

# Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed: A Concept Paper

## I. Introduction

This concept paper is focused on approved new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs) containing antimicrobial drugs important to human medicine (“medically important antimicrobial drugs” as discussed further in section [III. Scope](#) below) for use in or on the medicated feed of food-producing animals that are currently approved with one or more indications that have an undefined duration of use. The purpose of this concept paper is to obtain early input from the public on a potential framework for how sponsors could voluntarily change the approved conditions of use to establish appropriately defined durations of use for such products where none currently exist. The potential framework outlined in this concept paper, if it were later to be adopted through guidance, would help to ensure all medically important antimicrobial new animal drugs are administered in alignment with the principles of judicious use.<sup>1</sup> Establishing appropriately targeted durations of use to mitigate the development of antimicrobial resistance would be consistent with previous efforts by FDA to protect public health by promoting the judicious use of medically important antimicrobial drugs in animals.

*Disclaimer:* This concept paper is for discussion purposes only. The intent of this concept paper is to obtain public comment and early input on a potential framework for how sponsors could voluntarily change the approved conditions of use for medically important antimicrobial drugs used in or on the medicated feed of food-producing animals to establish appropriately defined durations of use where none currently exist. This concept paper does not contain recommendations and does not constitute draft or final guidance by the Food and Drug Administration. It should not be used for any purpose other than to facilitate public comment. FDA intends to consider all comments received on this concept paper before issuing draft guidance for additional comment.

## 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.”<sup>2</sup> In GFI #209, FDA stated that the

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<sup>1</sup> Please see FDA CVM Webpage, “Judicious Use of Antimicrobials,” <https://www.fda.gov/animal-veterinary/antimicrobial-resistance/judicious-use-antimicrobials>. (Content current as of 4/30/2020)

<sup>2</sup> <https://www.fda.gov/media/79140/download>

development of resistance to medically important antimicrobial drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. To further address 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 animals:

- (1) Limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health (i.e., to treat, control, and prevent disease), and
- (2) Limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation.

In December 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."<sup>3</sup> 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 worked with FDA to voluntarily withdraw approval of indications that were not considered necessary for assuring animal health (production indications), and voluntarily changed 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.<sup>4</sup>

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. In a notice published in the *Federal Register* (81 FR 63187),<sup>5</sup> the Agency requested information from the public about how to establish appropriately targeted durations of use for therapeutic products affected by GFI #213 with no defined duration of use. Feedback received in response to that request for information was taken into consideration during development of this concept paper.

On September 14, 2018, FDA released a five-year action plan for supporting antimicrobial stewardship in veterinary settings.<sup>6</sup> 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,<sup>7</sup> 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

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<sup>3</sup> <https://www.fda.gov/media/83488/download>

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

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

<sup>6</sup> FDA's five-year plan is entitled "Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023." (<https://www.fda.gov/media/115776/download>)

<sup>7</sup> <https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance>

diseases. Action item 1.1.2 included in this plan is to “ensure that all medically important antimicrobial drugs used in or on the feed or drinking water of food-producing animals have an appropriately defined duration of use.”<sup>8</sup>

Starting in 2019, CVM began offering multiple funding opportunities<sup>9</sup> to support the conduct of studies that are intended to generate data to help establish targeted durations of use for certain medically important antimicrobial drugs approved for use in the feed of food-producing animals. This funding is intended to provide publicly available data that may be used by sponsor(s) of affected approved new animal drugs to help support revisions to the conditions of use for products consistent with the objectives outlined in this concept paper.

### III. Scope

The scope of this concept paper encompasses all medically important antimicrobial drugs that are approved 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 concept paper, an “undefined duration of use” means that the labeling for the identified product includes no information regarding duration of administration or otherwise does not provide an appropriately targeted duration of use. The scope of this concept paper is limited to those drugs that are approved for use in or on medicated feed because all the approved uses of medically important antimicrobial drugs in other (non-feed) dosage forms already have appropriately defined durations of use.<sup>10</sup> FDA has made public on its website a listing of all medically important antimicrobial drugs that currently have undefined durations of use.<sup>11</sup> FDA intends for all drugs that appear in this listing, hereinafter referred to as “affected products,” to be included within the scope of this concept paper.

Published in October 2003, GFI #152, “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern,”<sup>12</sup> contains an appendix (Appendix A) in which FDA ranked antimicrobial drugs according to their relative importance to human medicine. FDA has indicated that it considers all antimicrobial drug classes

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<sup>8</sup> See Action 1.1.2 on page 7 of FDA’s five-year action plan.

<sup>9</sup> <https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-2020-funding-opportunity-help-define-durations-use-certain-medically-important>

<sup>10</sup> Although FDA’s five-year action plan 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.

<sup>11</sup> <https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/list-approved-medically-important-antimicrobial-drugs-administered-feed-food-producing-animals-lack>

<sup>12</sup> <https://www.fda.gov/media/69949/download>

listed in Appendix A of GFI #152 to be “medically important” for purposes of its strategy to promote the judicious use of antimicrobial drugs in animals.<sup>13</sup>

FDA recognizes that the list of medically important antimicrobial drugs in Appendix A is not static and has previously stated its intent to periodically reassess this list consistent with contemporary science and current human clinical practices.<sup>14</sup> Therefore, the antimicrobial products within the scope of this concept paper may change in the future if FDA revises the list of antimicrobial drugs that are considered medically important.

