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Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals

Guidance for Industry

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2023-D-2925.

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, U.S. Food and Drug Administration, Center for Veterinary Medicine, CPK1, 5001 Campus Drive, College Park, MD 20740-3835,, 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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Contains Nonbinding Recommendations

Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals

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 for sponsors of approved new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs) containing antimicrobial drugs: (1) important to human medicine (medically important antimicrobial drugs), (2) for use in or on the medicated feed of food-producing animals, and (3) that are currently approved with one or more indications that have an undefined duration of use. Medically important antimicrobial drugs and undefined duration of use are discussed further in section III. *Scope* of this guidance. The framework outlined in this guidance is intended to facilitate voluntary changes to have all medically important antimicrobial new animal drugs administered in alignment with the principles of judicious use.[1] Establishing appropriately defined durations of use to mitigate the development of antimicrobial resistance is consistent with previous and ongoing efforts by FDA to protect public health by promoting the judicious use of medically important antimicrobial drugs in animals. This guidance provides specific recommendations on how sponsors may facilitate changes to the approved conditions of use of affected products in support of ongoing efforts to mitigate the development of antimicrobial resistance.

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.

[1] Judicious use is defined as the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance. See "Supporting Antimicrobial Stewardship in Veterinary Settings, Goals for Fiscal Years 2024-2028," (https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-plan-supporting-antimicrobial-stewardship-veterinary-settings-fy-2024-2028).

II. Background

On April 13, 2012, FDA issued Guidance for Industry (GFI) #209, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals."[2] In GFI #209, FDA stated that the development of resistance to medically important antimicrobial drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. As part of addressing this issue, FDA recommended in GFI #209 the following two principles to help promote the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals:

(1) Limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for ensuring animal health (i.e., to treat, control, and prevent disease), and

(2) Limit medically important antimicrobial drug uses in food-producing animals to uses that include veterinary oversight or consultation.

On December 12, 2013, FDA issued GFI #213, "New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209."[3] Based on recommendations in that final guidance, sponsors of medically important antimicrobial drugs approved for use in or on the feed or drinking water of food-producing animals voluntarily worked with FDA to accomplish withdrawal of approval of indications that were not considered necessary for ensuring animal health (i.e., production indications), and change of all remaining approved uses of such new animal drugs from over-the-counter (OTC) to either veterinary feed directive (VFD) or prescription (Rx) marketing status, as applicable. FDA, working in conjunction with sponsors of the affected animal drug products, successfully completed implementation of GFI #213 in January 2017.[4]

On September 14, 2016, FDA announced that it intended to enter the next phase of its efforts to mitigate antimicrobial resistance by focusing on medically important antimicrobials used in animal feed or water that have at least one therapeutic indication without a defined duration of use. These older products were approved prior to FDA's current understanding of the importance of including a defined duration as one of the principles of judicious use. In a notice published in the *Federal Register* (81 FR 63187),[5] the Agency requested public comment regarding the establishment of appropriately defined durations of use for therapeutic products affected by GFI #213 with no defined duration of use. Feedback received in response to that request for comments was taken into consideration during development of this guidance.

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[2] https://www.fda.gov/media/79140/download (April 2012).

[3] https://www.fda.gov/media/83488/download (December 2013).

[4] https://wayback.archive-it.org/7993/20190423131636/https:/www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm

[5] https://www.federalregister.gov/documents/2016/09/14/2016-21972/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing

On September 14, 2018, FDA released a 5-year action plan for supporting antimicrobial stewardship in veterinary settings.[6] This plan builds upon the important steps the FDA Center for Veterinary Medicine (CVM) has already taken to support the judicious use of antimicrobials in food-producing animals,[7] and is driven by the concept that medically important antimicrobial drugs should only be used in animals when necessary for the treatment, control, or prevention of specific diseases. Action item 1.1.2 included in this plan is to "ensure that all medically important antimicrobial drugs used in the feed or drinking water of food-producing animals have an appropriately targeted duration of use."[8]

Starting in 2019, CVM began offering multiple funding opportunities[9] to support the conduct of studies that are intended to generate data to help establish appropriately defined durations of use for certain medically important antimicrobial drugs approved for use in the feed of food-producing animals. This funding was intended to provide publicly available data that may be used by sponsors of affected approved new animal drugs to help support revisions to the conditions of use for products consistent with the objectives outlined in this guidance. When the studies are complete, CVM intends to make the final study reports and data available in a Public Master File, and they may be used as applicable to inform labeling changes discussed in this guidance.

On January 11, 2021, FDA published and requested public comment on a concept paper titled "Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed: A Concept Paper" (86 FR 1979).[10] The concept paper described a potential framework for how animal drug sponsors could voluntarily work with FDA to make changes to the approved conditions of use for certain medically important antimicrobial drugs (i.e., those described in section III. *Scope* of this guidance), to establish an appropriately defined duration of use for those indications that currently lack a defined duration of use. FDA considered all information and public feedback received in response to the concept paper during development of this guidance.

III. Scope

This guidance is applicable to all medically important antimicrobial drugs that are approved[11] for use in or on medicated feed of food-producing animals that have one or more indications with undefined durations of use on currently approved labeling. For purposes of this guidance, an "undefined duration of use" means that the labeling for the identified product includes no information regarding duration of feeding or otherwise does not provide an appropriately

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[6] "Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023," (https://www.fda.gov/media/115776/download).

[7] https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance

[8] See Action 1.1.2 on page 7 of FDA's 5-year action plan for fiscal years 2019-2023.

[9] https://public4.pagefreezer.com/browse/FDA/29-01-2023T09:49/https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-2020-funding-opportunity-help-define-durations-use-certain-medically-important

[10] https://www.fda.gov/media/144927/download (January 2021).

[11] Including products that are not currently marketed.

targeted duration of use. For purposes of this guidance, an "appropriately defined duration of use" means that the information regarding duration of feeding on the labeling ensures that the drug is used only when animals need it and provides the veterinarian appropriate flexibility to use the drug consistent with the labeling in a range of scenarios that may be encountered in practice. The scope of this guidance is limited to those drugs that are approved for use in or on animal feed because all the approved uses of medically important antimicrobial drugs in other (non-feed) dosage forms already have appropriately defined durations of use.[12] FDA has made public on its website a listing of all medically important antimicrobial drugs administered in the feed of food-producing animals that currently have one or more approved indications with an undefined duration of use.[13] FDA intends for all drugs that appear in this listing, hereinafter referred to as "affected products" or "affected applications," to be included within the scope of this guidance. FDA refers to Appendix A of GFI #152 for FDA's determination of which antimicrobial drugs/drug classes are considered "medically important" for purposes of its strategy to promote the judicious use of antimicrobial drugs in animals. The list of medically important antimicrobial drugs/drug classes in Appendix A is not static and FDA has previously stated its intent to periodically reassess this list consistent with contemporary science and current human clinical practices.[14] Therefore, the antimicrobial products within the scope of this guidance may change in the future as FDA revises the list of antimicrobial drugs that are considered medically important.

IV. Objectives

FDA's objective in issuing this guidance is to provide specific recommendations to animal drug sponsors on how to revise the product use conditions (e.g., dosage regimen, instructions for use) of affected products, as necessary, to better target when and for how long a drug may be used to effectively treat, control, or prevent the disease(s) for which the product is indicated. Such revisions are intended to provide for the continued effective use of these products while minimizing the extent of antimicrobial drug exposure, thereby supporting efforts to mitigate the development of antimicrobial resistance. Establishing appropriately defined durations of use for the affected applications supports the FDA's ongoing efforts to slow the development of antimicrobial resistance by fostering the judicious use of medically important antimicrobial drugs in animals.

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[12] Although FDA's 5-year action plan (fiscal years 2019-2023) for supporting antimicrobial stewardship included an action item calling for the Agency to develop a strategy for establishing appropriately defined durations of use for medically important antimicrobial drugs used in or on the feed or drinking water of food-producing animals, CVM has determined that all of the approved uses of medically important antimicrobial drugs used in drinking water already have appropriately defined durations of use.

[13] https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/list-approved-medically-important-antimicrobial-drugs-administered-feed-food-producing-animals-lack

[14] See Action 1.3.1 on page 9 of FDA's 5-year action plan (fiscal years 2019-2023). See also Table A1 of Appendix A in draft GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," (https://www.fda.gov/media/69949/download) (January 2023). When final, this guidance will represent FDA's current thinking on this topic.

