOOD SAFETY (FOOD-PRODUCING SPECIES)
- ENVIRONMENTAL IMPACT
- CHEMISTRY, MANUFACTURING, AND CONTROLS
- LABELING
- ALL OTHER INFORMATION (AOI)

When you believe you have enough evidence to meet FDA's requirements for approval, you can submit an NADA. The application must contain data or information relating to each of the technical sections listed above, as appropriate to support the particular application.[61]

Rather than submitting all data for review of all technical sections at one time as part of a complete application, you have the option of submitting data supporting each technical section for review separately under the INAD file. For additional information about the INAD file, see section VI.C. *Investigational New Animal Drug (INAD) File* above. Under this process of "phased review," CVM encourages you to submit data at the most appropriate and productive times during the drug development process. After CVM has reviewed and issued a "technical section complete" letter for each technical section, you then would submit an "administrative NADA" for approval of the new animal drug.

If you choose to pursue "phased review," we recommend that you consult with representatives of ONADE and OMUMS prior to submitting any material. It is important to consider how the different technical sections relate to each other when choosing the order in which you will address them – often the information provided for one technical section informs the evaluation of another component of review of the new animal drug. This is especially important if you are coordinating the submission of technical sections with multiple research partners. For example, if changes to the formulation or manufacturing process of a product are required for the Chemistry, Manufacturing, and Controls (CMC) technical section, it is possible that some of the work completed for other technical sections prior to these changes would need to be repeated. Some effectiveness information is needed to determine a target dose and ensure that appropriate doses are evaluated in Target Animal Safety and Human Food Safety studies; however, safety

[61] 21 CFR 514.1

concerns identified during those studies may also put boundaries around an acceptable dose range for effectiveness.

C. Associated Considerations

The information in this section may apply to the entire application or may pertain to one or more technical sections. It contains general descriptions and explanations of some specific terms and components of the INAD file, NADA, or CNADA.

1. The Freedom of Information (FOI) Summary

An FOI Summary is generally made public at the time that a drug is approved or conditionally approved.[62] It includes general information about the product and a summary of the safety and effectiveness information the Agency relied upon to support approval. While a sponsor may submit a draft FOI Summary as part of the application, CVM is responsible for the content of the final document.

2. Marketing Status

A new animal drug can be approved or conditionally approved with one of three possible marketing statuses: either over-the-counter (OTC), prescription (Rx), or, for a feed-use drug requiring veterinary oversight, as a veterinary feed directive (VFD) drug.

3. Final Formulation

For the target animal safety and effectiveness studies used to support approval, the final formulation of the drug (i.e., the intended marketed product) should be used and administered by the proposed route. Before these studies are conducted, the development of the drug product should be to the point that no other formulation changes are expected, so that the formulation used in the studies supporting approval will be representative of the anticipated marketed product. Be sure to discuss any deviation from this with ONADE to make certain that you can bridge to the final formulation, if needed.

Please note that human food safety toxicology studies are typically conducted with the active pharmaceutical ingredient (API) rather than the final formulation.

4. Food-Producing Animals

The major species of food-producing animals are cattle, swine, chickens, and turkeys. Food-producing minor species include a wide array of species, such as sheep, deer, rabbits, goats, many species of fish, gamebirds, and honeybees. It is important to note that a drug intended for

[62] 21 CFR 514.11(e)

use in any food-producing species will need to address *all* technical sections of the application, including human food safety.[63] See section X.I.B. *Parts of the Application* above.

For purposes of determining the food- or nonfood-producing status of minor species, historically we have considered a minor animal species to be food-producing when some members of the species are bred, cultured, farmed, ranched, hunted, caught, trapped, or otherwise harvested for the purpose of having the animals or edible products derived from the animals commercially distributed for consumption by humans or food-producing animals in the United States. This applies to any intended use in a food-producing minor species. For example, many deer are hunted and harvested for personal use and are not in "commercial distribution." However, some deer are farmed and introduced into commercial distribution for consumption by humans or food-producing animals; therefore, the entire species is considered to be a food-producing species and human food safety must be demonstrated for the application to be complete.[64] CVM has a number of guidance documents relevant to addressing the human food safety requirements for a new animal drug, and it is recommended that you begin with GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals." For the purpose of drug approval, the Division of Human Food Safety will determine the extent to which studies will be required. This will be in accordance with product labeling and driven by the indication. When adding products to the Index, more flexibility will be offered in cases where a reasonable certainty that the animals will not be eaten can be demonstrated.

5. Nonfood-Producing Animals

The nonfood-producing major species are horses, cats, and dogs. These species are also referred to as companion animals.

Minor species in the nonfood-producing category include ferrets, pet birds, most laboratory animals, most zoo animals, llamas, ornamental fish, and pocket pets such as hamsters and gerbils.

Because there are a wide variety of intended uses for new animal drugs for use in nonfood-producing species, PDPs are tailored to the specific project on a case-by-case basis.

6. Indications

Indications for use include the disease or condition to be treated, controlled, or prevented, or the structure or function of the body affected, and specifics about the animal population for which the use is intended.

We recommend that you and ONADE reach agreement on the indication and the plan for approval before beginning studies. This can make the pathway to approval more efficient. For

[63] 21 CFR 514.1

[64] 21 CFR 514.1

example, for aquaculture products it may be beneficial to consider a broad indication for use, such as one covering multiple fish species.

Examples of indications for use include "control of mortality due to columnaris disease associated with *Flavobacterium columnare* in channel catfish," "for treatment of adult liver flukes (*Fasciola hepatica*) in farm-raised whitetail deer," "to anesthetize mice," "for synchronization of estrus in dairy goats," or "for skeletal marking of finfish fry and fingerlings."

Remember, if the drug product is designated, you must be sure that the label indication for use remains consistent with the designated intended use to maintain the designation status.[65]

7. Data Extrapolation

CVM recognizes that there is a scarcity of approved drugs for minor uses/minor species and limited resources available for associated drug research. Therefore, CVM is prepared to consider use of interspecies data extrapolation (if appropriate) to minimize the amount of new research, expense, and difficulty involved in gaining approval of a new animal drug for a minor species.

Interspecies data extrapolation to support indications for use for MUMS drugs may be proposed whenever scientifically justifiable. Minor species applications often derive benefit from interspecies extrapolation when the drug is already approved for an indication for use in a closely related (usually major) species and such data already exist in the approved application(s). This is especially true for food-producing minor species; if the drug is approved for use in a related food-producing species, data extrapolation may be appropriate.

The appropriateness of data extrapolation between species depends on the nature of the drug, proposed indication(s) for use, and proposed target species and production class. A sponsor should provide this information, along with the data to be extrapolated and how it supports the proposed indication, to us early in the project development. We recommend talking to us prior to submission of any data.

Examples of data extrapolation include comparative pharmacokinetics as part of the effectiveness technical section, and identification of target tissues and metabolites for human food safety studies.

To rely on data extrapolation, you must be the sponsor of the application that contains the data you wish to extrapolate, have a right of reference to the data in another sponsor's file, or refer to data in a PMF.[66]

8. Use of Literature

Scientific literature may be used to respond to specific regulatory questions, identify data gaps, inform protocol design, and/or support one or more approval requirements. Although

[65] 21 CFR 516.26 and 516.31

[66] 21 CFR 514.1(a)

information provided in a single published article may be insufficient, for CVM to make inferences and regulatory decisions, it may be used in a supportive fashion to fill critical gaps.

Please see CVM GFI #106, "The Use of Published Literature in Support of New Animal Drug Applications," for a more in-depth discussion of this topic.

9. Aquaculture Species Grouping

Aquaculture species grouping allows representative species of a group to provide data which can be extrapolated to support use of the drug in that group. Grouping strategies should be designed to address known or potential differences among the species included in the overall use pattern, and to develop information that will allow the product to be labeled for safe and effective use in the group covered by the approval. If you wish to use a grouping strategy for a proposed indication, you should have discussions with CVM relative to all technical sections early in the project. Such discussions may include the grouping strategy and identification of the most representative species to study for the group across technical sections. Representative species should be appropriate for the indication, conditions of use, and provide appropriate inferential value.

10. Aquaculture Systems

Aquatic species can be cultured for many purposes including, but not limited to, human food, population management, sport fishing bait, and home aquaria (non-food/ornamentals). You should consider whether the drug will be used by the food fish industry, State/Federal/private hatcheries, the baitfish industry, the ornamental fish industry (non-food), or a combination of these industry sectors. CVM currently considers an "all finfish" indication to allow use of the drug in all sectors and management practices. Data from all sectors may be needed to complete one or more of the technical sections to obtain an "all finfish" indication; CVM may ask for a label statement that precludes use in one or more sectors or management practices if data are not provided.

CVM recognizes four general types of aquaculture systems that should be considered when pursuing drug approval. These are:

- recirculating aquaculture systems (RAS)
- flow-through raceways
- ponds
- net pens

The differences in aquaculture systems create vastly different treatment environments and potentially different dosing instructions for each aquaculture system on the labeling. In some cases, the application of drugs in these varied systems may require additional monitoring of some study parameters and consideration of external influences that may affect study results (e.g., use of ozone or ultraviolet light in recirculating systems may deactivate some drugs). Information regarding any known external influences that may impact the effectiveness or safety

of the drug should be provided to CVM. This information may be relevant to multiple technical sections in an application, including effectiveness, target animal safety, environmental impact, and human food safety. If your proposed drug is intended for use in more than one aquaculture system, then studies may need to be conducted in the aquaculture system that represents the worst-case scenario.

You may want to consider the broadest use pattern when determining the indication of the drug and the aquaculture system, because it may help streamline data collection and enable approval of a broader indication for use. It may also help avoid labeling limitations. On the other hand, should you narrow the scope of the indication, there may be a reduction in the total amount of data or information needed to support approval of the drug product. The type of aquaculture system should be addressed and considered during the PSC. The aquaculture system, including water quality parameters to be tested, should be specified in protocols, and described in final study reports.