#### **IV. Objective**

FDA’s objective in issuing this concept paper is to outline for animal drug sponsors and other stakeholders a potential framework for how to voluntarily revise the product use conditions (e.g., dosage regimen, instructions for use, etc.), 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 possible revisions, if effectuated through the issuance of guidance, are intended to provide for the continued effective use of these products while minimizing the extent of antimicrobial drug exposure. The expectation is that optimizing dosage regimens in this manner would help reduce risks of antimicrobial resistance development. Defining appropriately targeted durations of use for the affected applications would support the FDA’s ongoing efforts to slow the development of antimicrobial resistance by fostering the judicious use of medically important antimicrobial drugs in animals.

This concept paper is intended to share, for the purpose of generating discussion and obtaining early input from the public, specific points to consider on how sponsors could potentially facilitate voluntary changes to the approved conditions of use of affected products in support of ongoing efforts to slow the development of antimicrobial resistance. While FDA recognizes that individual affected products may need to be considered on a case-by-case basis, potential revisions to product use conditions (as reflected through revisions to the approved labeling) might generally 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 administration to animals in a manner consistent with the principles of judicious use.

##### **A. Appropriately defining the duration of use**

For affected products that currently lack a defined duration of use for one or more indications in animals, the labeling would be revised to include appropriate criteria regarding when to stop administration of the antimicrobial drug. As discussed in more detail in section [VII. Supplemental New Animal Drug Applications \(NADAs, Pioneer Drugs\)](#) of this concept paper, the maximum duration of use would potentially be defined in terms of time, animal age, animal body weight, or be based on observed resolution of

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<sup>13</sup> See page 5 of GFI #213.

<sup>14</sup> See Action 1.3.1 on page 9 FDA’s five-year action plan.

disease signs in the affected animals or other factors as determined by the veterinarian, depending upon the indicated disease and animal species/class.

Under the potential framework outlined in this concept paper, instructions such as “feed until market weight” would not be considered to be an appropriately defined duration of use. Likewise, instructions to stop administration by a certain age when that age equals or exceeds the typical slaughter age of that species and class, would not be considered to be an appropriately defined duration of use. In addition, a slaughter withdrawal period on the labeling would not be considered to appropriately define the duration of use.

## **B. Providing additional information for the veterinarian**

In revising the approved labeling for the affected products to provide appropriately defined durations of use, it may be appropriate to take into consideration that these products, which were originally approved for over-the-counter (OTC) availability, are now marketed as veterinary feed directive (VFD) products that require the oversight of a licensed veterinarian.<sup>15</sup> Because of the change in marketing status of these products from OTC to VFD, it might be appropriate in some cases to revise the approved product labeling to include additional information intended to assist the veterinarian in determining when drug administration should be initiated or stopped in accordance with the approved labeling and consistent with the principles of judicious use of antimicrobials. Such information would potentially vary depending on the specific indication of use in question, including whether the indication is for disease treatment, control, or prevention.

For the purposes of this concept paper, 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 label 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 diagnosing the specific bacterial disease indicated on the approved labeling in the animals and 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:

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<sup>15</sup> In January 2017, FDA completed implementation of GFI #213. This process transitioned medically important antimicrobial drugs used in the feed or drinking water of food-producing animals from over-the-counter status to VFD or prescription status requiring veterinary oversight and eliminated production uses (e.g., growth promotion). (<https://wayback.archive-it.org/7993/20190423131636/https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm>)

- 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 of the animals in the group have been diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.

Relevant label 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 diagnosing the specific bacterial disease indicated on the approved labeling in a proportion of the animals in the group, and to 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 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 Label Information: The veterinarian's decision to use a medically important antimicrobial drug approved for prevention purposes (including prevention-like purposes such as for reduction of incidence) in a judicious manner ordinarily includes consideration of factors relevant to determining the risk of the specific disease indicated on the approved labeling occurring in the animals, and to 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 include:

- Environmental risk factors for the indicated disease (e.g., related to temperature, ventilation)
- 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 a voluntary approach is the most effective and efficient means to achieve the common goal of judicious use of medically important antimicrobial drugs in animals. In the potential framework outlined in this concept paper, FDA would work with affected drug sponsors to help them voluntarily revise the use conditions for those product indications that are currently approved with an undefined duration of use.

## VI. Potential Timelines for Voluntarily Implementing Changes

This section describes the timelines that would potentially apply if the framework described in this concept paper were ultimately to be adopted through Agency guidance.