Revisions to product use conditions (as reflected through revisions to the approved labeling) generally should include appropriately defining the duration of use for the product and, where appropriate, providing additional information to facilitate the veterinarian's oversight of the product's feeding to animals in a manner consistent with the principles of judicious use. As discussed in more detail in section VII. *Supplemental NADAs (Pioneer Drugs)* of this guidance, the recommendations in this guidance are not expected to impact any technical sections other than Labeling and Environmental Impact.

A. Appropriately Defining the Duration of Use

For affected products that currently lack a defined duration of use for one or more indications, the labeling should be revised to include appropriate criteria regarding when to begin and end feeding of the antimicrobial drug. As discussed in more detail in section VII. *Supplemental NADAs (Pioneer Drugs)* of this guidance, an appropriately defined duration of use should describe the approximate duration range that veterinarians should first consider for the indication (typical duration range) and be bounded by a maximum permitted duration. The directions for use on the labeling should also be defined in terms of evidence of disease in the group of animals (in the case of treatment or control indications) or the period during which animals are at risk for the disease (in the case of prevention and prevention-like indications).

When determining the specific duration to authorize, veterinarians should first consider whether a duration within the typical duration range on the labeling would be adequate and appropriate for the animals under consideration. Veterinarians ultimately may authorize, in accordance with their professional judgment in varying clinical circumstances, a duration that falls outside of the typical duration range up to the maximum permitted duration described on the labeling.

The maximum permitted duration of use is the duration that cannot[15] be exceeded for a single course of therapy authorized by a veterinarian. The maximum permitted duration is not intended to be routinely authorized. It should:

- provide the veterinarian appropriate flexibility to use the drug consistent with the labeling in a range of scenarios that may be encountered in practice,
- be consistent with what is known about the risk factors, pathogenesis, and progression of the indicated disease, and
- be defined in terms of maximum time that the drug may be used (e.g., days or weeks). Depending on the disease, target species, and class, it may be more appropriate to define the maximum permitted duration of use in terms of maximum animal age or maximum animal body weight, rather than time.

[15] Extralabel use of medicated feeds is prohibited. See section 512(a)(4)(A) of the FD&C Act; 21 CFR 530.11(b).

A sponsor should not use instructions such as "feed until market weight" to define the duration of use. Likewise, sponsors should not use instructions to stop feeding by a certain age, when that age equals or exceeds the typical slaughter age of that species and class, to define the duration of use. In addition, a slaughter withdrawal period on the labeling should not be used to define the duration of use.

B. Providing Additional Information for the Veterinarian

These products are now VFD products requiring the oversight of a licensed veterinarian. Therefore, in addition to establishing defined durations as required conditions of use, it is appropriate to revise the approved product labeling to include additional information intended for the authorizing veterinarian to consider when writing a VFD. Such information is expected to vary depending on the specific indication for use in question, including whether the indication is for disease treatment, control, or prevention. Such information should appear in an "Additional Recommendations" section of the labeling and be presented in a manner that does not imply limits on the veterinarian's ability to exercise professional judgement.

For purposes of this guidance, the terms treatment, control, and prevention are defined as follows:

Treatment: The drug is administered only to animals diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.

Relevant labeling information: The veterinarian's decision to use a medically important antimicrobial drug approved for treatment purposes, in a judicious manner, ordinarily includes consideration of factors relevant to: (1) diagnosing in the animals the bacterial disease indicated on the approved labeling, and (2) determining whether use of the drug in question to treat the disease is appropriate in a particular situation. The types of information provided on product labeling to assist veterinarians in deciding whether and how to use an antimicrobial drug indicated for disease treatment may include:

- Information to support disease diagnosis
- Clinical pharmacology information
- Microbiology information
- Clinical effectiveness information

Control: The drug is administered to a group of animals once a proportion[16] of the animals in the group have been diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.

[16] A percentage that is greater than 0% and less than 100%, unless otherwise specified on the labeling.

Relevant labeling information: The veterinarian's decision to use a medically important antimicrobial drug approved for control purposes, in a judicious manner, ordinarily includes consideration of factors relevant to: (1) diagnosing the bacterial disease indicated on the approved labeling in a proportion of the animals in the group, and (2) determining whether use of the drug in question to control the disease is appropriate in a particular situation. The types of information provided on product labeling to assist veterinarians in deciding whether and how to use an antimicrobial drug indicated for disease control may include:

- Information to support disease diagnosis
- Epidemiologic information regarding the indicated disease
- Clinical pharmacology information
- Microbiology information
- Clinical effectiveness information

Prevention: 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.

Relevant labeling information: The veterinarian's decision to use a medically important antimicrobial drug approved for prevention purposes (including prevention-like purposes such as reduction of disease incidence) in a judicious manner ordinarily includes consideration of factors relevant to: (1) determining the risk that the disease indicated on the approved labeling will occur in the animals, and (2) determining whether use of the drug in question to prevent the disease is appropriate in a particular situation. The types of information provided on product labeling to assist veterinarians in deciding whether and how to use an antimicrobial drug indicated for disease prevention may include:

- Environmental risk factors for the indicated disease that cannot be practically mitigated (e.g., related to temperature, ventilation, animal transportation conditions)
- Host risk factors for the indicated disease (e.g., related to age, production class or production stage, nutrition, breed or genetics, stressors, immune status)
- Epidemiologic information regarding the indicated disease
- Clinical pharmacology information
- Microbiology information
- Clinical effectiveness information

V. Voluntary Adoption of Judicious Use Principles

Based on the successful implementation of the recommendations made in GFIs #209 and #213, FDA believes the approach outlined in this guidance is an effective and efficient means of furthering the goal of judicious use of medically important antimicrobial drugs in animals. CVM will work with affected drug sponsors who opt to revise the use conditions for those product indications that are currently approved with an undefined duration of use.

VI. Timelines for Implementing Changes

In order to ensure progress under the cooperative framework outlined in this guidance, FDA will monitor progress to assess whether changes are being adopted along the timelines discussed below. If, after approximately 3 years as discussed below, FDA determines that adequate progress has not been made, FDA will consider whether further action under the existing provisions of the FD&C Act may be appropriate.

A. Timeline for Sponsors Defining a Duration of Use on the Labeling

As discussed in section VII.A.1. *Submit Proposals with Justification to CVM for Review* of this guidance, the following types of information should be addressed in labeling proposals for applicable pioneer[17] products: (1) revised directions for use including the typical duration range and maximum permitted duration of use (see section VII.A.1.a. *Defining the Revised Directions for Use Including Typical Duration Range and Maximum Permitted Duration*); (2) appropriate antimicrobial resistance mitigation statement(s); and (3) additional information for the veterinarian to consider.

The timeframes described in this guidance are intended to fully implement the recommendations in this guidance within as short a time as possible following finalization of this guidance. FDA anticipates that sponsors of affected products should be able to have revised labeling approved that incorporates the changes discussed in this guidance within approximately 3 years from the date of publication of the final version of this guidance. To achieve this goal, sponsors should provide the various submissions for their affected applications in a timely manner as outlined below.

1. Step 1 (Proposal and Support for Intended Labeling Revisions for Affected NADA Type A Medicated Articles and Non-Animal Drug Availability Act (ADAA) Feed-Use Combinations)

Sponsors of affected NADA Type A medicated articles (including fixed-ratio combination Type A medicated articles)[18] and NADA non-ADAA[19] feed-use

[17] NADA single-ingredient and fixed-ratio combination Type A medicated articles, and NADA feed-use combinations that are approved under section 512(d)(1)) of the FD&C Act.

[18] Type A medicated articles are defined in 21 CFR 558.3(b)(2).

[19] NADA, Animal Drug Availability Act (ADAA), and NADA non-ADAA feed-use combinations are discussed further in section VII.B. *Pioneer (NADA) Feed-Use Combinations* of this guidance.

combinations (for purposes of this guidance, these will be referred to as "top-level" applications) should submit proposals and information that would support the labeling changes described in this guidance. Sponsors should submit these proposals in one or more STARS[20] G submissions (general correspondence submissions) for CVM review.[21] Sponsors may choose to coordinate with each other if they are interested in seeking approval for the same conditions of use across the same or similar indications. CVM generally responds to G submissions within 180 days.

For purposes of this guidance, a "downstream" application or file type is one that relies on and conforms to the conditions of use established for the application(s) that it references. CVM is not able to review labeling supplements for downstream applications and files until the supplement for the referenced application has been received. Sponsors of top-level NADAs who are unsure whether their application serves as a reference for one or more downstream applications or files are encouraged to contact CVM's Office of New Animal Product Evaluation to confirm. Of the applications affected by this guidance, ANADA Type A medicated articles, NADA ADAA feed-use combinations, and ANADA feed-use combinations are downstream applications. Veterinary Master Files (VMFs) are a type of downstream file that maintains labeling for reference in an application. Step 1 does not apply to downstream applications or VMFs.