11. Water Quality for Studies in Aquatic Species

The testing of water quality parameters is paramount in the determination of a healthy environment for fish.

Poor water quality can be a primary cause of fish mortalities in aquaculture. In all effectiveness and target animal safety studies, basic water quality tests should be conducted. The type of water quality tests you should perform depends on various factors, such as the aquaculture system, type of drug, type of study, length of study, water source, etc.

Monitoring water quality during studies is also important if the drug's effectiveness and/or safety depend on the value of certain water quality variables (e.g., pH, dissolved oxygen, water temperature). In addition, water quality variables may contribute to drug reactions and drug interactions, alter drug bioavailability, or otherwise impact a study outcome.

When you write study protocols to be conducted in an aquaculture system, ONADE will generally recommend that key factors affecting the aquatic environment, such as pH, dissolved oxygen, and water temperature be tested at least daily. If you have information to support less frequent testing (e.g., the water source provides stable values throughout the year or season), you should submit it for consideration. Alkalinity and hardness should be tested at least once during the course of a study, but additional testing may be necessary if the in-life phase of a study is greater than 30 days, if the history of the study facility dictates increased frequency of testing, or if knowing these parameters is necessary to determine drug interaction or could influence study outcome.

Additional tests, such as those for ammonia, nitrite, nitrate, salinity, and turbidity are also recommended for all aquaculture systems. Certain water quality parameters may be more important to monitor in specific systems, such as ammonia and nitrite in recirculating aquaculture systems or salinity in saltwater systems.

The type of aquaculture system, water salinity, and type of drug (e.g., drugs with the potential for chelation) may dictate additional testing and this should be determined during protocol development. Additional water quality tests may include tests for heavy metals (including copper), chlorine, ozone oxidation reduction potential, etc.

CVM is often asked if historical water quality parameters may be used to obtain the needed information during the in-life phase of studies. While historical data (e.g., stable water temperature over an earlier time period at a specific facility) can support an argument for a decrease in the frequency of testing, it is important to still collect real time data during the in-life phase of the study. CVM encourages the submission of historical water quality test results even if not part of the study protocol.

In the final study reports, you should include information about the water system and any test results for water quality parameters that may not have been included in the protocol. This information may support the use of the product in environmental conditions beyond those normally tested.

This guidance is not intended to provide standards for water quality testing methods. Details on frequency of testing should be worked out during protocol development. CVM will evaluate the water quality testing method as we review the study protocol or final study report.

XII. Effectiveness

CVM lists guidance documents with more detailed information on effectiveness evaluation in Appendix 1 – Additional Resources. We encourage you to consult these guidance documents and talk with ONADE before developing your approach to completing the effectiveness technical section.

A. Overview

The effectiveness technical section contains full reports of all studies that show whether or not the new animal drug is effective for the use indicated on the proposed labeling.[67] Section 512(d)(1)(E) of the FD&C Act provides that CVM must refuse to approve an application unless the sponsor demonstrates by substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. This technical section also includes any additional pertinent information that is known about the effectiveness of the drug at the time the technical section is submitted.[68]

B. Special Considerations for MUMS Drug Products

1. Pharmacokinetic and Pharmacodynamic (PK/PD) Data

[67] 21 CFR 514.1(b)(8)(i)

[68] 21 CFR 514.1(b)(8)(iv)

You can sometimes use PK/PD data to extrapolate aspects of the safety and effectiveness data from a major species to a similar minor species. For example, this may apply when a drug is approved in the major species for the same indication, the drug targets the same pathogen, and the pathology of the disease is similar in the major and minor species. However, such extrapolations, even between physiologically similar species (e.g., between large and small domestic ruminants), may not always be appropriate because of interspecies differences in drug bioavailability, metabolism, and response.

When you use PK/PD data to extrapolate aspects of the safety or effectiveness components of a MUMS drug application, you should include a justification for the interspecies extrapolation of the data. You should discuss interspecies extrapolations of data with CVM to determine if such extrapolations will be acceptable to support the approval before conducting studies.

2. Pharmacokinetics for Aquatic Species

Comparative pharmacokinetics may be useful information as part of your product development. One resource is the Fish Drug/Chemical Analysis database "Phish-Pharm" (FDAPP) (https://www.fda.gov/animal-veterinary/tools-resources/phish-pharm) that CVM has constructed and maintains on its website. The database is a compilation of information from published literature that includes residue and pharmacokinetic data from finfish, shellfish, and other aquatic species. You can use this database to rapidly compare data between studies in regard to experimental conditions, such as water temperatures and salinity. The database is searchable and data fields include: genus, species, water temperature, average animal weight, sample types analyzed, drug name, dosage, route of administration, metabolites identified, protein binding, clearance, volume of distribution, and drug half-lives. The information in the database may be useful for protocol development and study design. While an examination of the literature has been conducted to provide data for the Phish-Pharm database, this has not provided FDA with the opportunity to review critical aspects of the literature, such as raw data, study conduct, and conclusions. Because such published studies may not be specifically conducted to support new animal drug approval, the published literature does not always contain an adequate representation of study plans, study conduct, and outcomes. Therefore, you will need to critically evaluate these studies and their utility for the relevant technical section.

3. Model Studies

Model studies (i.e., studies using models) may be an option to provide a portion or all of the substantial evidence of effectiveness[69] for certain therapeutic indications in minor species. A model study may include a challenge of a bacterial pathogen to establish an infection or of a parasite in aquatic species to establish an infection or infestation. In general, study designs for induced infections and infestations of parasites in terrestrial species, while technically model studies, do not require further validation or justification as they are well-characterized by other guidance documents cited in section XII.C. *Indication-Specific Considerations*. An infection or infestation challenge model study may be considered in lieu of a natural infection/infestation

[69] 21 CFR 514.4(b)(3)(ii)

field study for situations when a natural infection/infestation field study may be recommended but is impractical or difficult to execute (for example, if occurrence of the disease is uncommon or unpredictable, or natural disease dynamics confound evaluation). A model study may be an option to supplement or confirm information obtained from the natural infection study (for example, to demonstrate that the drug has an effect on a pathogen that was present in the natural infection study but is associated with mild clinical signs that may be overshadowed by a more virulent pathogen). A model study may also be an option for evaluation of a drug other than an antimicrobial or antiparasitic where an endpoint other than resolution of disease or infection/infestation is used to demonstrate effectiveness (e.g., pain, pain associated with a bacterial infection).

Models must be validated prior to acceptance of the study.[70] Validation means establishing an adequate relationship of parameters measured and effects observed in the model with one or more significant effects of treatment. There are particular considerations for validating models to address antimicrobial and antiparasitic drugs. These include aspects related to general study design (including, among other things, timing of challenge and key observations), dynamics and extent of the disease or condition produced by the model, and how well the specific challenge organism used in the model represents current wild-type pathogen strains. Validation of the study design may be accomplished by referencing a previously conducted model study or one that is described with sufficient detail in the published literature, or by prospectively conducting the proposed model at least twice. In the latter case, both studies typically are used in the overall demonstration of substantial evidence of effectiveness. When using a published model or previously conducted model study for validation, sponsors should ensure that the induced disease is sufficiently representative of a natural outbreak in terms of onset, severity, and extent of clinical signs or other key observations. To provide a fair test for the drug and to provide inferential value to the target animal population under actual conditions of use, the level of disease induced by the model should appropriately mimic that seen in a natural infection/infestation that would be recognized and treated. Some modifications to a model used for validation purposes may be acceptable as long as the general design for the proposed study remains sufficiently similar. Depending on the type and extent of modifications to a published or previously-conducted model study, additional information, justification, or studies may be needed to validate the model used in the proposed study. The challenge organism strain used in the proposed study should be demonstrated to be representative of recent, North American strains in terms of virulence and susceptibility to the investigational drug. A different strain may be used in the proposed study than was used in the study used to validate the model.

If you are considering using a model study to demonstrate substantial evidence of effectiveness, we recommend you meet with CVM early about the indication, study design details, and other effectiveness requirements before conducting a model study. Generalizability of any model study to the intended target population should be carefully considered.

[70] 21 CFR 514.4(b)(3)(ii)

4. Effectiveness for Aquatic Species

Generally, for single species claims (e.g., Atlantic salmon), we recommend two independent studies to complete the effectiveness technical section. For aquatic species, CVM generally supports pursuit of indications covering the broadest range of species appropriate for the intended use. However, considering the diversity of fish species and habitats, CVM cannot assume that the effectiveness of drugs will be consistent across all fish species or conditions because legitimate differences have been demonstrated to exist. Wherever possible, CVM uses a risk-based approach to consider a limited number of studies from representative species within sponsor-proposed "species groups" to complete the effectiveness technical section for the entire fish species group (see section XI.C.9. *Aquaculture Species Grouping*).

The specific species included in the studies, the number of study sites, number of studies, and additional considerations depend on the proposed indication and may vary by project. CVM encourages sponsors to request a presubmission conference to discuss the requirements for the technical section. In that request, the sponsor should propose a plan for completing the technical section with consideration given to the following points:

- the indication, including the intended species;
- the intended life stage(s), age, and/or size of fish;
- a description of the disease or condition, clinical signs, and measurable endpoints;
- seasonality (e.g., disease occurrence only occurs at certain times a year or a discrete spawning season);
- geographical range of drug use;
- dosage (or dosage range), informed by pilot studies or literature;
- life stage or species sensitivities to the drug;
- culture systems where the drug would be used (e.g., raceways, ponds, RAS, net pens);
- environmental conditions that may affect the drug's effectiveness (e.g., salinity, temperature, pH, hardness);
- drug class, mechanism of action, target tissue; and
- pharmacokinetic information (to include non-fish species).