### A. A Potential Timeline for Sponsors Defining a Duration of Use with Data or Other Information Supporting Substantial Evidence of Effectiveness

The process of establishing appropriately defined durations of use is expected to involve the review of data or other information supporting effectiveness at the new, shortest duration of use proposed for the labeling, as discussed in section [VII.A.1. Effectiveness](#) below. CVM would use available evidence to the extent possible. In cases where such evidence does not already exist in the application file, new data or information may need to be collected (e.g., a new study or studies may need to be conducted) to complete the Effectiveness technical section in accordance with 21 CFR 514.1(b)(8). Because of this, and due to the uncertainties associated with addressing the scientific data gaps that may exist for certain applications, under this potential framework FDA believes that a multi-phase strategy would help, as outlined below:

**Phase 1 (Assessment/Project Planning):** In this potential framework, FDA would work with the drug sponsors during the first year to assess existing data and information used to support the original approval of the affected indications and consider what additional data or information may be needed. Within this 1-year period, FDA would expect that project planning and development discussions (i.e., presubmission conferences) would be held, as necessary, to formulate plans for affected products.

**Phase 2 (Project Completion/Data Review):** Within the next 3 to 5 years, sponsors would be able to progress toward approval of revisions to the conditions of use for their affected products consistent with the objective of this concept paper. FDA would work with affected sponsors to determine the appropriate project timeline for specific drug applications based on the extent to which additional data is needed to address relevant scientific questions. Shorter project timelines may be appropriate in cases where existing data are available to support product revisions. Conversely,

extended project timelines may be appropriate in cases where new effectiveness data needs to be generated or other scientific data gaps need to be addressed regarding the indicated disease in question.

**B. A Potential Timeline for Sponsors Making Conforming Labeling Changes to Combination and Proprietary Free-Choice Medicated Feeds and Generic Products**

In this potential framework, the labeling for pioneer Animal Drug Availability Act of 1996 (ADAA) combination medicated feeds and proprietary free-choice medicated feed labeling maintained under a veterinary master file (VMF) would be revised to align with the changes made to the labeling for each individually approved Type A medicated article affected by this concept paper and included in the ADAA medicated feed combination or proprietary free-choice medicated feed. Likewise, the labeling for abbreviated new animal drug applications (ANADAs) would align with the revisions made to the reference listed new animal drug (RLNAD). In this potential framework, sponsors of affected products fitting these categories would submit a supplement or request a presubmission conference within 60 days following notification by CVM of the revisions needed for the individually approved Type A medicated article(s) or RLNAD. Under the potential framework, FDA would request that applications to align with approved changes to the individually approved Type A medicated article(s) or RLNAD be submitted within 1 year following notification by CVM.

**C. A Potential Timeline for Sponsors Choosing to Voluntarily Withdraw the Approval of an Indication or the Approval of an Entire Application**

In this potential framework, if sponsors intend to voluntarily withdraw the approval of an indication or an entire application, rather than submit data or other information to define a duration of use, FDA would request that they initiate the withdrawal process as described in section [IX. Voluntary Withdrawal of Approval of an Indication with an Undefined Duration of Use or the Entire \(A\)NADA](#) of this document, within 1 year of the completion of Phase 1.

## **VII. Supplemental New Animal Drug Applications (NADAs, Pioneer Drugs)**

This section of the concept paper describes ways sponsors could potentially meet the information requirements in FDA's regulations at 21 CFR part 514 associated with the technical sections that would need to be addressed to support approval of their supplemental applications.<sup>16</sup> (See 21 CFR 514.1(b) and 514.8(a)(1)). In addition, this section describes administrative processes and

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<sup>16</sup> As is the case with original applications for approval of new animal drugs (e.g., NADAs), supplemental new animal drug applications also must include various technical sections in accordance with FDA's regulations at sections 21 CFR 514.1(b) and 514.8(a)(1), which are: effectiveness; target animal safety; human food safety (if the drug is intended for use in food-producing species); chemistry, manufacturing, and controls; environmental impact; labeling; and all other information (AOI). For additional information, see also GFI #132, "Administrative Applications and the Phased Review Process," <https://www.fda.gov/media/70029/download>.

marketing exclusivity considerations that also should be taken into account within this potential framework. The following potential procedures are intended to provide sufficient information to support approval of a supplemental application to establish an appropriately defined duration of use. In this framework, CVM also would consider other scientifically- and legally-appropriate alternatives that sponsors may propose.

The potential procedures in this section are intended to apply to situations where the only substantive change to the approval would be defining previously undefined durations of use and no new indications or other substantive changes to the application would be proposed.<sup>17</sup> Increasing or decreasing the dosage level, changing the product formulation, or making other substantive changes is likely to involve information or data to address other technical sections beyond those described in this concept paper. These potential procedures also assume that the currently-approved dosage level administered to target animals (drug inclusion rate in feed, amount of drug per head or per unit body weight, etc.) and the formulation of the product would not be changing.

#### **A. Pioneer Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles**

##### **Potential Procedures for Technical Section Requirements**

###### **1. Effectiveness**

In this potential framework, for each undefined duration of use, sponsors would provide a science-based justification (e.g., white paper) for the proposed revised conditions of use. Sponsors would justify the proposed duration, regardless of whether a range or a single point would be proposed for the duration of use.