Sponsors of top-level applications should submit their proposals in G submissions as soon as practicable within the timeframe indicated below:

- Top-level NADAs that serve as references for one or more downstream applications or files: submit the G submission(s) no later than 6 months following finalization of this guidance.

- Top-level NADAs that do not serve as references for any downstream applications or files: submit the G submission(s) no later than 1 year following finalization of this guidance.

If desired, sponsors may contact CVM to discuss their plans informally or formally (e.g., in a presubmission conference) before submitting their G submission(s). Whether or not such discussions are held, sponsors of top-level NADAs should cooperate with the above submission timeframes, to facilitate the submissions described in Step 2 below being submitted and reviewed in a timely manner.

[20] STARS is CVM's Submission Tracking and Reporting System. For information on electronic submission through eSubmitter, see https://www.fda.gov/animal-veterinary/development-approval-process/electronic-submissions.

[21] Sponsors may choose to submit all proposals for a given application in the same G submission, or they may choose to submit their various proposals across multiple G submissions (e.g., submit a separate G submission for each impacted indication).

When review of each G submission is complete, CVM will issue a letter to the sponsor. CVM anticipates that only in some exceptionally complex cases will more than 180 days be needed.

2. Step 2 (Labeling Supplement Submission and Approval/Project Completion for all Affected Applications)

As soon as possible after CVM has issued a letter regarding each relevant G submission (for top-level NADAs), or after they are contacted by CVM (for downstream applications and files), sponsors should submit one non-fee[22] supplemental application (labeling supplement) for each affected application to request approval of the revised conditions of use and associated labeling components.

Because of the way downstream applications and files are structured, sponsors will face constraints on the sequencing of certain submissions. Those structures are:

- ANADA Type A medicated articles, ANADA feed-use combinations that reference an NADA non-ADAA feed-use combination, NADA ADAA feed-use combinations, and Veterinary Master Files (VMFs) rely directly on the submission and review of a top-level NADA.

- ANADA feed-use combinations that reference an NADA ADAA feed-use combination rely on the submission and review of a downstream application, which itself relied on previous submission and review of a top-level NADA.

- Approvals for use of proprietary free-choice medicated feeds based on VMFs[23] under the application for the source Type A medicated article rely on submission and review of revised labeling submitted to the VMFs.

Due to the inherent complexity of interactions between top-level and downstream applications, CVM does not intend to synchronize approval of any of these supplements. However, CVM will work with sponsors as requested to determine the appropriate submission timing for specific labeling supplements based on: (1) expected workload of CVM and the sponsor, (2) existence of any impacted combination or proprietary free-choice medicated feeds and generic products, and (3) whether sponsors wish to coordinate with each other to minimize the time that elapses between approval of labeling supplements for products with similar indications.

[22] Supplemental animal drug applications that do not require safety or effectiveness data (such as the labeling changes recommended in this guidance) do not incur fees under the Animal Drug User Fee Act (ADUFA) program. Supplemental abbreviated applications for generic new animal drugs do not incur fees under the Animal Generic Drug User Fee Act (AGDUFA) program. See sections 739, 740, and 741 of the FD&C Act.

[23] Discussed further in section VII.C. *Proprietary Free-Choice Medicated Feed Labeling Maintained under a VMF* of this guidance.

CVM intends to notify sponsors of downstream applications and files within approximately 2 weeks of receiving the labeling supplement for the referenced application. For each type of downstream application or file, sponsors should submit their labeling supplement as soon as practicable within the following timeframes:

- ANADA Type A medicated articles: submit supplement within 60 days of notification of submission of the supplement for the reference listed new animal drug (RLNAD) Type A medicated article.
- NADA ADAA feed-use combinations: submit supplement within 60 days of notification of submission of the supplement for the referenced NADA Type A medicated article.
- ANADA feed-use combinations: submit supplement within 60 days of notification of submission of the supplement for the RLNAD feed-use combination.
- VMFs for proprietary free-choice medicated feeds: submit revised labeling to the VMF within 60 days of notification of submission of the supplement for the referenced Type A medicated article.
- NADA Type A medicated articles that are the source for proprietary free-choice medicated feeds based on VMFs: submit supplements (one corresponding to each VMF) to the NADA within 60 days of notification of submission of the revised labeling for the applicable VMFs.

CVM will review these labeling supplements as sponsors submit them, according to established review timeframes. NADA labeling supplements are assigned a 180-day review time, and ANADA labeling supplements are assigned a 270-day review time.[24]

B. Timeline for Sponsors Choosing to Request Withdrawal of the Approval of an Indication or of an Entire Application

If sponsors intend to request withdrawal of the approval of an indication or an entire application, rather than define a duration of use, they should initiate the withdrawal process as described in section IX. *Voluntary Withdrawal of Approval of a Regimen or an Indication with an Undefined Duration of Use from an NADA or Voluntary Withdrawal of the Entire (A)NADA* of this guidance within 1 year following finalization of this

[24] The Agency agreed to these review time goals for labeling supplements in the goals letters that accompanied the 2023 reauthorization of the Animal Drug User Fee Act (ADUFA) (https://www.fda.gov/media/116001/download and the 2023 reauthorization of the Animal Generic Drug User Fee Act (AGDUFA) (https://www.fda.gov/media/116328/download).

guidance. CVM will review these requests as sponsors submit them, according to established review timeframes.

VII. Supplemental NADAs (Pioneer Drugs)

This section describes the labeling changes that sponsors should request, how sponsors should propose and justify a maximum permitted duration of use for each affected indication, and the additional information sponsors should include in their labeling supplements. In addition, this section describes administrative processes and marketing exclusivity considerations that should be taken into account. Sponsors should use the process set forth in this section to provide appropriate information to support approval of their labeling supplement to establish a defined duration of use. CVM also will consider other scientifically and legally appropriate alternatives that sponsors may propose.

Because the affected indications are approved (safety and effectiveness have already been demonstrated) and the formulation is not expected to change, the establishment of appropriately defined durations of use is not expected to require review of safety, effectiveness, or chemistry, manufacturing, and controls information. The steps recommended in this section are intended to apply to situations where the only substantive change to the approved application is defining previously undefined durations of use and no new indications or other substantive changes to the application are proposed.[25] Making changes unrelated to defining previously undefined durations of use (for example, increasing or decreasing the dosage level, changing the product formulation, or making other substantive changes) is likely to require submission and CVM review of additional information or data. The process recommended in this guidance also assumes that the currently approved dosage level administered to target animals (for example, drug inclusion rate in feed or the amount of drug per head or per unit body weight) and the formulation of the product are not changing.

A. Pioneer (NADA) Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles

For each indication with an undefined duration of use, the labeling should provide directions for use that are defined in terms of evidence of disease (or risk period for disease, as applicable) in the group, the typical duration range to be considered, and the maximum permitted duration of use.[26] The labeling also should provide information as appropriate that would support the principles of judicious use and minimize the

[25] Sponsors choosing to propose new indications or make other substantive changes to the application (including changes to the labeling other than those described in this guidance) are encouraged to do so under a separate supplemental application that includes all applicable technical sections, following established procedures. These procedures are described elsewhere and are beyond the scope of this guidance. Sponsors choosing to pursue all labeling changes close in time (e.g., for a single future printing of labeling) may submit the subsequent supplemental application at any time, as early as the next day after the supplemental application for approval of revised labeling containing the defined duration of use is submitted.

[26] See section VII.A.1.a. *Defining the Revised Directions for Use Including Typical Duration Range and Maximum Permitted Duration* of this guidance.

development and spread of antimicrobial resistance,[27] and provide additional information for the veterinarian to consider when authorizing use of the drug.[28]

To help ensure efficient review of these labeling changes, for each affected application, sponsors should first submit proposed labeling changes in one or more G submissions for CVM review and then submit a single labeling supplement for approval, as described in this section.

1. Submit Proposals with Justification to CVM for Review

Sponsors should submit proposals with appropriate justification in one or more G submissions before submitting the labeling supplement. For each affected indication, the G submission should include the following, as discussed in this section:

- the proposed revised conditions of use including:
  - the typical duration range veterinarians should first consider for the indication (along with appropriate justification);
  - the maximum permitted duration of use (along with appropriate justification);
- appropriate antimicrobial resistance mitigation statement(s);
- any additional information for the veterinarian to consider; and
- acknowledgement of intent to incorporate any additional labeling changes that may be needed.