A proposal that includes the above information on the drug will better enable CVM to come to agreement with the sponsor's plan for completion of the technical section. This information can come from a wide variety of sources, such as literature reports, pilot studies, foreign marketing materials, etc. We understand that some of this information may not be known early in project development and may change as data are developed. You may submit new information that could help refine the data requirements as your project advances.

CVM accepts a variety of studies and study designs to support the effectiveness technical section. Sponsors should be aware of GFI #265, "Use of Data from Foreign Investigational

Studies to Support Effectiveness of New Animal Drugs"; GFI #268, "Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs"; GFI #266, "Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs"; GFI #267, "Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs"; GFI #106, "Use of Published Literature in Support of New Animal Drug Applications"; and GFI #215, "Target Animal Safety and Effectiveness Protocol Development and Submission." Early discussion with CVM is recommended to reach agreement regarding effectiveness data requirements.

C. Indication-Specific Considerations

1. Therapeutic Indications – Overview

Therapeutic indications are generally for treatment, control, or prevention of specific diseases or conditions. Considerations for the design of studies and wording of indications for use of some common therapeutic drug classes for minor species are provided below:

2. Therapeutic Indications – Antimicrobial Drug Indications for Minor Species

Antimicrobial indications can be worded for treatment, control, or prevention of diseases based on the intended conditions of use. For the purposes of this guidance, the terms treatment, control, and prevention are generally defined as follows, depending on the dosage form of the drug and whether the drug is intended to be administered to individuals or groups of animals. For a treatment indication, the drug is administered only to animals diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease. For a control indication, the drug is administered to a group of animals once a proportion of the animals in the group have been diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease. For a prevention indication, the drug is administered to a group of animals none of which have been diagnosed with the indicated disease, when transmission of existing undiagnosed infections, or the introduction of pathogens, is anticipated based on history, clinical judgment, or epidemiological knowledge. Early discussion with CVM is recommended in selecting the most appropriate indication for drug development.

The indication selected correlates with the endpoints, the design, and the success criteria used for the effectiveness study(ies). One example of common antibacterial and antifungal indication wording on approved drugs for fish and birds is "for the control of mortality" for a disease or condition because percent cumulative mortality is often the primary endpoint.

This indication wording is used because bacterial diseases often cause mortality at a level that can be monitored and provide an objective endpoint to measure. However, you may propose an alternative endpoint that is clinically relevant and supports the drug's conditions of use.

An indication for control of disease may be considered when clinicals signs and measures of disease occurrence are present in diseased animals, can be observed or measured, and serve as primary endpoints in evaluating the effectiveness of a drug. Clinical signs of disease other than

mortality include, but are not limited to, skin or mucus membrane color, measures of activity/lethargy, visible lesions, respiratory rate, abnormal fecal consistency, and body temperature. The clinical signs selected would be assessed before and after drug administration to establish the presence of disease. The clinical signs selected may be assessed for effectiveness either individually or combined using a scoring system to produce a composite score that defines when animals or groups of animals are considered diseased or no longer diseased.

Indications may include one or multiple target pathogens. An appropriate target pathogen(s) should be associated with the disease in question and identified in a sufficient number of study animals to demonstrate the pathogen contributed to the disease observed in the study. If the natural history of a disease indicates it can be associated with multiple pathogens, an effectiveness study can be designed to evaluate effectiveness for those multiple pathogens. In order for a pathogen(s) to be included in the indication, the number of animals from which the pathogen(s) will be recovered should be determined in advance and stated in the protocol. A sponsor should meet with CVM to reach agreement or submit a protocol for review and reach concurrence regarding the methods used to identify target pathogens included in the indication.

3. Therapeutic Indications – Antiparasitic Drug Indications for Minor Species

a. Antiparasitic Drug Indications for Terrestrial Minor Species

i. Anthelmintics and Ectoparasiticides for Terrestrial Minor Species

For anthelmintics, indications are typically granted for the "treatment and control" of the parasite species and, where applicable, the life stages of the parasite for which effectiveness has been demonstrated and is generally based on reduction in parasite numbers. For ectoparasiticides, indications may be granted for the treatment and/or control of the parasite species, and where applicable, the life stages of the parasite, depending on the effectiveness study design. Exceptions exist for some parasites, including consideration of indications covering parasite genus if parasites cannot be speciated. You are encouraged to discuss the proposed indication(s) with CVM early in the drug development process.

The study protocol should identify the parasite genus, species, and life stage (where applicable) that the drug is intended to treat and/or control. Definitions of adequate infections/infestations for each experimental unit should be developed based on historical, parasitological, and/or statistical criteria, and included in the protocol.

You should confirm the effectiveness of antiparasitic drugs for minor terrestrial species for each parasite species and life stage proposed for the indication and demonstrate a reduction in parasite numbers using dose confirmation stud(ies) and/or field studies as described below.

For both internal and external parasites, data from two dose confirmation studies should generally be provided for each parasite species and life stage proposed for the indication. Data from a dose confirmation study(ies) conducted outside of North America or a published study(ies) that was designed and reported appropriately may satisfy the requirement for one of the two studies. Generally, at least one study should be conducted in North America for each

proposed parasite species and life stage, preferably using natural infections. However, if the dose-limiting parasite within the spectrum of parasite species and life stage(s) proposed for the indications in the US has been identified (based on data that you own, have right of reference to, or is available in the public domain), you may conduct a dose confirmation study using only the dose-limiting parasite. For minor poultry species, you should conduct the North American dose confirmation study under field conditions, if possible.

Generally, for dose confirmation studies of anthelmintics, percent effectiveness should be calculated and interpreted using procedures described in CVM GFI #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations." For sheep and goats, a field study should also be conducted at a single site under actual use conditions in representative class(es) using fecal egg counts as the primary variable.

Effectiveness studies of ectoparasiticides in a ruminant minor species should generally be conducted in accordance with the "World Association for the Advancement of Veterinary Parasitology (WAAVP) second edition: Guideline for evaluating the efficacy of parasiticides against ectoparasites of ruminants," and updated versions as they are published.[71]

ii. Anticoccidial Drug Indications for Terrestrial Minor Species

CVM has issued guidance with more information on effectiveness study design for anticoccidial drugs. We encourage you to refer to GFI #217, "Evaluating the Effectiveness of Anticoccidial Drugs in Food-Producing Animals," before designing an effectiveness study for anticoccidial drugs.

The following are additional considerations for demonstrating effectiveness of anticoccidial drugs in minor species.

In general, the most appropriate indication for an anticoccidial drug is "For the control of coccidiosis caused by (insert name of specific coccidial species)"; however, a treatment indication may be considered. If you conduct a field study using a mixed inoculum of the same genus, the indication may be based on the genus rather than the species (e.g., *Eimeria* spp.).

When studies are conducted using a mixed inoculum and the variables used to evaluate effectiveness do not provide results differentiated by species, the indication should not identify the specific species of coccidia. This approach is different than the one used for determination of effectiveness in chickens and turkeys, where battery studies are conducted with single-species inoculums for each coccidial species proposed for the indication, followed by mixed inoculum studies. If you want an indication for a specific coccidial species, you may conduct additional studies to support the indication. You should communicate with ONADE early in the

[71] Peter Holdsworth, Steffen Rehbein, Nicholas N. Jonsson, Rose Peter, Jozef Vercruysse, Josephus Fourie, World Association for the Advancement of Veterinary Parasitology (WAAVP) second edition: Guideline for evaluating the efficacy of parasiticides against ectoparasites of ruminants, Veterinary Parasitology, Volume 302, 2022, 109613. https://www.sciencedirect.com/science/article/pii/S0304401721002739 (accessed December 12, 2023).

development process to discuss the number and design of studies that may be necessary to support the proposed indication.

b. Antiparasitic Drug Indications for Aquatic Species

Antiparasitic drug indications are commonly granted for the "treatment and control" of the parasite species and, where applicable, the life stages of the parasite for which effectiveness has been demonstrated. You are encouraged to discuss the proposed indication with CVM early in the drug development process because indication wording and effectiveness study design may vary based on the characteristics of specific parasites and drugs.

When developing your indication and study protocol you should consider the life history, diversity, and range of the targeted parasite because these factors will influence study design. Your study protocol should include methods to identify the parasite species treated in clinical trials. Even if you are pursuing an indication for a broader group of parasite species (e.g., a parasite genus as discussed in this section below), it is important to know what species were treated during the clinical trials to account for any differences in effectiveness are identified between parasite species. Additionally, where applicable, the study protocol should identify which life stages of the parasite are targeted.

As you identify the life stages of the parasite that the drug is intended to treat and/or control, it may be helpful to consider which life stages are:

- expected to be most susceptible to the drug;
- generally used for diagnostic purposes; and
- most pathogenic.

In addition, it may be important for you to consider the normal generation time of the parasite, the potential effects of any resting stage (e.g., egg or cyst), and other sources of re-infection/re-infestation pressure on the length of the post-treatment period and the potential need for re-treatment.

The effectiveness of antiparasitic aquaculture drugs is generally based on a reduction of parasite numbers/density, but could also be based on the reduction of measurable pathology (e.g., characteristic lesion) associated with infection. It may be useful to consider the following points when determining a clinically relevant endpoint for effectiveness studies:

- the mode of pathogenesis (e.g., steric blocking of respiration, physical injury, systemic infection);
- the threshold number/density that would impair animal health; and
- the threshold number/density that would indicate the need to induce treatment.

Success criteria for effectiveness should be established before studies are conducted and should be included in the protocol. A 90% reduction in parasite numbers (total number of parasites on a fish) or parasite density (number of parasites on a defined section of a fish) is generally considered to be the threshold of effectiveness for antiparasitic drugs. Parasite reductions of less than 90% may be considered for approval if their clinical relevance is justified or if no other approved treatment exists for the indication. Justification of clinical relevance should include a description of the level of disease that would require treatment and the degree of clearance that would be expected by producers for a treatment to be considered effective. Data from pilot studies or literature can inform this justification.