In addition, when necessary, sponsors would provide substantial evidence to demonstrate that the proposed revised conditions of use are effective for the indication. The definition of and requirements for substantial evidence of effectiveness are described in this Agency's regulations at 21 CFR 514.4. Notably, substantial evidence of effectiveness to support dose range labeling for therapeutic indications would consist of information demonstrating that the new animal drug will be effective for the intended use "at the lowest dose" in the proposed labeling for that intended use [21 CFR 514.4(b)(2)(i)]. The "lowest dose" is commonly understood to mean "lowest exposure" and includes considerations of both the lowest dosage level (or drug inclusion rate in feed) and the shortest duration for which the drug may be administered.

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<sup>17</sup> In this potential framework, 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 document) would be encouraged to do so under a separate supplemental application, submitted to be approved after approval of the defined duration(s) of use, that includes all applicable technical sections following established procedures. These procedures are described elsewhere and are beyond the scope of this concept paper. Sponsors choosing to pursue all labeling changes at a single future printing would be able to submit the subsequent supplemental application at any time (e.g., immediately) after the supplemental application for approval of the defined duration of use is submitted.

Establishing a defined duration of use where the currently-approved duration is completely undefined means, in part, that the revised labeling would typically need to describe a duration that is inherently shorter than that which is currently approved for use. When a duration range is proposed for a therapeutic indication, the regulation does not require substantial evidence of effectiveness to be demonstrated for the maximum duration in the range. However, consistent with the principles of judicious use, the maximum duration in a range would be consistent with available safety evidence and would be scientifically supportable with respect to the characteristics of the drug and the disease risk periods, pathogenesis, progress, and expected outcomes.

Accordingly, within this potential framework, the Effectiveness technical section for each affected indication would consist of the sponsor's proposed revisions to the conditions of use, their justification that the proposed new conditions of use are appropriately targeted to the indicated disease, and substantial evidence of effectiveness when necessary, as further discussed below:

- a. The sponsor would propose revisions to the conditions of use and appropriate justification for them. In most cases, sponsors could support the proposed revisions with a science-based justification (e.g., white paper) showing that the new conditions of use are appropriately targeted to the indicated disease.
  - (1) Depending on the indicated disease and animal species and class, it may be appropriate to define the duration of use in terms of time, animal age, animal body weight, or, observed resolution of disease signs in the affected animals as diagnosed by the veterinarian. If time, age, or body weight is used, it would be expected that the value generally would be significantly less than the animals' typical production lifespan and slaughter weight, unless otherwise justified. For durations of use that are not defined in terms of time or other clear criteria (e.g., if the duration of use is defined in terms of observed resolution of clinical signs), the labeling would include language that would clearly state that the veterinarian is to determine when (or under what circumstances) to stop administration of the drug.
  - (2) Sponsors may choose to propose and justify several regimen durations to account for different administration scenarios that may be encountered in practice. 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 period or other factors associated with an indicated disease. Such scenarios would be described as part of the justification, along with proposed label language, as needed, to clarify when each regimen duration would apply.
  - (3) The justification would provide a balanced assessment of all available information relevant to the proposed duration of use (it would consider the range of available information supporting the proposed duration as well as any alternatives), would be based on the pathophysiology of and risk factors

for the indicated disease, and would consider the characteristics of the drug (pharmacokinetics, pharmacodynamics, and other factors associated with the onset and duration of action of the drug). Scientific literature, other publicly available scientific information, expert opinions, and existing data could be used as appropriate for this justification.

- (4) No justification would be needed if the currently approved labeling already describes a minimum duration and the sponsor proposed to revise the approved conditions of use to be equal to that duration (e.g., revise “feed for at least 5 days” to read “feed for 5 days”). However, sponsors would need to provide justification if they proposed a duration range using the currently approved minimum duration as the shortest duration in the range, including if their proposal was to include label instructions that provide for extending the duration of use at the discretion of the authorizing veterinarian.
- b. As necessary, sponsors would submit appropriate scientific data and information to support the proposed changes to the product conditions of use, consistent with the requirements for substantial evidence of effectiveness.
- (1) Sponsors would first consider using publicly available or other existing scientific data and information to the extent possible. In some cases, the final reports for studies conducted for the original approval of the indication may have duration information that may be relevant to establishing an updated duration on the label.
  - (2) A new study might need to be conducted to provide all or part of substantial evidence (i.e., if public or existing data was not available or to fill information gaps after existing information was considered).
  - (3) Effectiveness data from studies conducted outside North America may be considered if sponsors would be able to demonstrate that the results are relevant to the use of the drug in the U.S. Some factors considered would include similarities and differences in animal breeds, husbandry, and management, as well as the sensitivity and virulence of the pathogen(s) encountered in the study compared to recent North American isolates.
  - (4) No additional effectiveness information would be needed if the currently approved labeling already describes a minimum duration of use (e.g., “feed for at least 5 days”) and the sponsor proposed to revise the duration to be equal to that duration (e.g., revise “feed for at least 5 days” to read “feed for 5 days”), or if they proposed a duration range, using that duration as the shortest duration in the range.
- c. If appropriate, proposed informational text would be included on the labeling, supported by literature and other information, to assist the veterinarian in making appropriate decisions regarding judicious use of the drug for mitigation of the indicated disease. Such information may include factors to consider

regarding when to start the regimen, known risk factors for the disease, or considerations for selecting a specific duration of use from within an approved range.