During Step 1, described in section VI.A. *Timeline for Sponsors Defining a Duration of Use on the Labeling* of this guidance, and before submitting a labeling supplement, sponsors of top-level NADAs should submit their proposals and supporting information to address the labeling changes discussed in this section in one or more G submissions to each affected application file. These should be submitted to CVM's Office of New Animal Product Evaluation, Division of Food Animal Drugs for review and comment. Sponsors may address all affected indications for a product in the same G submission or they may choose to address the affected indications across multiple submissions. Sponsors may choose to request a presubmission conference to discuss proposals with CVM before submitting the G submission(s). Sponsors are encouraged to include draft revised labeling for all affected labeling components in the G submission(s) to allow CVM to provide comments or concurrence in advance of the future labeling supplement. If draft revised labeling is not included in the G

[27] See section VII.A.1.b. *Inclusion of Antimicrobial Resistance Mitigation Statements* of this guidance.

[28] See section VII.A.1.c. *Providing Additional Information for the Veterinarian* of this guidance.

submission(s), sponsors should provide a detailed text description of the proposed changes to the labeling.

CVM considers each application individually. CVM does not intend to consider proposals that may be submitted for one application when evaluating proposals submitted for another. CVM is only able to communicate with sponsors regarding their own application files; however, CVM recognizes that the body of available information may support a range of durations that would be appropriate for use to treat, control, or prevent a given disease and that some sponsors may be interested in aligning the directions for use across products approved for the same or similar indications to the extent possible, even across products owned by different sponsors. CVM will not object if sponsors choose to coordinate among themselves to prepare and submit identical proposals and supporting information to their respective application files.

Following review of each G submission, CVM will issue a letter to the sponsor. The letter will indicate whether CVM generally agrees with the sponsor's proposals and will provide additional comments as warranted. CVM will work with sponsors to review and comment on planned labeling revisions in an efficient manner.

a. Defining the Revised Directions for Use Including Typical Duration Range and Maximum Permitted Duration

For all affected indications across all affected products, the Directions[29] section of the labeling should be revised as follows:

- Provide language to ensure that the drug is only used (1) when there is evidence of disease in the group (in the case of treatment or control indications), or (2) during the period in which animals are at risk for the disease (in the case of prevention indications);

- Describe the typical duration range that the veterinarian should consider, and;

- State the maximum permitted duration.

Typical Duration Range

The typical duration range encompasses the durations that veterinarians would authorize for the indication in most circumstances, and should be consistent with current veterinary standards of practice for the indication. To allow veterinarians flexibility to deviate from the typical duration range when warranted, this range should appear on the labeling using the phrasing, "…continue for approximately

[29] Some currently approved product labeling may title this section differently (e.g., "Directions for Use") or may not have a specific section title.

A to B days…." The Directions section of the labeling should be clear that the veterinarian is to determine the actual duration to authorize on a VFD for use in a specific group of animals.

Maximum Permitted Duration of Use

For each affected indication on the product labeling, the Directions section should state the maximum duration of use that is permitted for a single course of therapy authorized by a VFD. The maximum permitted duration of use should appear in a "Do not feed for more than a [insert maximum duration of use (days)] course of therapy as authorized by this VFD" or similar statement. The maximum permitted duration of use should be appropriate for each indication and likely will be different for different indications. The maximum permitted duration of use on the labeling should not be the duration veterinarians would routinely authorize, but instead should provide the veterinarian with adequate flexibility to use the drug consistent with the principles of judicious use in a range of legitimate circumstances or scenarios that may occasionally be encountered in the United States. CVM anticipates that for most affected indications, it will be difficult to justify a proposed maximum permitted duration of use that approaches either the production lifespan of the target animal or the maximum VFD expiration date.[30] However, CVM acknowledges that for some affected indications, there likely are scenarios in which it will be necessary and consistent with the principles of judicious use to feed the drug for an extended period.

Proposal and Justification

Sponsors should propose the typical duration range and maximum permitted duration of use for each indication based on typical and potential disease risk periods, observed disease progress, self-cure timeframes, usual and maximum time frames to expected outcomes, and other relevant information as applicable. Sponsors should support the proposal with a scientific justification (e.g., white paper) that is based on relevant available information such as peer-reviewed scientific literature, recognized standards of veterinary practice, a consensus of expert opinions (e.g., statements from veterinarians regarding how long they currently use the drug), and other such information. If appropriate and the sponsor chooses to do so, the justification may also draw on existing information relevant to the drug itself (including studies in the application file that were used to support the original approval of the indication, or information related to mechanism of action, pharmacokinetics, and pharmacodynamics), that may help inform how long the drug should typically be used and the maximum duration that it may need to be used, to be effective for the indicated disease in commonly encountered and potential worst-case scenarios.

[30] If not otherwise specified in the approval, the VFD expiration date must not exceed 6 months after the date of issuance. See 21 CFR 558.6(b)(3)(v).

The justification should be comprehensive, focused, balanced, and limit bias. It should build the argument logically and present information that both supports and counters (if such information exists) the proposed typical duration range and maximum permitted duration. It is important that the justification include any information that is unfavorable as well as favorable to the proposal and explain why any apparently unfavorable information may not be applicable. If there are major differences among sources, the justification should discuss possible reasons for those differences. Finally, the justification should draw overall conclusions and explain the reasoning (with reference to the specific information used) behind those conclusions.

If literature is used, the justification should include information on the database(s) searched, the keyword(s) and search string(s) used, and any limitations, such as date range(s) imposed. Sponsors should provide complete copies of the papers referenced and a reference list with the justification. If any information used for the justification is in a foreign language, an accurate and complete English translation of the information must also be included. [31]

Sponsors choosing to refer to completed studies that have not yet been submitted to CVM should only include a study report or summary of relevant observations, and not include raw data with the justification. For studies previously submitted to CVM, sponsors may simply refer to the location of the reports by study title or other identifying information, submission date, and file number.

Format and Phrasing of Revised Directions for Use

For consistency and clarity across affected products, one of the following statements (as applicable according to indication type and other considerations) should be included in the Directions section of the labeling for each affected indication. The statements should incorporate the typical duration range, the maximum permitted duration, and (if applicable) preserve any required directions for use (e.g., a minimum duration) that appear on the currently approved labeling.

- **Treatment Indications:**

For most treatment indications, the following statement should be used:

> "Feed only to animals that are diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for approximately A to B days until the animals no longer require this medication, as determined by the veterinarian. Do not feed for more than X days."

[31] See 21 CFR 514.1(a).

For indications that have a minimum duration of use required by the currently approved labeling, the following statement should be used:

> "Feed only to animals that are diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for at least [*currently approved minimum duration (A)*] days up to approximately B days until the animals no longer require this medication, as determined by the veterinarian. Do not feed for more than X days."

If warranted by unique aspects of the disease or drug (e.g., veterinary practice standards related to the disease or specifics related to the drug's mechanism of action), an alternative statement similar to the following is recommended:

> "Feed only to animals that are diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for approximately A to B days until C days after resolution of clinical signs, as determined by the veterinarian. Do not feed for more than X days."

Sponsors who consider that such an alternative statement is applicable to their product indication should propose and justify the need for the statement, the specific wording, and the number of days that will appear in place of "C."

- **Control Indications:**

For most control indications, the following statement should be used:

> "Feed to a group of animals in which a proportion of the animals in the group has been diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for approximately A to B days until an acceptable degree of control has been reached in the group or the animals no longer require this medication, as determined by the veterinarian. Do not feed for more than X days."

For indications that have a minimum duration of use required by the currently approved labeling, the following statement should be used:

> "Feed to a group of animals in which a proportion of the animals in the group has been diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for at least [*currently approved minimum duration (A)*] days up to approximately B days until an acceptable degree of control has been reached in the group or the animals no longer require this medication, as determined by the veterinarian. Do not feed for more than X days."

If warranted by unique aspects of the disease or drug (e.g., veterinary practice standards related to the disease or specifics related to the drug's mechanism of action), an alternative statement similar to the following is recommended:

> "Feed to a group of animals in which a proportion of the animals in the group has been diagnosed with the disease. Begin feeding after the disease is diagnosed and continue for approximately A to B days until C days after an acceptable degree of control has been reached in the group or until resolution of clinical signs, as determined by the veterinarian. Do not feed for more than X days."

Sponsors who consider that such an alternative statement is applicable to their product indication should propose and justify the need for the statement, the specific wording, and the number of days that will appear in place of "C."

- **Prevention, Reduction in Incidence, and Similar Indications:**

For most prevention and similar indications, the following statement should be used:

> "Feed to a group of animals that are at risk of developing the disease, but in which no animals have yet been diagnosed. Begin feeding at the start of the risk period and continue for approximately A to B days until animals are no longer at risk, as determined by the veterinarian. Do not feed for more than X days."