Your protocol should state how parasite numbers will be assessed in your study. The best method for a particular study will depend on the size, visibility, and mobility of the parasite, as well as the conditions under which the parasites will be counted. It is important that enumeration methods be independently reproducible, provide an accurate assessment of parasite numbers or density, and be capable of determining a significant, clinically relevant outcome. Where possible, enumeration methods should be consistent between studies and use methods that are comparable to those commonly used for clinical diagnosis.

In some cases, it may be possible to group closely related parasite species into a single indication. For example, a drug may be indicated for use against a parasite genus. Because even closely related parasite species may have important differences in virulence and drug susceptibility, any grouping of parasites should be approached with careful consideration of parasite biology and the characteristics of the drug. For CVM to consider a proposed indication for a parasite species grouping, you should provide justification for the grouping that includes information on:

- the mode of action of the drug;
- the biology, distribution, and diversity of the parasite species within the grouping; and
- any differences in prevalence, virulence, and drug susceptibility within the grouping.

This information can be used to propose the parasite species that will be evaluated in the effectiveness studies.

Multiple parasites can be evaluated in a single study. In these cases, the parasites should be specified in the protocol prior to the start of the study and reduction in parasite numbers should be evaluated independently.

Alternatively, a dose-limiting parasite can be established. In this approach the group of parasites typically present or which will be included in the approved indication will be agreed upon and the parasite in the group requiring the highest dose of the investigational drug or the most difficult to treat will be identified. With this information, demonstrating effectiveness to the dose-limiting parasite may be sufficient to demonstrate effectiveness for the agreed upon group of parasites.

4. Production Indications

Production indications are generally a subset of uses that affect the structure or function of a healthy animal. This includes indications such as "for increased rate of weight gain" or "for improved feed efficiency." Many reproductive aids, such as those for estrus synchronization and spawning aids, fall in this category. Products intended "for increased production of marketable milk" or "for increased carcass leanness" are also considered production drugs.

XIII. Reasonable Expectation of Effectiveness for Conditional Approval

As noted earlier, conditional approval allows the marketing of a MUMS drug, or certain other new animal drugs that are not MUMS drugs in limited circumstances, when all requirements for the drug's approval have been met except the "substantial evidence" standard for effectiveness. Instead, conditional approval requires sponsors to submit evidence that a new animal drug meets the "reasonable expectation of effectiveness" standard.[72]

CVM should be able to evaluate the evidence and confirm the reasonable expectation of effectiveness of the new animal drug for the proposed intended use. Evidence may include pilot studies in the target species, studies in the published literature, foreign studies, or extrapolation of data from effectiveness studies for other similar species, related diseases, or related dosage forms. Evidence to support reasonable expectation of effectiveness may include studies that also contribute to the substantial evidence that is required for full approval.

XIV. Target Animal Safety (TAS)

CVM has issued guidance documents with more detailed information on TAS evaluation (see Appendix 1 – Additional Resources). We encourage you to consult these guidance documents and talk with ONADE before developing your approach to completing the TAS technical section or designing TAS studies.

A. Overview

The TAS technical section contains full reports of all studies required by FDA to demonstrate whether the new animal drug is safe for use in the target animal species. This technical section should include those studies conducted by or on behalf of the sponsor, or that are available to the sponsor by right of reference. References and authorizations to other applications or documents containing applicable safety information should also be included. This section includes any additional pertinent information that is known about the target animal safety of the drug at the time the technical section is submitted.[73]

[72] Section 571 of the FD&C Act

[73] 21 CFR 514.1(b)(8)

The TAS technical section also contains any relevant studies or references regarding the safety of humans that administer or may come into direct contact with the new animal drug (user safety).

Refer to GFI #185 (VICH GL43), "Target Animal Safety for Veterinary Pharmaceutical Products," for more information on TAS evaluation for regulatory submission. Although GFI #185 states that the recommendations in it may not be applicable to drug products for minor species, CVM has found that the general principles can still be useful for minor species and recommends that sponsors consider the GFI in that context.

B. Special Considerations for Aquatic Species

Similar to effectiveness for aquatic species, CVM uses a risk-based approach to consider a limited number of studies from representative species within sponsor-proposed "species groups" to complete the target animal safety technical section for the entire fish group (see section XI.C.9. *Aquaculture Species Grouping*). The specific species included in the studies, number of studies, and additional considerations depend on the proposed indication and may vary by project. If sponsors are pursuing single species claims, generally, a single target animal safety study in that species would suffice.

CVM encourages sponsors to request a presubmission conference to discuss the requirements for the technical section. The following points, similar to those found in section XII.B.4. *Effectiveness for Aquatic Species*, should be considered when proposing a plan for completing the technical section:

- the indication, including the intended species;
- the intended life stage(s), age, and/or size of fish;
- dosage (or dosage range), informed by pilot studies or literature;
- life stage or species sensitivities to the drug;
- culture systems where the drug would be used (e.g., raceways, streamside, ponds, RAS, net pens);
- environmental conditions that may affect the drug's safety (e.g., salinity, hardness, temperature, pH);
- drug class, mechanism of action, target tissue; and
- known pharmacologic or toxicologic properties of the API.

This list of considerations is not all inclusive, and some points may not be relevant for all drug projects. CVM encourages sponsors to explore a variety of sources of information or data that could provide the above information. This information can then be used to develop a risk-based approach to completing or justifying the technical section when submitting the NADA. It is understandable that some of this may not be known early in project development and some information can change as data are developed. A sponsor should submit new information for CVM to consider as the project advances. This may help refine the data requirements through the course of the project.

CVM recommends that sponsors follow the study design concepts in GFI #185 (VICH GL43), "Target Animal Safety for Veterinary Pharmaceutical Products"; however, alternatives to the traditional TAS study design (i.e., the margin of safety study) may be proposed. Generally, you should use animals of the most sensitive category for which the product is intended (species, size/age, and physiological status), and discuss the representative species with CVM prior to conducting the study. It may also be prudent for sponsors to submit a pharmacological-toxicological characterization before the protocol submission to help refine the study design. This type of submission may justify overdose levels, study duration, endpoints, and other pertinent parts of the study design.

Tissues from animals in all dose groups in the margin of safety study should be examined grossly and preserved for microscopic evaluation. The tissue list recommendation in GFI #185 for major, terrestrial species is an appropriate reference for aquaculture sponsors and the list) should be adapted as appropriate for the fish species being evaluated (e.g., use of the list to determine relevant corresponding organs or tissues). CVM has no defined complete tissue list for fish; sponsors should contact us if they have difficulty determining what the most appropriate tissues are for evaluation for a particular species or a particular drug.

Microscopic examination of relevant tissues of fish in all dose groups is generally recommended when there is a lack of safety information available for a drug product. However, the evaluation of fewer tissues and/or fewer dose groups may be appropriate. If you propose an alternative approach, it should be based on appropriate scientific justification (e.g., knowledge of the investigational drug, route of administration, mechanism of action, information from other species) and pre-specified in the study protocol. Sponsors should discuss the design of the TAS study, including the justification for an alternative microscopic evaluation scheme, with CVM before conducting the study.

XV. Human Food Safety (HFS)

CVM has issued guidance documents with more detailed information about how to conduct HFS evaluations for new animal drugs intended for use in food-producing animals. See Appendix 1 – Additional Resources for links to these documents. We encourage you to consult the following CVM guidance documents and talk with ONADE before developing your approach to completing the HFS technical section or designing HFS studies:

- GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food Producing Animals";
- GFI #149 (VICH GL33), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing";
- GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern";
- GFI #159 (VICH GL36), "Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI";

- GFI #207 (VICH GL48), "Marker Residue Depletion Studies to Establish Product Withdrawal Periods";

- GFI #232 (VICH GL54), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD)"; and

- GFI #257 (VICH GL57), "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species."

A. Overview

The HFS technical section is submitted only for applications for new animal drugs intended for use in species that are used for human food (food-producing animals). This technical section includes a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of the drug's use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of the drug will be safe for humans who may consume food derived from treated animals. This section should also contain any data relating to toxicology (including the effect of residues of antimicrobials on human intestinal microflora), residue chemistry, and, if the new animal drug is an antimicrobial, microbial food safety.

This section also should include any additional pertinent information that is known about the human food safety of the drug at the time the technical section is submitted.

B. Components of a Human Food Safety Evaluation

If you intend to pursue approval of a new chemical entity for use in a food-producing minor species, you will be responsible for providing all the information necessary to demonstrate human food safety, i.e., all information needed to support toxicology, residue chemistry, and microbial food safety (if applicable). CVM guidance GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals," provides one approach for developing scientific information to support an HFS technical section. It includes a more detailed discussion of all the topics discussed briefly in this section. Alternative approaches that use other types of scientific information (e.g., published literature) may also be appropriate. You should discuss alternative approaches with ONADE before conducting any studies.

C. Extrapolation of Human Food Safety Data to Minor Species

When a MUMS drug proposed for a food-producing minor species is already approved for use in another (major or minor) food-producing species, the extent of human food safety information needed for an approval may in some instances be reduced by extrapolating human food safety information from the previously approved species to the minor species that is the subject of the proposed indication for use. The appropriateness of data extrapolation between species depends on the nature of the drug, proposed indications for use, and proposed target species and

production class. CVM determines the appropriateness of data extrapolation on a case-by-case basis. Note that the extrapolation of human food safety information from one species to another species applies primarily to the residue chemistry data described below. Because the toxicology information is specific to the active pharmaceutical ingredient (API), not the food-producing species in which it will be used, if the drug has already been approved for use in another food-producing species, the toxicology information in that application for the API may be appropriate for use in the proposed minor species application.