- d. All further information related to the effectiveness of the drug for the indication in question that was not previously submitted to CVM.<sup>18</sup>

## **2. Target Animal Safety, Human Food Safety, and Chemistry, Manufacturing, and Controls**

In this potential framework, it would generally not be necessary for sponsors to provide additional information relevant to target animal safety, human food safety, or chemistry, manufacturing, and controls. However, sponsors would be encouraged to confirm with CVM that this is appropriate in the context of the changes being proposed for a given affected new animal drug application.

## **3. Environmental Impact**

Because the sole objective of this concept paper is to define the previously undefined duration(s) of use for the affected products, it would not be expected to result in an increase in use of the originally approved drug. Therefore, a claim of categorical exclusion (CE) in a supplemental application to establish a defined duration of use would generally be submitted under 21 CFR 25.33(a) for an action that does not increase the use of the drug. However, only one basis for CE would be cited. It would not be expected that CEs would be claimed under 21 CFR 25.33(a)(1) for these actions.

With the claim of CE, the sponsor would need to certify 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. See 21 CFR 25.15(a).

## **4. Labeling**

In this potential framework, sponsors would 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 order(s) reflecting the revised conditions of use.

The revised labeling would include, as applicable:

- The newly defined duration of use for each affected regimen, and any other language developed during review of other technical sections, such as information that may be needed for the veterinarian to understand how long the

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<sup>18</sup> See CVM Program Policy and Procedures (P&P) Manual 1243.4085, "All Other Information," <https://www.fda.gov/media/80867/download>.

drug may or must be administered in different use situations, risk-mitigating text, or additional information to assist the veterinarian in making administration decisions that are consistent with the principles of judicious use.

- Information that would support the principles of judicious use and minimize the development and spread of antimicrobial resistance. Examples of statements that may address this concern would include, but are not limited to:
  - “Do not follow this use of [DRUG] with another period of use of an antimicrobial of the same drug class – consider using a drug from a different class if available.”
  - “Do not administer this drug following prior use of another antimicrobial from the same drug class in the same group of animals”
  - “After X days treatment, if animals do not show signs of improvement, the veterinarian should evaluate the health status of the treated animals and determine the need for an additional period of antimicrobial treatment or a change in treatment.”
  - “Administer this drug in feed only to the number of animals necessary to treat, prevent or control the diagnosed disease.”
- Any other labeling changes previously directed by the Agency that were not yet implemented (e.g., storage statement updates).

In addition, sponsors would be encouraged to take the opportunity to make the following additional revisions to the labeling, as applicable:

- Revise the directions for use to replace “feed continuously” (or similar wording) with “feed as the sole ration,” to more accurately describe the feeding pattern intended by this direction and to reduce the chance for inadvertent misunderstanding regarding the approved duration of use. For example, if the directions for use currently state, “Feed continuously for X to Y days,” an appropriate revision would be, “Feed as the sole ration for X to Y days.”
- Revise or add the “Approved by FDA under NADA # XXX-XXX” statement, as required in section 502(w)(3) of the FD&C Act.<sup>19,20</sup>

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<sup>19</sup> 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.

<sup>20</sup> It is expected that it would be implemented as described on FDA’s Resources for Industry webpage, “‘Approved by FDA’ Labeling Statement for Approved New Animal Drugs recommendations,” <https://www.fda.gov/animal-veterinary/resources-you/approved-fda-labeling-statement-approved-new-animal-drugs>.

## 5. All Other Information (AOI)

In this potential framework, sponsors would submit AOI that was not previously submitted to CVM, related to the safety and effectiveness of the drug for the proposed conditions of use, or a statement that there was no other information.<sup>21</sup>

## 6. Freedom of Information (FOI) Summary

CVM would be responsible for preparing the FOI Summary. Sponsors would be encouraged to provide proposed draft FOI Summary language for CVM's consideration.

### B. Pioneer Feed-Use Combinations

A feed-use combination is an approved use of two or more active pharmaceutical ingredients or Type A medicated articles intended to be used in the creation of a complete medicated animal feed. There are three different types of pioneer feed-use combinations: fixed-ratio combination Type A medicated articles, ADAA feed-use combinations, and non-ADAA feed-use combinations. 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 Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles](#) of this concept paper. Both ADAA feed-use combinations and 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 combination of new animal drugs in a Type C medicated animal feed. ADAA feed-use combinations and non-ADAA feed-use combinations differ in the way they meet approval requirements. 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) (generally referred to as the "ADAA combination requirements") are approved using modified requirements for establishing safety and effectiveness.<sup>22</sup> 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. Non-ADAA feed-use combinations are combinations that were approved before the enactment of ADAA

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<sup>21</sup> See CVM Program P&P Manual 1243.4085

<sup>22</sup> It seems unlikely that the ADAA feed-use combination applications identified in this concept paper would require additional safety or effectiveness information in order to appropriately define a duration of use. We note, however, that there could be situations where additional safety or effectiveness information may be needed to support approval of an ADAA feed-use combination. Such information would supplement the safety or effectiveness information available in the individually approved Type A medicated article applications and would be required if any of the conditions identified in sections 512(d)(4)(B)(i)-(ii) or (D)(i)-(iv) of the FD&C Act were implicated (e.g., a combination of Type A medicated articles with overlapping indications may require additional effectiveness information).