For indications that have a minimum duration of use required by the currently approved labeling, the following statement should be used:

> "Feed to a group of animals that are at risk of developing the disease, but in which no animals have yet been diagnosed. Begin feeding at the start of the risk period and continue for at least [*currently approved minimum duration (A)*] days up to approximately B days until the animals are no longer at risk, as determined by the veterinarian. Do not feed for more than X days."

Antimicrobials approved for prevention and similar indications should not be labeled for use beyond when the animals are at risk of the disease.

Sponsors should explain in their G submission(s) how they intend to revise their labeling after considering the guidance above. Sponsors do not need to provide any information to support the statements shown in this section except where noted above, or if a sponsor considers that none of the above statements are appropriate to a particular product indication. Sponsors should appropriately justify any alternative statements they may choose to propose.

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b. Inclusion of Antimicrobial Resistance Mitigation Statements

The labeling for affected applications may benefit from including information in the appropriate section(s) of the labeling that supports the principles of judicious use by encouraging practices that would minimize the development and spread of antimicrobial resistance. Sponsors should consider antimicrobial resistance risk mitigation statement(s) that are appropriate for their product and approved use conditions, including where and under what heading(s) they should appear on the labeling, and provide their proposal in the G submission(s). CVM will also consider the need for such statement(s) during review of the G submission(s) and may provide comments on the proposed changes for labeling revision.

For illustrative purposes, examples of such statements include but are not limited to:

- "Using an antimicrobial of the same drug class for the same indication immediately following use of this drug may increase the risk of antimicrobial resistance development. Consider using a drug from a different class if available."
- "Using an antimicrobial of the same drug class in the same group of animals immediately following use of this drug may increase the risk of antimicrobial resistance development. Consider using a drug from a different class if available."
- "After [X] days of therapy, if animals do not show signs of improvement, the veterinarian should evaluate the health status of the animals and, based on appropriate diagnostics, determine the need to continue antimicrobial therapy with this drug or a drug from a different class."
- "Feed this drug only to the number of animals necessary to treat, control, or prevent the indicated disease in accordance with the approved conditions of use."

c. Providing Additional Information for the Veterinarian

All Type A medicated article labels and representative (Blue Bird)[32] Type B and Type C medicated feed[33] labeling should include additional information for the veterinarian to consider when authorizing use of the drug. This information should appear in an "Additional Recommendations" section. Information in this section does not constitute required conditions of use. This information is not

[32] See GFI #181, "Blue Bird Medicated Feed Labels," (https://www.fda.gov/media/70452/download) (July 2019).

[33] Type B medicated feed and Type C medicated feed are defined in 21 CFR 558.3(b)(3) and (4), respectively.

required to appear on the VFD,[34] but sponsors may propose to include it on the VFD submitted for approval to serve as a model for aiding communication with veterinarians and other end users. The Additional Recommendations section should appear on labeling immediately following the Warnings section.

The Additional Recommendations section should include the following statements:

> "The maximum permitted duration of use specified on the labeling is not intended to be routinely authorized, but instead is intended to provide the veterinarian with adequate flexibility when necessary to ensure effectiveness while still using the drug consistent with the principles of judicious use. In determining the specific duration to authorize, the veterinarian should first consider whether the approximate duration range described in the Directions is adequate and appropriate for the animals under consideration. The approximate duration range(s) and maximum permitted duration(s) of use for <list affected indication(s) [and affected regimen(s) if appropriate]> was(were) established according to an assessment of information relevant to the characteristics and dynamics of this(these) disease(s), including <briefly describe the types of information used: e.g., peer-reviewed scientific literature, etc.>. "

Labeling approved for prevention, reduction of incidence, and similar indications should include the following statement in the Additional Recommendations section:

> "Animals may be considered at risk for a disease when transmission of existing undiagnosed infections, or the introduction of pathogens, is anticipated based on history, clinical judgment, or epidemiological knowledge."

In addition, the Additional Recommendations section should include information for each indication, as appropriate, to assist the veterinarian in determining when drug feeding should be initiated or stopped in accordance with the approved conditions of use and consistent with the principles of judicious use of antimicrobials. Such information should be oriented to the specific indication or indication type in question and may include factors to consider regarding when to begin the regimen, known risk factors for the disease, or considerations for selecting a specific duration of use under different scenarios. For example, beef cattle may spend differing lengths of time in finishing feed yards depending on their age and condition when first entering the yard, which may affect the risk

[34] See 21 CFR 558.6(b)(3) for information that must appear on a lawful VFD. Among other things, the VFD is required to include various information such as cautionary statements "necessary for use of the drug in conformance with the approval." See 21 CFR 558.6(b)(3)(xi). The information in the Additional Recommendations section is not intended to be necessary for use of the drug in conformance with the approval.

period or other factors associated with an indicated disease. Not all indications will benefit from such additional information.

For all indications, sponsors should consider whether the types of additional information described in section IV.B. *Providing Additional Information for the Veterinarian* of this guidance would be of value to the veterinarian when considering use of the drug or when determining an appropriate duration of use to authorize on the VFD. Sponsors should include their proposal(s) and any necessary supporting information in the G submission(s). CVM will also consider this question during review of the G submission(s) and may provide comments on the proposed changes for labeling revision.

d. Additional Labeling Changes

Sponsors should also plan to incorporate the following revisions to their labeling as applicable:

- Any other labeling changes previously directed by the Agency that have not yet been implemented (e.g., storage statement updates).

- Revised directions for use for all approved indications that are otherwise not affected by this guidance to delete "feed continuously" (or similar wording) to reduce the chance for inadvertent misunderstanding regarding the approved duration of use. The term should be replaced with either "consecutive days" or "at every feeding," as appropriate for clarity with respect to the approved feeding regimen. For example, if the directions for use currently state, "Feed continuously for X to Y days," appropriate revisions include, "Feed for X to Y consecutive days," and "Feed at every feeding for X to Y days."

If not previously implemented, sponsors must also revise or add the "Approved by FDA under NADA # XXX-XXX" statement, as required in section 502(w)(3) of the FD&C Act.[35]

Sponsors should assess whether any of the above changes are warranted for their product labeling and include proposed changes in the revised labeling included with the G submission(s) or otherwise indicate the changes they intend to make. CVM will also consider this during review of the G submission(s) and may provide comments on the proposed changes for labeling revision.

[35] This requirement was added by section 303 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018, Public Law 115-234, and requires the inclusion of this statement on the labeling (except representative medicated feed labeling) of approved new animal drugs by September 30, 2023. For further information, see "'Approved by FDA' Labeling Statement Provides Assurance of Safety, Effectiveness of Animal Drugs," (https://www.fda.gov/animal-veterinary/cvm-updates/approved-fda-labeling-statement-provides-assurance-safety-effectiveness-animal-drugs).

2. Submit Non-Fee Labeling Supplement

After CVM has issued all relevant letters regarding planned labeling revisions for a given application, as described in Step 2 in section VI.A. *Timeline for Sponsors Defining a Duration of Use on the Labeling* of this guidance, sponsors should submit a single non-fee labeling supplement (STARS C submission, NF subclass code, 180-day review time[36]) to CVM's Office of New Animal Product Evaluation, Division of Food Animal Drugs. The labeling supplement should include the following, as discussed below: revised labeling, Environmental Impact information, and permission for CVM to contact sponsors of applications affected by changes to the pioneer application in advance of approval of the labeling supplement. Other technical sections should not need to be addressed unless the sponsor makes changes that are outside the scope of this guidance.

a. Labeling

Sponsors should submit a single, clean copy of each revised labeling component (i.e., color facsimile or final printed labeling [electronic FPL, eFPL] for the Type A medicated article, and representative [Blue Bird] Type B and Type C medicated feed labeling, as applicable) and a revised VFD, all reflecting the changes that were previously affirmed by CVM.

b. Environmental Impact

Because the sole objective of this guidance is to define the previously undefined duration(s) of use for the affected products, these labeling changes are not expected to result in an increase in use of the originally approved drug. Therefore, sponsors should request, in the labeling supplement, a claim of categorical exclusion (CE) from the requirement to prepare an environmental assessment (EA) or an environmental impact statement (EIS), pursuant to 21 CFR 25.33(a), for an action that does not increase the use of the drug. (Sponsors should not claim a CE citing a subcategory of 21 CFR 25.33(a) [e.g., 21 CFR 25.33(a)(1)] for these actions.) With the claim of CE, sponsors must[37] include a statement that, to their knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment as described in 21 CFR 25.21. Sponsors with questions or who are unable to provide this statement should contact CVM's Office of New Animal Product Evaluation, Division of Statistical and Biological Sciences, Environmental Branch.