D. Residue Chemistry

Meeting the residue chemistry requirements for food-producing minor species may, in some cases, be facilitated through use of information already provided for another food-producing species. Guidance documents with recommendations for the general residue chemistry information needed to satisfy concerns regarding the metabolism in and depletion of the proposed drug from edible tissues are listed in Appendix 1 – Additional Resources. In addition, general residue chemistry information that has a direct bearing on minor species applications is included below in this section.

1. Tolerance

Applicants seeking approval or conditional approval of a new animal drug intended for use in a food-producing species will be required to submit a proposed tolerance as part of the application process when needed to ensure that the proposed use of the drug will be safe.[74]

The tolerance is the maximum concentration of a marker residue, or other residue indicated for monitoring, that can legally remain in a specific edible tissue of a treated animal. The tolerance is established in reference to the acceptable daily intake (ADI). The ADI is the daily intake which, during up to an entire life of a human, appears to be without adverse effects or harm to the health of the consumer. The ADI most often will be established based on the drug's toxicological, microbiological, or pharmacological properties and expressed in terms of micrograms or milligrams of the chemical per kilogram of body weight per day.[75]

In some instances, the tolerance for a drug approved for use in a food-producing species may be appropriate for extrapolation to the same drug for use in a food-producing minor species. When a tolerance has not been established for an approved drug in any food-producing species, total residue and metabolism information in the food-producing minor species is needed to allow the establishment of a tolerance for the drug when used in the food-producing minor species.[76]

[74] 21 CFR 514.1(b)(7) and 556.1(a)

[75] 21 CFR 556.3

[76] 21 CFR 514.1(b)(7)

2. Analytical Method

In most cases, it will be necessary to include as part of the application an analytical method to monitor residues and establish a withdrawal period in edible tissues of the food-producing minor species.[77] If the drug has already been approved for use in another food-producing species, the official analytical method may be adaptable for use in the food-producing minor species; however, you will need to demonstrate that the analytical method performs satisfactorily in the new species. [78] If the proposed drug has not yet been approved for use in any food-producing species, you will need to develop the analytical method.[79] The analytical method typically consists of both a determinative and a confirmatory procedure. These may be combined into a single procedure as instrumentation allows. Typically, a second laboratory verification of the determinative procedure should be sufficient if the analytical method has gone through a method transfer trial. If the analytical method has not gone through a method transfer trial, a more extensive demonstration of transferability may be appropriate. It is strongly recommended that the method be validated and reviewed by ONADE before starting any residue studies.

3. Withdrawal Period/Milk Discard Time

In most cases, residue depletion information will be necessary to establish the appropriate withdrawal period for the use of the drug in food-producing animals. If the drug is intended for use in lactating animals that produce milk for human consumption, information will be needed to establish the milk discard time.[80] For drugs intended for use in birds producing eggs for human consumption, residues in eggs should qualify for a zero withdrawal.

4. Edible Tissues

Residue depletion studies should be conducted using the edible tissue(s) collected from the target animal. The edible tissue(s) depend on the species (target animal) in which the residue depletion studies will be conducted.

In avian species, the edible tissues are considered to be the muscle, liver, skin with adhering fat, and eggs (when applicable).

In ruminant species, the edible tissues are considered to be the muscle (including injection site muscle and muscle underlying pour-on sites, as well as remote muscle), liver, kidney, fat, and milk (when applicable).

In rabbits, the edible tissues are considered to be the muscle, liver, and kidney.

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[77] 21 CFR 514.1(b)(7) and 556.5(d)

[78] 21 CFR 514.1(b)(7)

[79] 21 CFR 514.1(b)(7)

[80] 21 CFR 514.1(b)(7)(i)

In finfish, the edible tissues are considered to be the muscle with adhering skin. For those species for which the skin is inedible (such as catfish or eel), the edible tissue is considered to be muscle. Residue depletion studies for those fish with edible skin should be conducted using muscle fillet with adhering skin as the tissue sample. Alternatively, skin and muscle samples may be collected and analyzed separately.

The relative contribution by weight of each portion (muscle and skin) should be reported, in addition to the residue concentrations, so that the concentration of the analyte in muscle with adhering skin may be determined.

The eggs of some finfish species are considered edible. Species with edible eggs include, but are not limited to, shad, salmon, paddlefish, trout, herring, and sturgeon. (Note that these are unfertilized eggs used for caviar, sushi, etc.)

In mollusks, the entire soft tissue mass of hard-shell clams, soft shell clams, and oysters is considered to be the edible tissue. Muscle is considered to be the edible tissue in scallops and giant clams.

In crustaceans, the edible tissue is considered to be muscle. The internal organs (the "gob") need not be included as an edible tissue at this time. For those species which are marketed as "soft shell" (such as soft-shell crabs), the entire animal, including the unhardened shell, is considered the edible tissue. The edible tissue for shrimp with hard (inedible) shell is considered to be the soft tissue, excluding shell. The edible tissue for shrimp (during molting) with soft (edible) shell is the entire animal, including the shell. The edible tissue for all shrimp includes the mid-intestinal gland (i.e., the shrimp should not be "de-veined").

For honeybees, honey is the edible tissue.

E. Special Considerations for Aquatic Species – LIFe Stage Considerations and Species Groups

1. Life Stage Considerations

Aquatic food-producing animals in their early life stages (sac-fry, fry, juvenile) may still be considered food-producing animals. Fish eggs are evaluated on a case-by-case basis, as some are used as human food (unfertilized ova), and some are not (early life stage). Other early life stages will be evaluated individually in accord with the product in question and the conditions of use.

CVM intends to consider, on a drug and indication basis, the amount of human food safety information needed to support the approval of a new animal drug proposed for use in an inedible life stage of a food-producing minor species. Depending upon the drug proposed, circumstances of use, and available human food safety information, the information needed may range from not needing any human food safety information to needing the standard human food safety information package.

A specific drug and indication may be considered low risk with respect to human food safety if:

- the drug is proposed for use in the early life stages of an aquatic food-producing species and is not offered for human consumption at that life stage;

- there is no significant risk that harmful residues will be present in the market-size fish as a result of treatment at the early life stage and subsequent grow-out; and

- FDA has no concerns that the drug will be diverted for use at later life stages (e.g., a tolerance and analytical method are available or there is no practical use for the drug in later life stages).

2. Species Groups

Recommendations on groupings of aquatic species for residue depletion studies are found in GFI #257 (VICH GL57), "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species." CVM has traditionally considered salmonids to be a species group with Atlantic salmon, Pacific salmon, or rainbow trout serving to represent all salmonids. This species grouping may not be appropriate for all drugs or use conditions (e.g., freshwater vs. saltwater, coldwater vs. warmwater). CVM intends to consider this and other species groups and encourages the submission of information that supports such groupings along with discussion with CVM. See section XI.C.9. *Aquaculture Species Grouping* for more information

Information should be available to support the hypothesis that the selected representative species is typical of the larger group. In general, the members of the species group should be sufficiently alike such that drug absorption, distribution, metabolism, and excretion would not be anticipated to be significantly different for any species within the group. Alternatively, it is possible that data may be available to show that a particular member of the proposed grouping represents the most conservative estimates for that group. The nature of the studies conducted to support a species group are anticipated to be driven by the specific drug, use condition, and the species group that is being evaluated. A combination of studies may be necessary to address a particular species group.

The data to support a full human food safety information package (metabolism and residue chemistry) may be collected in one or more representative species in the group, and some combination of bridging studies should be conducted to verify the appropriateness of the proposed grouping.

XVI. Environmental Impact

CVM has issued guidance documents with more detailed information on the evaluation of environmental impacts of regulatory actions, including the indexing or approval of new animal drugs for minor use or minor species (see Appendix 1 – Additional Resources). We encourage you to consult these guidance documents and talk with Environmental Team 1 or 2 before developing your approach to completing the Environmental Impact requirements, and before designing or conducting supporting studies.

It is important to note that under the INAD phased-review process, the Environmental Impact technical section can be submitted at any time. However, CVM recommends that all sponsors wait on making this submission until they are confident that the dose, frequency, indication(s), species to be treated, and route of administration will not change prior to approval because the Environmental Impact technical section should reflect the proposed drug approval conditions. If anything changes with the drug product during the review of the Environmental Impact technical section or after receiving an Environmental Impact technical section complete letter, you should contact Environmental Team 1 or 2. Changes to the drug product may require further evaluations and/or additional submissions for the Environmental Impact technical section. Although the Environmental Impact technical section reflects the proposed action, which may not be finalized during the initial development of the drug, it is highly recommended that you discuss your proposed approach for addressing the Environmental Impact technical section early in the drug development process to avoid unnecessary delays in completing this section.

A. Overview

Under the National Environmental Policy Act (NEPA), CVM must evaluate whether Agency actions will have significant environmental impacts. Therefore, in accordance with FDA's NEPA implementing regulations, your request for Agency action must include either an environmental assessment (EA) or a claim of categorical exclusion (CE) from the requirement to prepare an EA.[81] Agency actions include, but are not limited to, the investigational use of a drug under the investigational new animal drug (INAD) file, requests for eligibility for indexing, and the approval of new animal drug applications.

B. Categorical Exclusions

1. Overview

The classes of actions for animal drugs that may be categorically excluded and ordinarily do not require the preparation of an EA are listed in FDA regulations under 21 CFR 25.33. The investigational use of the product under the INAD will typically qualify for a claim of CE pursuant to 21 CFR 25.33(e), for an action on an INAD. The other CE citations under 21 CFR 25.33 may apply for other requests for Agency actions, including actions on an NADA and requests for eligibility for addition to the Index. Table 1 below lists the most commonly applicable CEs for minor use and minor species.