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.

## 1. ADAA Feed-Use Combinations

In this potential framework, pioneer feed-use combinations that were originally approved using the modified requirements offered by ADAA would submit a supplemental application using the same modified requirements. When using this pathway to supplement an existing ADAA feed-use combination approval, it would be important for sponsors of such drugs to first ensure that revisions to each individually approved Type A medicated article affected by this concept paper and included in the combination were approved before they would submit a supplemental application (see section 512(d)(4) of the FD&C Act).

### **Potential Procedures for Technical Section Requirements for ADAA Feed-Use Combinations**

In this potential framework, when applicable, sponsors would 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 would be referenced by the principal submission identification number and submission date.

#### **a. Effectiveness**

Section 512(d)(4)(D) of the FD&C Act allows drugs intended to be fed in combination in or on medicated feed to be approved without additional demonstration of their effectiveness when the drugs intended for use in the combination have previously been separately approved for the uses and conditions of use for which they are intended for use in the combination and the following conditions are met:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness;
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population; and
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

In such cases, the FD&C Act provides that the ADAA feed-use combination's effectiveness is adequately demonstrated by referencing the new animal drug applications for each of the individually approved Type A medicated articles contained in the combination.

As part of the supplemental application, the sponsor would reference the individually approved NADAs for each of the Type A medicated articles included in the feed-use combination and confirm that the above conditions continue to be met.

**b. Target Animal Safety, Human Food Safety, and Chemistry, Manufacturing, and Controls**

In this potential framework, it generally would not be necessary for sponsors to provide additional information relevant to target animal safety, human food safety, or chemistry, manufacturing, and controls. However, sponsors would be encouraged to confirm with CVM that this is appropriate in the context of the changes being proposed for a given affected new animal drug application.

**c. Environmental Impact**

In this potential framework, a claim of CE under 21 CFR 25.33(a), for an action that does not increase the use of the drug, would be submitted. For example, a claim of CE under 21 CFR 25.33(a)(2), for a combination of previously approved animal drugs, would be applicable for the action. However, only one basis for CE would be cited. It would not be expected that CEs would be claimed under 21 CFR 25.33(a)(1) for these actions.

With the claim of CE, the sponsor would be required to certify 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. See 21 CFR 25.15(a).

**d. Labeling**

In this potential framework, sponsors would 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 order(s) reflecting the revised conditions of use. In addition to the changes described for Type A medicated articles in section [VII.A.6. Labeling](#) of this concept paper, sponsors would also include any additional revisions that would be needed to align the combination labeling with the Type A medicated article labeling for each drug in the combination.

**e. All Other Information**

In this potential framework, sponsors would submit AOI that was not previously submitted to CVM, related to the safety and effectiveness of the drug combination for the proposed conditions of use, or a statement that there was no other information.

#### f. FOI Summary

CVM would prepare the FOI Summary for approval. Sponsors would be encouraged, but not required, to provide proposed draft FOI Summary language for CVM's consideration.

### 2. Non-ADAA Feed-Use Combinations

In this potential framework, sponsors would approach the addition of a defined duration of use to a non-ADAA feed-use combination<sup>23</sup> in one of two ways.

- a. Sponsors would submit a supplemental application that addressed each of the technical sections as described in section [VII.A. Supplemental New Animal Drug Applications \(NADAs, Pioneer Drugs\)](#) of this concept paper.

When applicable, sponsors would 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 would be referenced by the principal submission identification number and submission date.

- b. Alternatively, if the combination is expected to meet the requirements for an ADAA feed-use combination, a sponsor could choose to voluntarily withdraw the current approval (discussed in section [IX. Voluntary Withdrawal of Approval of an Indication with an Undefined Duration of Use or the Entire \(A\)NADA](#) of this document) of the non-ADAA feed-use combination and resubmit the combination for approval under a new NADA as a "replacement" ADAA feed-use combination. If a sponsor were to choose this pathway, before submitting the request to voluntarily withdraw the current approval, the sponsor would be encouraged to contact CVM to discuss the appropriate pathway for maintaining information from the administrative file and to determine the appropriate steps for submission of the new "replacement" ADAA feed-use combination.

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

Free-choice medicated feeds<sup>24</sup> 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. In some

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<sup>23</sup> Pioneer feed-use combinations that were originally approved as a non-ADAA feed-use combination would not be eligible for the use of the modified requirements offered by section 512(d)(4) when submitting a supplemental application.

<sup>24</sup> Free-choice medicated feeds are discussed further in GFI #13, "Evaluation 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>) and in GFI #23, "Medicated Free-Choice Feeds - Manufacturing and Control" (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-23-medicated-free-choice-feeds-manufacturing-control>)

cases, a publicly available free-choice medicated feed formulation (i.e., published in the Code of Federal Regulations upon approval) is manufactured to include a proprietary mix of ingredients, creating a proprietary free-choice medicated feed. The approval of a proprietary free-choice medicated feed formulation is completed under an NADA submitted under section 512 of the FD&C Act; however, the underlying data, labeling for the proprietary Type C free-choice medicated feed, and VFD order(s) to support the approved use are maintained under a VMF.