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[36] Sponsors should not check "yes" for the question on the eSubmitter template that asks if they are submitting a "Qualifying Labeling Supplement" (QLS) because the supplements covered by this guidance will not qualify for a 60-day review timeframe. If this option is inadvertently selected, ONAPE will change the submission review time from 60 to 180 days. See footnote 24 on page 11 regarding review times.

[37] See 21 CFR 25.15(a).

c. Permission for CVM to Contact Affected Sponsors

Sponsors should include permission for CVM to contact sponsors of any affected feed-use combinations, proprietary free-choice medicated feeds, and affected generic copies of the drug to discuss changes being made to the pioneer drug's labeling, in advance of FDA's approval of the pioneer sponsor's labeling supplement. For example:

> "[Sponsor] gives permission for CVM to contact sponsors of any affected feed-use combinations, proprietary free-choice medicated feeds, and affected generic copies of this drug to discuss changes being made to this drug's labeling, in advance of FDA's approval of this labeling supplement."

d. Other Technical Sections

For supplemental applications that only propose the labeling changes recommended in this guidance, it is not necessary for sponsors to provide additional information relevant to target animal safety, effectiveness, human food safety, or chemistry, manufacturing, and controls (CMC). Safety and CMC related information are not needed because the overall exposure is not increasing, and the feed inclusion rates and drug formulations are not changing. CVM recognizes that the affected drugs have previously been demonstrated to be effective for their respective indications, as reflected by the original approvals. Further, CVM considers that although the directions for use for the affected indications did not originally define a duration of use, the underlying assumption was that these drugs would be used only for the duration needed in any given group of animals. Therefore, labeling changes to define the duration of use in terms of evidence of disease in the group or the period during which animals are at risk for the disease (as applicable to the indication type) are understood to be in conformance with the intent of the original approvals and thus inherently consistent with the effectiveness information that was used for approval. It is not necessary for sponsors to submit an All Other Information technical section because no safety or effectiveness information is required for the changes recommended in this guidance.

Accordingly, sponsors should not need to address these technical sections in a presubmission conference or in the supplemental application. However, if sponsors propose changes beyond those recommended in this guidance, additional information for one or more of these technical sections may be needed, and a labeling supplement may not be an appropriate administrative submission type.

Sponsors choosing to establish defined durations of use through submission and review of safety or effectiveness data (or equivalent information) should not submit a labeling supplement as described in this guidance, but instead should request a presubmission conference with CVM to discuss technical section requirements and the appropriate administrative pathway for approval. If pioneer

sponsors choose such an approach, they are strongly encouraged, consistent with FDA's goal of establishing appropriately defined durations of use on a timely basis for all medically important antimicrobials that currently have undefined durations of use, to also provide written permission waiving the pioneer sponsor's right to marketing exclusivity as discussed in section VII.D. *Marketing Exclusivity Considerations* of this guidance.

B. Pioneer (NADA) Feed-Use Combinations

A feed-use combination is an approved use of two or more active pharmaceutical ingredients or Type A medicated articles to create a complete medicated animal feed. There are three different types of pioneer feed-use combinations: NADA fixed-ratio combination Type A medicated articles, NADA ADAA feed-use combinations, and NADA non-ADAA feed-use combinations. NADA fixed-ratio combination Type A medicated articles are those that provide two or more active pharmaceutical ingredients as a single Type A medicated article and are discussed in section VII.A. *Pioneer (NADA) Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles* of this guidance. Both NADA ADAA feed-use combinations and NADA non-ADAA feed-use combinations provide for two or more individually approved Type A medicated articles to be combined (either directly or via intermediate Type B or Type C medicated feeds) to manufacture a Type C medicated animal feed containing a combination of new animal drugs. NADA ADAA feed-use combinations and NADA non-ADAA feed-use combinations differ in the way they meet approval requirements. NADA ADAA feed-use combinations that meet the qualifying criteria set forth in section 512(d)(4) of the FD&C Act and its implementing regulations in 21 CFR 514.4(c)(2)(ii) (generally referred to as the "ADAA combination requirements") are approved using modified requirements for establishing safety and effectiveness. NADA non-ADAA feed-use combinations are approved under section 512(d)(1) of the FD&C Act, after the sponsor provides, among other things, a full demonstration of effectiveness and target animal safety when each drug is combined in Type C medicated animal feed. NADA non-ADAA feed-use combinations are combinations that were approved before the enactment of ADAA or those combinations that do not meet the qualifying criteria set forth in section 512(d)(4) of the FD&C Act at the time of approval.

For supplemental applications that only propose the labeling changes recommended in this guidance, it is not necessary for sponsors of feed-use combinations to provide additional information relevant to target animal safety, effectiveness, human food safety, or CMC.

1. NADA ADAA Feed-Use Combinations

CVM intends to contact sponsors of affected NADA ADAA feed-use combination applications after receiving a supplemental application to revise the labeling of the affected component Type A medicated article. Sponsors of these feed-use combinations should submit a labeling supplement (C submission, NF subclass code,

180-day review time[38]) or otherwise formally initiate the alignment process (i.e., in a G submission or presubmission conference request) within 60 days after CVM notifies them that the approved conditions of use for the affected component Type A medicated article have been or are going to be revised. Submissions should be directed to CVM's Office of New Animal Product Evaluation, Division of Food Animal Drugs.

CVM does not anticipate that sponsors of affected NADA ADAA feed-use combination applications would commonly need to submit proposals to CVM prior to submitting their labeling supplements. CVM will request amendment(s) to each labeling supplement as necessary to work with the sponsor towards approval. However, in some cases, it may not be readily apparent how best to align the labeling of some feed-use combinations with the revised affected Type A medicated article labeling. As such, sponsors may choose to first submit a G submission or request a presubmission conference with CVM to propose changes and obtain CVM's comments before then submitting a labeling supplement.

The labeling supplement for an NADA ADAA feed-use combination should include the following:

a. Labeling

Sponsors should submit a single, clean copy of each revised labeling component (i.e., representative [Blue Bird] Type B and Type C medicated feed labeling, as applicable) and a revised VFD reflecting the changes to align with the affected component Type A medicated article.

b. Environmental Impact

Because the sole objective of this guidance is to define the previously undefined duration(s) of use for the affected products, these labeling changes are not expected to result in an increase in use of the originally approved drug. Therefore, sponsors should request, in the labeling supplement, a claim of CE from the requirement to prepare an EA or an EIS, pursuant to 21 CFR 25.33(a), for an action that does not increase the use of the drug. (Sponsors should not claim a CE citing a subcategory of 21 CFR 25.33(a) [e.g., 21 CFR 25.33(a)(1)] for these actions.) With the claim of CE, sponsors must[39] include a statement that, to their knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment as described in 21 CFR 25.21. Sponsors with questions or who are unable to provide this statement

[38] See footnote 24 on page 11 regarding review times.

[39] See 21 CFR 25.15(a).

should contact CVM's Office of New Animal Product Evaluation, Division of Statistical and Biological Sciences, Environmental Branch.

c. Permission for CVM to Contact Affected Sponsors

Sponsors should include permission for CVM to contact sponsors of any affected generic copies of the drug to discuss changes being made to the pioneer drug's labeling, in advance of FDA's approval of the pioneer sponsor's labeling supplement. For example:

> "[Sponsor] gives permission for CVM to contact sponsors of any affected generic copies of this drug to discuss changes being made to this drug's labeling, in advance of FDA's approval of this labeling supplement."

d. Other Technical Sections

For the labeling changes recommended in this guidance (i.e., if the only change is to establish appropriately defined durations of use for the affected indications as recommended in this section of this guidance), it is not necessary for sponsors to provide additional information relevant to target animal safety, effectiveness, human food safety, or CMC. It is not necessary for sponsors to submit an All Other Information technical section because no safety or effectiveness information is needed for the changes recommended in this guidance.

Accordingly, sponsors should not need to address these technical sections in a presubmission conference or in the supplemental application. However, if sponsors propose changes beyond those recommended in this guidance, additional information for one or more of these technical sections may be needed, and a labeling supplement may not be an appropriate administrative submission type.

2. NADA Non-ADAA Feed-Use Combinations

Sponsors of NADA non-ADAA feed-use combinations[40] should follow the steps described in section VII.A. *Pioneer (NADA) Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles* of this guidance.