[81] 21 CFR 25.15(a)

Table 1. List of CE citations that are most commonly applicable to actions on animal drugs for minor use and minor species. *

CE citation	Purpose
21 CFR 25.33(a)	For an action that does not increase the use of the drug
21 CFR 25.33(c)	For substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment
21 CFR 25.33(d)(1)	For drugs intended for use in nonfood animals
21 CFR 25.33(d)(2)	For anesthetics, both local and general, that are individually administered
21 CFR 25.33(d)(3)	For nonsystemic topical and ophthalmic animal drugs
21 CFR 25.33(d)(4)	For drugs for minor species, including wildlife and endangered species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used
21 CFR 25.33(d)(5)	For drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species
21 CFR 25.33(e)	For an action on an INAD

* This list is not a comprehensive list of all claims of CE, and other CE citations under 21 CFR 25.33 may also be applicable.

A request for Agency action may qualify for a claim of CE if: (1) the action meets the criteria for the claim of CE, as provided for under 21 CFR 25.33; and (2) no extraordinary circumstances exist that may significantly affect the quality of the human environment (see 21 CFR 25.21).

To claim a CE, you must: (1) state that the action requested qualifies for a CE; (2) cite the specific CE that is claimed; and (3) state that to your knowledge, no extraordinary circumstances exist that could have a significant environmental impact.[82]

In accordance with 21 CFR 25.21, the FDA will require at least an EA for any specific action that would ordinarily be categorically excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment. Examples of extraordinary circumstances are provided at 21 CFR 25.21.

2. Special considerations for aquaculture drugs

The following should be considered if you claim a CE pursuant to 21 CFR 25.33(d)(1) or 21 CFR 25.33(d)(4) for the Environmental Impact technical section for an animal drug in an aquatic species:

> 21 CFR 25.33(d)(1) provides for a CE for drugs intended for use in nonfood animals. This claim of CE is based on an expectation of limited environmental exposure, and hence, limited

[82] 21 CFR 25.15(d)

environmental risk. For animal drugs used in aquatic species, the environmental exposure may not be limited, increasing the possibility that extraordinary circumstances may exist that would require the preparation of an EA.[83]

21 CFR 25.33(d)(4) provides for a CE for drugs intended for use in minor species, including wildlife and endangered species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used (e.g., recirculating aquaculture systems, flow-through raceways, ponds and/or net pens). However, for aquatic species, it is rare that the drug has already been approved for use in another aquatic species or the same aquatic species and where similar management practices are used. Therefore, most actions related to aquaculture drugs would not meet the criteria for this CE.

C. Environmental Assessment (EA)

In general, preparation of an EA is required for any proposed action that does not meet the criteria for a categorical exclusion,[84] or if extraordinary circumstances indicate that any specific proposed action that ordinarily would be categorically excluded may significantly affect the quality of the human environment.[85] If an EA is required, we recommend that you meet with CVM to discuss the requirements for the EA.

An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment.[86] Directions for preparing an EA can be found at 21 CFR 25.40 (Environmental assessments) and additional guidance can be found in GFI #89, "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I," and GFI #166, "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase II." Links to GFI #89 and GFI#166 are included in Appendix 1 – Additional Resources.

XVII. Chemistry, Manufacturing, and Controls (CMC)

CVM's website provides guidance documents with more detailed information on the CMC evaluation; you should consult these guidance documents and talk with ONADE before developing your approach to completing the CMC technical section, see Appendix 1 – Additional Resources for a list of the relevant guidance documents.

[83] 21 CFR 25.21

[84] 21 CFR 25.20

[85] 21 CFR 25.21

[86] 21 CFR 25.15(a)

A. Overview

1. Pre-approval

The CMC technical section contains complete information regarding the manufacture of the new animal drug active ingredient and the new animal drug product. It includes information on personnel, facilities, components and composition, manufacturing procedures, analytical specifications and methods, control procedures, stability, containers and closures, current good manufacturing practice (CGMP) compliance, and many other aspects of the chemistry and manufacturing processes.[87]

2. Post-approval

CVM review of the manufacturing information continues throughout the life cycle of the product, including the manufacturing process of clinical and pilot/production batches before the drug is approved, and any changes that are implemented thereafter. In this way, the CMC technical section helps ensure that the quality and characteristics of the drug sold to the public continue to conform to that of the drug determined to be safe and effective prior to approval.

After approval, all CMC changes must be reported to CVM in either supplemental applications or minor changes and stability reports (MCSRs) depending on the nature of the change. Significant manufacturing changes cannot be implemented prior to approval of the change by CVM. A sponsor is also required to submit annually, in the MCSR, updated stability data generated on marketed product, according to an approved stability commitment.[88]

B. Special Considerations for Minor Use or Minor Species

If you submit a supplemental application for a minor use or minor species indication to your already approved NADA, you may generally rely on the CMC technical section completed for the original approval. This presumes that the MUMS product is not a different formulation. Any changes in formulation or concentration need to be addressed as part of this technical section.[89] If the product has not already been approved, then the entire CMC technical section must be completed in accordance with 21 CFR 514.1(b).

Facilities used to manufacture clinical batches for studies supporting approval, pilot batches, and commercial drug batches must conform to CGMP.[90] CGMP is the same for major and minor species products. For further details about the applicable CGMP requirements, manufacturers of pharmaceutical dosage forms should refer to the Agency's regulations at 21 CFR parts 210 and

[87] 21 CFR 514.1(b)(4) and (5)

[88] 21 CFR 514.8

[89] 21 CFR 514.8

[90] 21 CFR 514.1(b)(5)(xi)

211, and manufacturers of Type A medicated articles or Type B or C medicated feeds should refer to the regulations at 21 CFR parts 225 and 226.

XVIII. Labeling

The labeling technical section includes facsimile or final copies of container labels, package inserts, and all other labeling components that will be associated with the product. For medicated feeds, copies of representative labeling for the Type B and Type C medicated feeds, often referred to as "Blue Bird" labeling, and a veterinary feed directive form, if required, should also be included. Facsimile labeling is nearly final labeling that adequately reproduces the package size (actual or to scale); graphics; pictures; type size, font, and color of text; and the substance of the text to demonstrate that the final printed labeling will be in compliance with applicable regulations.[91]

XIX. All Other Information (AOI)

The AOI technical section includes all other information not included in the effectiveness, target animal safety, or human food safety technical sections that is pertinent to an evaluation of the safety or effectiveness of the new animal drug for which approval is sought. All other information includes, but is not limited to, any information derived from other marketing (domestic or foreign) and favorable and unfavorable reports in the scientific literature. If there is no additional information that has not been previously submitted, the sponsor's AOI technical section should contain a statement to that effect.[92]

XX. Post-Approval Requirements

You need to be aware that your responsibilities do not end with the approval of the new animal drug application. There also are some post-approval responsibilities, including reporting requirements, described in 21 CFR 514.80. These reporting requirements can be discussed with the Office of Surveillance and Compliance at CVM. Other requirements that apply when making supplemental changes to your application are described in FDA's regulations.[93] These requirements can be discussed with your ONADE PM. See section XXI. *Other Incentives and Assistance Available for Minor Use and Minor Species Projects* below for the post-approval requirements associated with a conditional approval.

XXI. Other Incentives and Assistance Available for Minor Use and Minor Species Projects

There are several incentives available to sponsors of MUMS drugs in addition to user fee waivers and designation. The waiver and designation incentives are described above in sections V. *User Fee Waivers and MUMS Status* and IX. *Designation*. Other incentives provided for

[91] 21 CFR 514.1(b)(3)

[92] 21 CFR 514.1(b)(8)(iv)

[93] 21 CFR 514.8

under the MUMS Act are briefly described in this section. These include conditional approval and the Index.

A. Conditional Approval

Section 571 of the FD&C Act provides requirements for conditional approval of new animal drugs. The conditional approval process and associated timeframes are managed by ONADE.

1. General

The approval of a CNADA is referred to as conditional approval. There are limitations on the eligibility of MUMS drugs for conditional approval. For example:

- The same drug may not already be approved in the same dosage form for the same intended use. (Section 571(c)(3) of the FD&C Act)
- The new animal drug may not be contained in, or be a product of, a transgenic animal. (Section 571(a)(3)(A)(i) of the FD&C Act)[94]

In order to obtain conditional approval, you must prove that the new animal drug is safe and will be manufactured according to the same safety and manufacturing standards as a fully approved new animal drug.[95] However, conditional approval allows you to make your drug commercially available before collecting all the effectiveness data necessary to gain full NADA approval. For the effectiveness technical section, instead of meeting the NADA approval standard of "substantial evidence of effectiveness," a CNADA needs to demonstrate "a reasonable expectation of effectiveness."[96] The conditional approval effectiveness standard is briefly described above in section XIII. *Reasonable Expectation of Effectiveness for Conditional Approval* of this guidance.

For MUMS drugs, studies to support a reasonable expectation of effectiveness are eligible to compete for MUMS grants. Prior to applying for a MUMS grant, you must have a designation in place and the protocol for the study must have received concurrence from ONADE.[97] To apply

[94] We note that intentional genomic alterations (IGAs) in animals include those that are "transgenic," as defined in section 571(j) of the FD&C Act. Section 571(j) of the FD&C Act states that "transgenic animal" in this provision means "an animal whose genome contains a nucleotide sequence that has been intentionally modified in vitro, and the progeny of such an animal…." This definition includes animals containing heritable intentional genomic alterations (IGAs) made using genome editing technologies, like CRISPR. For example, a deletion is an "intentional modification made in vitro" so it is included in the section 571(j) definition of "transgenic animal" and, therefore, such heritable IGAs are not eligible for conditional approval. However, FDA does not consider an animal containing non-heritable alterations to be a "transgenic animal" within the meaning of section 571(j).