In this potential framework, CVM would contact sponsors of affected proprietary free-choice medicated feeds maintained under a VMF when revisions to the labeling for the publicly available free choice medicated feed formulation were submitted and approved. CVM would expect that the sponsor of the NADA for the proprietary free-choice medicated feed and the VMF holder would work together to submit the appropriate submissions (as described in section [VII.D. Administrative Processes for Appropriately Establishing Defined Durations of Use](#) below) to revise the proprietary free choice medicated feed labeling within 60 days after CVM notifies the VMF holder that the revisions to the labeling for the publicly available free-choice medicated feed formulation were approved.

The submission to the VMF would include:

- A request to revise the labeling of the proprietary free-choice medicated feed under a supplement to the appropriate NADA.
- A single, clean copy of each revised labeling component (e.g., color facsimile labeling) and a revised VFD order. In addition to the changes described for Type A medicated articles in section [VII.A. Pioneer Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles](#) of this document, VMF holders would also include any additional revisions that would be needed to align the proprietary free-choice medicated feed labeling with the Type A medicated article labeling.

## **D. Administrative Processes for Appropriately Establishing Defined Durations of Use**

### **1. Type A Medicated Articles and Medicated Feed-Use Combinations**

In this potential framework, sponsors would follow established procedures<sup>25</sup> for submission of information to complete the applicable technical sections. CVM would encourage sponsors to first request a presubmission conference to propose and agree on the requirements for completing each technical section, and then use the phased-review process to obtain appropriate technical section complete letters under the applicable Investigational New Animal Drug (INAD) file before submitting an administrative supplemental application to the NADA for approval. However, use of the phased-review process would not be required.

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<sup>25</sup> Discussed in GFI #132, "Administrative Applications and the Phased Review Process."

All applicable technical sections would be expected to be appropriately addressed in the supplemental application. Supplemental applications for Type A medicated articles and medicated feed-use combinations that contain safety or effectiveness data or other information would be submitted as major supplemental applications (STARS “C” submission, “B1” subclass code).<sup>26</sup>

Sponsors of pioneer applications would also include the following information in the supplemental application:

- Written permission for CVM to contact, as applicable, the 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.
- Written permission waiving the pioneer sponsor’s right to marketing exclusivity as discussed in section [VII.E. Marketing Exclusivity Considerations](#) of this concept paper.<sup>27</sup> The request for voluntary waiver should include the following language:

“[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.”

## 2. Veterinary Master Files (VMFs)

In this potential framework, once a defined duration of use is approved 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 would submit the appropriate labeling component(s) for the Type C proprietary free-choice medicated feed and copies of a revised VFD order(s) reflecting the revised conditions of use to the VMF under a STARS “C” submission. The VMF holder would then notify the sponsor of the Type A medicated article NADA that the STARS “C” submission has been submitted to the VMF. The sponsor of the Type A medicated article NADA

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<sup>26</sup> While the changes to establish an appropriately defined duration of use for an ADAA medicated feed combination would impact labeling components, it would be inappropriate to submit supplemental applications for these products as a prior-approval labeling supplement (STARS “NF” or “NL” subclass code) as such changes would rely on safety or effectiveness data in the NADA for each individually approved Type A medicated article. Further, sponsors would be reminded that a major supplemental application (STARS “supplement “B1” subclass code) to an application for an ADAA medicated feed-use combination would not be eligible for the reduced (60-day) review timeframe provided for original approvals of NADA ADAA feed-use combinations. See ONADE Program Policy and Procedures Manual 1243.5730, “Review of 60-day original animal drug availability act of 1996 (ADAA) feed-use combination new animal drug applications (NADAs)” at <https://www.fda.gov/media/117164/download>.

<sup>27</sup> Because a grant of exclusivity to a pioneer sponsor under section 512(c)(2)(F)(iii) of the FD& C Act would prevent any generic sponsor who referenced the pioneer sponsor’s product from adding the RLNAD’s (i.e., pioneer’s) newly-defined duration of use to the generic’s labeling for 3 years, it is possible that a pioneer sponsor who qualifies for such exclusivity may want to voluntarily waive it to allow the durations of use for the affected generic product(s) to be revised prior to the end of the 3-year exclusivity period.

would then submit a non-fee prior-approval labeling supplement (STARS “NF” subclass code, 180-day review clock) to the Type A medicated article NADA that references the submission identifier to the VMF and requests the supplemental approval of the labeling component(s) and VFD order(s) that were submitted to the VMF.

## E. Marketing Exclusivity Considerations

In this potential framework, CVM recognizes that in some cases pioneer sponsors seeking to add an appropriately defined duration of use would need to conduct effectiveness studies as described in section [VII.A.1. Effectiveness](#) of this concept paper. These studies might qualify the sponsor for 3-year exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act.<sup>28</sup> 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.