When applicable, sponsors should either include copies of or otherwise reference the location of the appropriate right of reference letter(s) in the file. Previously-submitted right of reference letters should be referenced by the principal submission identification number and submission date.

[40] Pioneer feed-use combinations that were originally approved as an NADA non-ADAA feed-use combination are not eligible to use the modified requirements offered by section 512(d)(4) when submitting a supplemental application.

C. Proprietary Free-Choice Medicated Feed Labeling Maintained Under a VMF

Free-choice medicated feeds[41] are those products which contain one or more animal drugs and are placed in feeding and grazing areas but are not intended to be fully consumed at a single feeding or to constitute the entire diet of the animal. The approval of a proprietary free-choice medicated feed formulation is completed under an NADA submitted under section 512 of the FD&C Act. For the applications affected by this guidance, the underlying data, labeling for the proprietary Type C free-choice medicated feed, and VFD(s) to support the approved use are maintained under a VMF.

CVM intends to contact sponsors of affected proprietary free-choice medicated feeds maintained under a VMF when revisions to the labeling for the source Type A medicated article are submitted and approved. The sponsor of the NADA for the proprietary free-choice medicated feed and the VMF holder should work together to submit the appropriate submissions to revise the proprietary free-choice medicated feed labeling within the timeframes described in section VI.A.2 *Timeline Step 2* of this guidance.

Once a defined duration of use is established for the Type A medicated article used to manufacture the proprietary free-choice medicated feed and CVM has notified the VMF holder of these changes, the VMF holder should submit the appropriate labeling component(s) for the Type C proprietary free-choice medicated feed and copies of a revised VFD(s) reflecting the revised conditions of use to the VMF under a C submission.

The submission to the VMF should include a single, clean copy of each revised labeling component (i.e., color facsimile labeling) and a revised VFD. In addition to the changes described for Type A medicated articles in section VII.A. *Pioneer (NADA) Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles* of this guidance, VMF holders should also include any additional revisions that are needed to align the proprietary free-choice medicated feed labeling with the Type A medicated article labeling.

The VMF holder should then notify the sponsor of the Type A medicated article NADA that the C submission has been submitted to the VMF. The sponsor of the Type A medicated article NADA should then submit a non-fee prior-approval labeling supplement (C submission, NF subclass code, 180-day review time[42]) to the Type A medicated article NADA that references the VMF submission identifier and requests the approval of the labeling component(s) and VFD(s) that were submitted to the VMF.

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[41] Free-choice medicated feeds are Type C medicated feeds and are discussed further in GFI #13, "Evaluation of Effectiveness of New Animal Drugs for Use in Free-Choice Feeds-Medicated Block," (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-13-evaluation-effectiveness-new-animal-drugs-use-free-choice-feeds-medicated-block) (January 1985) and in GFI #23, "Medicated Free-Choice Feeds - Manufacturing Control," (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-23-medicated-free-choice-feeds-manufacturing-control) (July 1985).

[42] See footnote 24 on page 11 regarding review times.

Submissions should be addressed to CVM's Office of New Animal Product Evaluation, Division of Manufacturing Technologies.[43]

D. Marketing Exclusivity Considerations

The labeling approach to establishing defined durations of use recommended in this guidance would not qualify pioneer sponsors for marketing exclusivity upon approval because no safety or effectiveness information is needed for approval (see section VII.A.2.d. *Other Technical Sections* of this guidance). This will enable sponsors of impacted generic applications to immediately implement changes to align with the RLNAD product labeling.

However, CVM recognizes that in some cases pioneer sponsors may choose to submit safety or effectiveness data (or equivalent information) to be used for approval of a defined duration of use.[44] If safety or effectiveness data (or equivalent information) is used for the approval, this may qualify the sponsor for 3-year exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act.[45] The grant of exclusivity would prevent a generic sponsor from adding the RLNAD's newly-defined duration of use to their labeling until the end of the 3-year exclusivity period, that is, the generic product may continue to be marketed during the 3-year exclusivity period with no defined duration.

CVM strongly encourages pioneer sponsors who choose to rely on safety or effectiveness data to voluntarily waive their 3-year exclusivity in order to permit the submission and approval of a supplement from a generic sponsor containing the RLNAD's newly-defined duration of use. A waiver of this exclusivity would allow for the durations of use for affected generic products to be revised before the end of the 3-year exclusivity period, consistent with FDA's goal of establishing appropriately defined durations of use on a timely basis for all medically important antimicrobials that currently have undefined durations of use.

Sponsors who intend to waive their 3-year exclusivity should do so in writing, in their supplemental application.

The request for voluntary waiver should include the following language:

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[43] The Division of Manufacturing Technologies will internally reassign these submissions to the Division of Food Animal Drugs for review. VMF submissions are initially submitted to the Division of Manufacturing Technologies based on how eSubmitter is currently structured.

[44] The technical section requirements and administrative processes that may be involved in such an approach are outside of the scope of this guidance.

[45] Supplemental applications, as described in this guidance, submitted to add the defined duration of use to an NADA ADAA feed-use combination would not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because they would not contain the types of studies needed to qualify for 3-year exclusivity.

> "[Sponsor name] voluntarily waives its right to 3-year exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, in connection with the defined duration of use that is the subject of this supplemental application."

Pioneer sponsors who follow the labeling approach described in this guidance (i.e., one that does not involve submission of safety or effectiveness data) should not include the above language in their supplement because no exclusivity would apply.

VIII. Supplemental ANADAs (Generic Drugs)

Consistent with current practice, if the conditions of use for an NADA for a medically important antimicrobial drug are changed, the labeling for any approved ANADA(s) that references the original new animal drug application must be revised in a similar fashion.[46] CVM intends to work expeditiously with the sponsors of affected ANADAs to align their products with the revised conditions of use specified in the RLNAD (i.e., pioneer) applications. Sponsors of generic applications affected by this guidance must align their labeling with the revised labeling of the RLNAD to reflect a defined duration of use.[47] If approval of the RLNAD has been withdrawn, sponsors of generic applications should (1) define a duration of use; or (2) request voluntary withdrawal of the approval of the specific indication(s) with an undefined duration of use or the entire generic application as described in section IX. *Voluntary Withdrawal of Approval of a Regimen or an Indication with an Undefined Duration of Use from an NADA or Voluntary Withdrawal of the Entire (A)NADA* of this guidance. These options apply even if the affected ANADA is not currently marketed.

Consistent with section VII. *Supplemental NADAs (Pioneer Drugs)* of this guidance, this section of the guidance assumes that the currently approved dosage level administered to the animals (drug inclusion rate in feed, amount of drug per head or per unit body weight, etc.) and the formulation of the product are not changing. Additionally, this section assumes that the RLNAD sponsor either does not qualify for or waives any marketing exclusivity associated with the approval of the supplemental application establishing appropriately defined durations of use for the RLNAD. Sponsors of generic products affected by this guidance that do not meet these assumptions are encouraged to discuss their proposals with CVM in a presubmission conference.

A. Revising Conditions of Use through Conforming Labeling Changes

CVM intends to contact sponsors of affected ANADAs after a supplemental application to revise the labeling of the RLNAD has been received. Consistent with current practice, CVM recommends that the generic sponsor submit a supplemental application to come into alignment with the revised labeling of the RLNAD within 60 days after CVM notifies the generic sponsor that the approved conditions of use for the RLNAD have been or are being revised. In addition, any future generic sponsor that wants to use a pioneer drug as its RLNAD for which the labeling has been revised as recommended in

[46] See sections 512(c)(2)(A)(vii) and (n)(1)(F) of the FD&C Act (21 U.S.C. 360b(c)(2)(A)(vii) and (n)(1)(F)).

[47] Ibid.

this guidance must submit labeling that is the same as the labeling approved for the RLNAD, with a few, non-relevant, exceptions.

B. Administrative Recommendations and Submission Content

Sponsors of affected ANADAs should use eSubmitter to submit a prior-approval labeling supplement (C submission, "NF" subclass code, 270-day review time[48]) to the Office of Generic Animal Drugs and indicate that their supplemental application is being submitted as recommended by this guidance. Sponsors should not propose labeling changes in this supplement other than those made to the RLNAD labeling, except for any additional changes that may be required by the Agency. The submission should include:

- A single, clean copy of each affected labeling component (i.e., color facsimile or final printed labeling [electronic FPL, eFPL] for the Type A medicated article and representative [Blue Bird] Type B and Type C medicated feed labeling, as applicable) and a VFD(s) reflecting the revised conditions of use, revised as follows[49]:
    - Revised conditions of use to include a defined duration of use as described on the RLNAD labeling;
    - Any other labeling changes necessary to align with the revised RLNAD labeling;
    - If not previously implemented, addition of or revision to the "Approved by FDA under ANADA # XXX-XXX" statement, as required in section 502(w)(3) of the FD&C Act; and
    - Any other labeling changes previously required by the Agency that were not yet implemented.
- A claim of CE under 21 CFR 25.33(a), for an action that does not increase the use of the drug. Sponsors should not cite a subcategory of 21 CFR 25.33(a) [e.g., 21 CFR 25.33(a)(1)] for these actions. With the claim of CE, sponsors must[50] include a statement that, to their knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment as described in 21 CFR 25.21. Sponsors with questions or who are unable to provide this statement should contact CVM's Office of New Animal Product Evaluation, Division of Statistical and Biological Sciences, Environmental Branch.