[95] Section 571(a)(2) of the FD&C Act

[96] Section 571(a)(2)(B) of the FD&C Act

[97] Section 573(b) of the FD&C Act

for a MUMS grant, see the current Notice of Funding Opportunity (NOFO). A link to the current MUMS drug NOFO can be found on CVM's MUMS Drug Designation web page.

Amendments to the FD&C Act associated with the 2018 reauthorization of CVM's animal drug user fee program expanded the eligibility of conditional approval to new animal drugs intended for use in *major species* for the treatment of serious or life-threatening diseases or conditions, or unmet animal or human health needs, for which the demonstration of effectiveness would require a complex or particularly difficult study or studies. See GFI #261, "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs."

2. Labeling Considerations

A new animal drug that is the subject of a CNADA may need to have its own separate labeling. If the new conditionally approved indication is for a new animal drug product that is already marketed with a fully approved indication, the sponsor needs to be aware that they may need to have two different sets of labeling, one for the new animal drug product with the conditionally approved indication and one for the same new animal drug product with the fully approved indication. This is an important point to consider early in planning and can be discussed with ONADE at a presubmission conference.

It is also important to know that extralabel use of a conditionally approved drug product is not permitted.[98]

3. Renewal of Conditional Approval

Section 571(d) of the FD&C Act sets out the requirements for renewing conditional approval. For your product to maintain its conditional approval status, you must renew the CNADA on an annual basis. As a condition to maintaining the CNADA, you must show, among other things, that you are making sufficient progress toward meeting the requirements for full approval. You must also show that you are likely to be able to fulfill those requirements and obtain full NADA approval before the expiration of the 5-year maximum term of the conditional approval.

4. Refusal to Renew a Conditional Approval

The failure to provide a timely request for the annual renewal of conditional approval, the failure of the request for annual renewal to contain information to demonstrate "sufficient progress" toward meeting the requirements for full approval, or if the same drug in the same dosage form for the same intended use has received approval under section 512 of the FD&C Act and the holder of the approved application is able to ensure the availability of sufficient quantities of the drug to meet the needs for which the drug is intended will result in a refusal to renew the CNADA.[99] The Agency will also refuse to renew the CNADA if any of the provisions of

[98] Sections 512(a)(4)(A) and 571(a)(1)(C) of the FD&C Act

[99] Sections 571(d)(2)(A) and (B) of the FD&C Act

sections 512(e)(1) (A) through (B) or (D) through (F) of the FD&C Act are applicable[100] (i.e., the drug is unsafe or no longer shown to be safe; the required patent information was not filed within 30 days after the receipt of written notice from the Agency; the application contains any untrue statement of a material fact; or the applicant has made any changes from the standpoint of safety or effectiveness beyond the variations provided for in the application unless they have supplemented the application and there is in effect an approval of the supplemental application). The CNADA is then considered withdrawn and no longer in effect. After that, FDA will provide the sponsor an opportunity for an informal hearing regarding whether the CNADA will be reinstated.[101]

5. NADA Following Conditional Approval

The NADA must be submitted under section 512 of the FD&C Act at least 180 days before the 5-year anniversary of the CNADA approval or else the CNADA is deemed no longer in effect at that point and FDA will take steps to remove any conditionally approved product from the market.[102] You should manage your timelines to ensure that you have developed, collected, and prepared for submission all data necessary to establish substantial evidence of effectiveness of the product for the indication for which approval is sought at least 180 days before the 5-year anniversary of the CNADA approval.

B. The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (The Index)

Section 572 of the FD&C Act provides a means of legally marketing unapproved new animal drugs intended for use in minor species where there is a reasonable certainty that they will not be eaten, or early non-edible life-stages of food-producing minor species, by including them on an Index maintained by FDA. The process for adding new animal drugs to the Index is referred to as "indexing." Indexing is managed by OMUMS.

Indexing provides sponsors with an alternate pathway to bring eligible products into a legal marketing status. The intention is to accommodate products that are not well suited to the NADA process. Making these products legally available is especially helpful to veterinarians or owners treating zoo or endangered animals, laboratory rodents, pocket pets such as hamsters or gerbils, or classes of animals that include numerous different species, such as ornamental fish or pet birds, who otherwise would have very few legal options for treating such animals.

The requirements for indexing are fully described in the regulations at 21 CFR part 516 subpart C. Addition to the Index is largely based on the report of a qualified expert panel external to FDA that evaluates effectiveness and target animal safety. The panel may consider a wide

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

[101] Section 571(d)(3) of the FD&C Act

[102] Section 571(h) of the FD&C Act

variety of information relevant to the determination of target animal safety and the effectiveness of the new animal drug at issue.

Those interested in indexing a new animal drug should consult guidance GFI #201, "Small Entities Compliance Guide for The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species," available on the CVM Guidance for Industry website. A link to the webpage for GFIs is provided in Appendix 1 – Additional Resources.

C. Office of Minor Use & Minor Species (OMUMS) Animal Drug Development

The MUMS Act established OMUMS within the FDA's Center for Veterinary Medicine. OMUMS is responsible for:

- managing the designation of MUMS drugs, and for administering grants and contracts under the designation provisions;
- making "minor use" assessments;
- reviewing requests for Index listing, and for managing reporting after addition to the Index;
- serving as liaison to other government agencies interested in MUMS drug development; and
- outreach to a wide variety of stakeholders interested in MUMS issues.

Appendix 1 – Additional Resources

CVM guidance documents, organized by number or subject, can be found at: https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry

To reach contacts mentioned in any GFI, you can contact CVM at AskCVM@fda.hhs.gov.

The following GFIs associated with the animal drug approval process are referenced in this guidance:

General:

GFI #108, "How to Register with the CVM Electronic Submission System"

GFI #132, "Administrative Applications and the Phased Review Process"

GFI #79, "Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by CVM"

Effectiveness:

GFI #85 (VICH GL9), "Good Clinical Practice"

GFI #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations"

GFI #106, "The Use of Published Literature in Support of New Animal Drug Approvals"

GFI #215, "Target Animal Safety & Effectiveness Protocol Development & Submission"

GFI #217, "Effectiveness of Anticoccidial Drugs in Food-Producing Animals"

GFI #265, "Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs"

GFI #266, "Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs"

GFI #267, "Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs"

GFI #268, "Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs"

Target Animal Safety:

GFI #185 (VICH GL43), "Target Animal Safety for Veterinary Pharmaceutical Products"

Human Food Safety:

GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food Producing Animals"

GFI #149 (VICH GL33), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing"

GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"

GFI #159 (VICH GL36), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI"

GFI #207 (VICH GL48), "Marker Residue Depletion Studies to Establish Product Withdrawal Periods"

GFI #232 (VICH GL54), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD)"

GFI #257 (VICH GL57) "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species."

Environmental Impact:

GFI #89 (VICH GL6), "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) - Phase I"

GFI #166 (VICH GL38), "Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase II"

Incentives:

User Fee Waivers:

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)" and Appendix

GFI #183, "Animal Drug User Fees: Fees Exceed Costs Waiver/Reduction"

Designation:

GFI #200, "Small Entities Compliance Guide for Designation of New Animal Drugs for Minor Uses/Minor Species"

The Index:

GFI #201, "Small Entities Compliance Guide for The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species"

Conditional Approval:

GFI # 261, "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs"

Other helpful information:

FDA CVM website: https://www.fda.gov/animal-veterinary

Electronic Code of Federal Regulations: https://www.ecfr.gov

Setting up accounts for electronic submissions (eSubmitter): https://www.fda.gov/animal-veterinary/development-approval-process/electronic-submissions

Minor Use Minor Species (MUMS) web page: https://www.fda.gov/animal-veterinary/development-approval-process/minor-useminor-species

MUMS Drug Designation web page: https://www.fda.gov/animal-veterinary/minor-useminor-species/drug-designation

The Minor Use and Minor Species Animal Health Act of 2004: https://www.gpo.gov/fdsys/pkg/PLAW-108publ282/pdf/PLAW-108publ282.pdf

Public Master Files: https://www.fda.gov/animal-veterinary/minor-useminor-species/public-master-files-pmfs-supporting-applications-minor-use-and-minor-species-drugs

Phish-Pharm (FDA-PP) Database: https://www.fda.gov/animal-veterinary/tools-resources/phish-pharm

Appendix 2 – Acronyms & Definitions

The following terms, abbreviations, initials, and acronyms are associated with the new animal drug approval process for minor uses and minor species and are provided for use with this guidance document.

ANADA – Abbreviated New Animal Drug Application. An ANADA, including all amendments and supplements, is the application that is submitted to seek approval for a generic new animal drug product (see 21 CFR 514.3). Although generic copies are possible for MUMS products, this document does not address the ANADA review process.

Adequate and Well-controlled Studies – These studies are used to demonstrate "substantial evidence" of effectiveness. The characteristics of adequate and well-controlled studies can be found at 21 CFR 514.117.

ADI – **Acceptable daily intake** means the daily intake which, during up to an entire life of a human, appears to be without adverse effects or harm to the health of the consumer. The ADI most often will be set on the basis of the drug's toxicological, microbiological, or pharmacological properties. It is usually expressed in micrograms or milligrams of the chemical per kilogram of body weight per day.

AOI – All Other Information.

Baitfish – Fish that are raised to be used to catch other fish. Because baitfish are part of the food chain, they may need to be considered food-producing minor species when drug approval requirements are considered.

Categorical Exclusion – An exclusion from the requirement to prepare an environmental assessment (EA) or an Environmental Impact Statement (EIS). These categorical exclusions are described in 21 CFR part 25 Subpart C.

CFR – Code of Federal Regulations. (eCFR – electronic CFR)

CGMP – Current Good Manufacturing Practice Regulations. Regulations which contain the minimum current good manufacturing practices for various classes of drugs (see 21 CFR 211 through 226).

CMC – Chemistry, Manufacture, and Controls.

CNADA – Application for conditional approval of a new animal drug.