We note that a pioneer sponsor may voluntarily waive their 3-year exclusivity and 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 the Agency’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 would intend to waive their 3-year exclusivity would do so in writing, in their supplemental application (see section [VII.D.1. Type A Medicated Articles and Medicated Feed-Use Combinations](#) above).

The request for voluntary waiver should include the following language:

“[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.”

This voluntary waiver would permit any generic sponsor who referenced the sponsor’s product to include this defined duration of use on its product labeling before the expiration of the exclusivity period.

## VIII. Supplemental ANADAs (Generic Drugs)

In this potential framework, consistent with current practice, if the conditions of use for an NADA for a medically important antimicrobial drug were changed, CVM would expect that the labeling for

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<sup>28</sup> Supplemental applications submitted to add the defined duration of use to an ADAA feed-use combination as described in the potential framework outlined in this concept paper 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.

any approved ANADA(s) that referenced the original new animal drug application would be revised in a similar fashion. CVM would intend 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 concept paper would either (1) align their labeling with the revised labeling of the RLNAD to reflect a defined duration of use, (2) request approval of a defined duration of use by providing data or other information supporting substantial evidence of effectiveness through a major supplemental application (STARS “C” submission, “B1” subclass code) application if the RLNAD’s approval has been withdrawn, or (3) request to voluntarily withdraw 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 an Indication with an Undefined Duration of Use or the Entire \(A\)NADA](#) of this concept paper. These options would apply even if the affected ANADA was not currently marketed.

#### **A. Generic Type A Medicated Articles and Generic Combination Medicated Feeds**

Consistent with section [VII. Supplemental New Animal Drug Applications \(NADAs, Pioneer Drugs\)](#) of this concept paper, this section of the concept paper 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 would not be changing. Additionally, this section assumes that the RLNAD sponsor would waive 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 concept paper that do not meet these assumptions would be encouraged to discuss their proposals with CVM in a presubmission conference.

##### **1. Updating Conditions of Use through Conforming Labeling Changes**

- a. In this potential framework, CVM would contact sponsors of affected ANADAs after a supplemental application to revise the labeling of the RLNAD is received. Consistent with current practice, CVM would expect that the generic sponsor would 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 going to be 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 described in this concept paper would need to submit labeling that is the same as the labeling approved for the RLNAD with a few exceptions not relevant here. See 512(c)(2)(A)(vii) and 512(n)(1)(F) of the FD&C Act (21 U.S.C. 360b(c)(2)(A)(vii) and (n)(1)(F)).

- b. Administrative Procedures and Submission Content

In this potential framework, sponsors of affected ANADAs would use eSubmitter to submit a prior-approval labeling supplement (STARS “C” submission, “NF” subclass code, 270-day review clock) to the Division of Generic Animal Drugs in ONADE and indicate that their supplemental application is being submitted in accordance with this concept paper. It would be expected that sponsors would not propose labeling changes in this supplement other than those made to align

with the revised RLNAD labeling, except for any additional changes that may be required by the Agency. The submission would include:

- (1) 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 order(s) reflecting the revised conditions of use, revised as follows:<sup>29</sup>
  - (a) Revised conditions of use to include a defined duration of use as described on the RLNAD labeling.
  - (b) Any other labeling changes necessary to align with the revised RLNAD labeling.
  - (c) If not previously implemented, labeling that includes the “Approved by FDA under ANADA # XXX-XXX” statement, as required in section 502(w)(3) of the FD&C Act.
  - (d) Any other labeling changes previously required by the Agency that were not yet implemented.
- (2) A claim of CE under 21 CFR 25.33(a), for an action that does not increase the use of the drug. It would not be expected that CEs would be claimed under 21 CFR 25.33(a)(1) for these actions. With the claim of CE, the sponsor would need to certify 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. See 21 CFR 25.15(a).
- (3) Other technical sections/information: Except in rare cases, it would not be expected that sponsors of generic applications would need to address any other technical sections for approval of these labeling supplements.

## **2. Defining a Duration of Use with Data or Other Information Supporting Substantial Evidence of Effectiveness**

In this potential framework, if a sponsor of an affected generic new animal drug product would choose to pursue approval of a major supplemental application (STARS “C” submission, “B1” subclass code) approval to provide data or other information supporting substantial evidence of effectiveness to define a duration of use because the approval of its RLNAD has been withdrawn, the principles described

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<sup>29</sup> 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 concept paper, it is not envisioned under the potential framework outlined in this concept paper that sponsors would propose other labeling changes in the context of this supplemental application. Rather, as previously noted, it would be expected that requests to approve other substantive changes would be submitted in a separate supplement.

under section [VII.A. Pioneer Single-Ingredient and Fixed-Ratio Combination Type A Medicated Articles](#) of this concept would apply. In such cases, the sponsor would be encouraged to discuss their proposals with CVM in a presubmission conference.

### **IX. Voluntary Withdrawal of Approval of an Indication with an Undefined Duration of Use or the Entire (A)NADA**

In this potential framework, as an alternative to establishing an appropriately defined duration of use for the affected indication(s) on their product labeling, sponsors might choose to request that an application be voluntarily withdrawn in whole or in part. Such sponsors would 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. As always, sponsors could contact CVM with any specific questions in advance of submitting such requests.