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[48] See footnote 24 on page 11 regarding review times.

[49] With the exception of minor formatting or layout adjustments as appropriate to revise the conditions of use, revisions to the component version date or number, and other changes as described in this guidance, it is not recommended under the framework outlined in this guidance that sponsors propose other labeling changes in the context of this supplemental application. Rather, as previously noted, requests to approve other substantive changes should be submitted in a separate supplement.

[50] See 21 CFR 25.15(a).

- Other technical sections/information. Except in rare cases, CVM does not recommend that sponsors of generic applications include any other technical sections for approval in these labeling supplements.

C. Defining a Duration of Use if Approval of the RLNAD is Withdrawn

If approval of the RLNAD referenced by an affected generic application has been withdrawn, the generic sponsor(s) should follow the process recommended under section VII.A. *Pioneer (NADA) Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles* or section VII.B. *Pioneer (NADA) Feed-Use Combinations* of this guidance, as applicable.

IX. Voluntary Withdrawal of Approval of a Regimen or an Indication with an Undefined Duration of Use from an NADA or Voluntary Withdrawal of the Entire (A)NADA

Sponsors who choose to not establish an appropriately defined duration of use for the affected indication(s) on their product labeling should submit a request to either: (1) voluntarily withdraw the approval of their entire application without prejudice under 21 CFR 514.115(d); or (2) voluntarily withdraw the approval of the regimen(s) or indication(s) with an undefined duration of use from their approved application. Sponsors may contact CVM with any specific questions in advance of submitting such requests.

A. Withdrawing Approval of a Regimen or an Indication from an NADA

Requests to withdraw approval of one or more affected regimen(s) or indication(s) without withdrawing approval of the entire application should be submitted as a labeling supplement (C submission, NF subclass code, 180-day review time[51]) to CVM's Office of New Animal Product Evaluation, Division of Food Animal Drugs. The labeling supplement should include the following:

- The sponsor's request to withdraw approval of one or more specific regimen(s) or indication(s). The request should be worded as follows:

  "<Sponsor Name> voluntarily requests withdrawal of approval of those portions of NADA <###-###> pertaining to the following [regimen(s) or indication(s)]: [describe the specific regimen(s) or indication(s) being withdrawn]."

- A single, clean copy of each revised labeling component (i.e., color facsimile or final printed labeling [electronic FPL, eFPL] for the Type A medicated article, and representative [Blue Bird] Type B and Type C medicated feed labeling, as

[51] See footnote 24 on page 11 regarding review times.

applicable) and a revised VFD reflecting the withdrawn regimen(s) or indication(s).

- A claim of categorical exclusion (CE) under 21 CFR 25.33(a) for an action that does not increase the use of the drug. Sponsors should cite only one basis for CE. Sponsors should not claim a CE under 21 CFR 25.33(a)(1) for these actions. With the claim of CE, the sponsor must[52] provide a statement that, to their knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment as described in 21 CFR 25.21.

- If applicable, written permission for CVM to contact any sponsors of affected feed-use combinations, proprietary free-choice medicated feeds, and affected generic copies to discuss changes to the pioneer application in advance of approval of the supplement. For example:

  "[Sponsor] gives permission for CVM to contact sponsors of any affected feed-use combinations, proprietary free-choice medicated feeds, and affected generic copies of this drug to discuss changes being made to this drug's labeling, in advance of FDA's approval of this labeling supplement."

B. Withdrawing Approval of an Entire Application

Requests to withdraw approval of the entire application should be submitted to CVM's Office of Surveillance and Compliance, Division of Pharmacovigilance and Surveillance, Marketed Product Information Branch, and should include the following:

- The sponsor's written request to voluntarily withdraw the approval of their entire application without prejudice under 21 CFR 514.115(d).

- The sponsor's acknowledgement that their written request shall be construed as a waiver of the sponsor's opportunity for a hearing in relation to the withdrawal of approval.[53]

- If applicable, written permission for CVM to contact any sponsors of affected generic copies of the drug in advance of publication of notice of the withdrawal of approval in the Federal Register (FR). The sponsor should use the following language for this request:

  "[Sponsor] grants CVM permission to contact the sponsor(s) of affected generic copies (if applicable) in advance of Federal Register (FR) publication."

[52] See 21 CFR 25.15(a).

[53] See 21 CFR 514.115(d).

- A claim of CE from the requirement to prepare an EA or an EIS, pursuant to 21 CFR 25.33(g), for withdrawal of approval of an NADA or an ANADA or removal of a new animal drug from the index. Other citations should not be used. With this claim of CE, sponsors must[54] also include a statement that, to their knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment as discussed under 21 CFR 25.21. Sponsors with questions or who are unable to provide this statement should, before submitting their request to voluntarily withdraw approval of the application, contact CVM's Office of New Animal Product Evaluation, Division of Statistical and Biological Sciences, Environmental Branch.

X. Glossary

The following terms used in this document are defined for the purposes of this guidance only. See the text of the guidance for complete explanation of and context for these terms.

Term	Definition for Use in This Guidance
Affected products / affected applications	Products / applications that appear on FDA's public list of medically important antimicrobial drugs administered in the feed of food-producing animals, that currently have one or more approved indications with an undefined duration of use.
Appropriately defined duration of use	The information regarding duration of feeding on the labeling ensures that the drug is used only when animals need it and provides the veterinarian appropriate flexibility to use the drug consistent with the labeling in a range of scenarios that may be encountered in practice.
C submission	CVM's STARS [see definition] code for a supplemental application to an NADA or ANADA.
Control (use)	The drug is administered to a group of animals once a proportion [see definition] of the animals in the group have been diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.

[54] See 21 CFR 25.15(a).

Term	Definition for Use in This Guidance
Downstream application / file type	Application or file that relies on and conforms to the conditions of use established for the application(s) that it references. For purposes of this guidance, downstream applications are ANADA Type A medicated articles, NADA ADAA feed-use combinations, ANADA feed-use combinations, and proprietary medicated feeds maintained in a Veterinary Master File.
Feed-use combination	A feed-use combination is an approved use of two or more active pharmaceutical ingredients or Type A medicated articles to create a complete medicated animal feed.
Free-choice medicated feeds	Free-choice medicated feeds are those products which contain one or more animal drugs and are placed in feeding and grazing areas but are not intended to be fully consumed at a single feeding or to constitute the entire diet of the animal.
G submission	CVM's STARS [see definition] code for a general correspondence submission to an application file.
Maximum permitted duration of use	The duration of use stated in the labeling that cannot be exceeded for a single course of therapy authorized by a veterinarian. The maximum permitted duration is not intended to be routinely authorized.
Medically important antimicrobial drugs	Antimicrobial drugs important to human medicine. Appendix A of GFI #152 indicates which antimicrobial drugs/drug classes FDA considers "medically important" for purposes of its strategy to promote the judicious use of antimicrobial drugs in animals.
Pioneer products	NADA single-ingredient and fixed-ratio combination Type A medicated articles, and NADA feed-use combinations that are approved under section 512(d)(1)) of the FD&C Act.

Term	Definition for Use in This Guidance
Prevention (use)	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.
Proportion	A percentage of animals in a group that is greater than 0% and less than 100%, unless otherwise specified on the labeling.
STARS	CVM's Submission Tracking and Reporting System.
Top-level application	Application that may serve as a reference or component for one or more downstream applications or files [see definition]. For purposes of this guidance, top-level applications are NADA Type A medicated articles (including fixed-ratio combination Type A medicated articles) and NADA non-ADAA feed-use combinations.
Treatment (use)	The drug is administered only to animals diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.
Typical duration range	The approximate duration range that the veterinarian should first consider when determining the actual duration to authorize in accordance with the labeled directions for use.
Undefined duration of use	The labeling for the identified product includes no information regarding duration of feeding or otherwise does not provide an appropriately targeted duration of use.