CVM – FDA's Center for Veterinary Medicine.

Designated Drug – A new animal drug intended for a minor use or for use in a minor species (MUMS drug) with a specific dosage form and intended use that has been granted "Designation" status by OMUMS and is therefore eligible for incentives. The incentives for MUMS-designated

drugs include grants to support safety and effectiveness testing and 7 years of exclusive marketing rights beginning on the date of approval or conditional approval.

EA – Environmental Assessment. – A document that addresses the relevant environmental issues associated with the application. An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(a)).

EPA – U.S. Environmental Protection Agency.

eSubmitter – A client-based software application that provides industry with a simple and intuitive user interface for creating electronic submissions and structuring data for transmission through the FDA Electronic Submission Gateway.

FDA – U.S. Food and Drug Administration.

FD&C Act – Federal Food, Drug, and Cosmetic Act.

Federal Register – An official Federal publication containing information such as proposed regulations, notices of public meetings, etc.

Field Study – A study designed to assess the effectiveness of the investigational new animal drug in the target animal under field conditions. Field conditions refers to conditions which closely approximate the conditions under which the new animal drug, if approved, is intended to be applied or administered (21 CFR 514.117(c)(1)). A field study intended to support approval of a new animal drug should have the characteristics of an adequate and well-controlled study (see 21 CFR 514.117(c)(2)). It is possible that certain kinds of safety information may be gathered during the conduct of the field study.

Finfish – Fish differentiated from shellfish and mollusks.

Food-producing Minor Species – Minor species of which some members are bred, cultured, farmed, ranched, hunted, caught, trapped, or otherwise harvested for the purpose of having the animals or edible products derived from the animals commercially distributed for consumption by humans or food-producing animals in the United States.

Food Use Authorization – Permits the use of edible tissues from terrestrial and aquatic animal species treated with investigational new animal drugs for food after FDA has evaluated any potential public health hazards. The food-use authorization recommends appropriate mitigations of those hazards to ensure the safety of the edible products (e.g., tissues, milk, eggs, and honey) entering the human or animal food chain (see 21 CFR 511.1(b)(5)).

FOI – Freedom of Information.

Functionally Superior – A drug that is functionally superior has been shown to provide a significant therapeutic or physiologic advantage over that provided by a conditionally approved or approved MUMS drug, that is otherwise the same drug (21 CFR 516.3(b)).

GADPTRA – Generic Animal Drug and Patent Term Restoration Act of 1988.

GFI – Guidance for Industry.

GLPs – Good Laboratory Practice Regulations. Regulations which establish requirements for the conduct of nonclinical laboratory studies for safety data to support approval. (See 21 CFR part 58).

HFS – Human Food Safety.

INAD – Investigational New Animal Drug.

INAD File – Investigational New Animal Drug File. An administrative file that contains information provided by the sponsor, CVM's review documentation related to that information, and any correspondence between CVM and the sponsor of the investigational new animal drug.

Index – FDA's list of Legally Marketed Unapproved New Animal Drugs for Minor Species. The Index may include new animal drugs for minor species where there is a reasonable certainty that the animals will not be eaten, or for non-food early life-stages of food-producing minor species.

Indexed Drug – A new animal drug, as defined in section 201 of the FD&C Act, intended for use in a minor species that has been added to the Index in accordance with section 572 of the FD&C Act and the regulations at 21 CFR part 516, subpart C.

Indication – This is the statement that appears on labeling to describe the intended use of the product – both the species of animal to be treated and the disease or condition or the structure or function of the body affected. Generally, this term is used when discussing the indication that is studied as the subject of a new animal drug application.

Intended Use – The intended treatment, control, or prevention of a disease or condition, or the intention to affect the structure or function of the body of animals within an identified species, subpopulation of a species, or collection of species (21 CFR 516.13).

Major Species – Cattle, horses, swine, chickens, turkeys, dogs, and cats.

Minor Species – Animals, other than humans, that are not major species.

Method Transfer Trial – An inter-laboratory study also termed a "method trial" designed to validate the reproducibility component of the precision of the analytical method. See GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food Producing Animals" for a complete description.

Minor Use – 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.

MUADP (Minor Use Animal Drug Program) – A USDA program that conducts studies in support of FDA approval of new animal drugs for minor species of agricultural importance. The successor to the NRSP-7 program.

MUMS – Minor use and/or minor species.

MUMS Act – The Minor Use and Minor Species Animal Health Act of 2004.

MUMS Drug – A new animal drug intended for a minor use or for use in a minor species.

MUMS-drug Exclusive Marketing Rights – Effective on the date of FDA conditional approval or approval of a MUMS-designated drug, no conditional approval or approval will be given to a subsequent application for the same drug, in the same dosage form, for the same intended use for seven years.

MUMS Grant – Money that may be competitively granted by FDA for the purpose of defraying the costs of qualified safety and effectiveness testing expenses incurred in the development of MUMS-designated drugs.

NADA – New Animal Drug Application. An application for approval of a specific new animal drug product, so that the drug may be legally marketed. The application must be supported by, among other things, data to support effectiveness, target animal safety, human food safety, environmental impact, chemistry and manufacturing controls, labeling, and all other information. The NADA also includes all amendments and supplements (see 21 CFR 514.3).

NCIE – Notice of Claimed Investigational Exemption for a New Animal Drug. A notice submitted to CVM prior to shipment of an investigational new animal drug for clinical tests in animals (see 21 CFR 511.1(b)(4)).

NRSP-7 – National Research Support Project Number 7. A past USDA program promoting drug studies for minor species of agricultural importance. See: MUADP.

OMUMS – Office of Minor Use and Minor Species Animal Drug Development within CVM.

ONADE – Office of New Animal Drug Evaluation within CVM.

Ornamental Fish – A wide variety of fish species maintained primarily for their appearance. Does not include fish that are ordinarily consumed by humans or food-producing animals.

Phased Review – A voluntary process a sponsor may use to complete any or all of the technical sections required for approval of a new animal drug before submitting an application.

PK/PD – Pharmacokinetic/Pharmacodynamic.

Pilot Data – Data collected from pilot studies that are generally conducted early in drug development to gather preliminary data for proof of concept to establish a dose, etc.

PMF – Public Master File. A file which holds publicly generated or otherwise publicly available data (generally effectiveness, target animal safety, residue chemistry, and environmental assessment) that may be referenced by a sponsor to support an original or supplemental new animal drug application or a conditional approval application.

PDP – Product Development Plan.

PSC – **Presubmission Conference**. A formal meeting between a sponsor and CVM in which binding agreements may be reached establishing a submission or investigational requirement (see 21 CFR 514.5).

Reasonable Expectation of Effectiveness – This is the effectiveness standard for conditional approval that is met by evidence on the basis of which it could fairly and reasonably be expected by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that there is a reasonable expectation that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested for use in the labeling or proposed labeling thereof. Such evidence may include, but not be limited to, pilot data in target species, extrapolation of effectiveness from other species or related diseases or related dosage forms, studies from the published literature, or foreign studies.

Residue – Any compound present in edible tissues that results from the use of a drug, and includes the drug, its metabolites, and any other substance formed in or on food because of the drug's use**.**

Small Number – Small numbers for each of the seven major species are published in regulation and represent the largest number of animals that can be affected by a disease or condition over the course of a year and still have the intended use qualify as a minor use (see also 21 CFR 516.3). See section *V.B.3. Small Numbers and the Eligible Population* of this document.

Sponsor – For purposes of this guidance, this term means the person requesting designation for a MUMS drug who must be the real party in interest of the development and the intended or actual production and sales of such drug (in this context, the sponsor may be an individual, partnership, organization, or association) (see 21 CFR 516.16). Sponsor also means the person responsible for an investigation of a new animal drug (in this context, the sponsor may be an individual, partnership, corporation, or government agency or may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of new animal drugs). Sponsor also means the person submitting or receiving approval for a new animal drug application (in this context, the sponsor may be an individual, partnership, organization, or association). In all contexts, the sponsor is responsible for compliance with applicable provisions of the FD&C Act and regulations.

Submission – Any correspondence or information from a sponsor to an INAD or other official file at FDA CVM.

Substantial Evidence of Effectiveness – Evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an *in vitro* study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect (see 21 CFR 514.4(a)).

Supplemental application, Supplemental NADA, or Supplement – Application for modification of an existing drug approval; this could include the addition of a label indication for a minor species, use in another animal species, changes in conditions of use, or other changes to the original approval.

TAS – Target Animal Safety.

Target Animal Safety Study – Study of the safety of an investigational new animal drug in the animal species for which drug approval is being sought. Refer to GFI #185, "Target Animal Safety for Veterinary Pharmaceutical Products VICH GL43."

Target Tissue – The edible tissue selected to monitor for residues in the target animal. The target tissue is usually, but not necessarily, the last tissue in which residues deplete to the permitted concentration.

Technical Section – A portion of an NADA related to a major requirement of the FD&C Act and approval regulations. The technical sections are: effectiveness, target animal safety, human food safety, environmental impact, chemistry and manufacturing controls, labeling, and all other information.

Tolerance – The maximum concentration of a residue indicated for monitoring, that can legally remain in a specific edible tissue of a treated animal.

Transgenic Animal – 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 (Section 571(j) of the FD&C Act; 21 CFR 516.115(a)).

USDA – U.S. Department of Agriculture.

Withdrawal Period or Milk Discard Time – The interval between the last administration of a new animal drug and when the animal can be safely slaughtered for food, or the milk can be

safely consumed. Note that the use of the word "slaughtered" here includes harvesting of fish or other species that are not slaughtered in the usual use of the word.

Zero Withdrawal – Refers to a labeling statement that allows entry of edible tissues into the food chain without regard to the time of last drug administration.

Zoo Animal – An animal that is maintained in captivity in a zoological park, aquarium or similar facility engaged in the public display of animals.