

#213

Guidance for Industry

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

DRAFT GUIDANCE

This draft guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm> or <http://www.regulations.gov>.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this draft guidance.

I. Introduction

This draft guidance is intended for sponsors of approved applications for new animal drugs and new animal drug combination products containing medically important antimicrobial new animal drugs for use in or on medicated feed or water of food-producing animals. The draft guidance contains information for sponsors of such new animal drugs and combination products to facilitate voluntary changes to the conditions of use for such new animal drugs and combination products consistent with FDA's recommendations included in the guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). In particular, the purpose of this draft guidance is to provide sponsors with specific recommendations on how to supplement their approved new animal drug applications to align with FDA's GFI #209.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. Background

On April 11, 2012, FDA finalized a guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). That final guidance represents the Agency's current thinking regarding antimicrobial drugs that are medically important in human medicine and used in food-producing animals. Specifically, the final guidance discusses FDA's concerns regarding the development

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of antimicrobial resistance in human and animal bacterial pathogens when medically important antimicrobial drugs are used in food-producing animals in an injudicious manner. In addition, the Judicious Use Guidance provides two recommended principles regarding the appropriate or judicious use of medically important antimicrobial drugs:

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

A. Therapeutic Uses that Assure the Health of Animals

As discussed in GFI #209, FDA believes that, in light of the risk that antimicrobial resistance poses to public health, the use of medically important antimicrobial drugs in food-producing animals for production purposes does not represent a judicious use of these drugs. Such uses are typically administered through the feed or water on a herd- or flock-wide basis and are approved for such uses as increasing rate of weight gain or improving feed efficiency.

Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. FDA believes that production use indications such as “increased rate of weight gain” or “improved feed efficiency” are no longer appropriate for the approved conditions of use for medically important antimicrobial drugs. In contrast, FDA considers uses that are associated with the treatment, control, and prevention of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals. As discussed further below, when a veterinarian determines that the use of antimicrobials is necessary to prevent the onset of diseases that are likely to occur, FDA considers this to be a judicious use of these products.

B. Veterinary Oversight

New animal drugs and new animal drug combination products are approved with one of three types of marketing status: (1) over-the-counter (OTC), (2) veterinary prescription (Rx), or (3) veterinary feed directive (VFD). Products for which adequate directions for use can be written for use by lay persons are labeled for OTC marketing status. When adequate directions can not be written in a manner that enables a layperson to use a drug safely and for the purposes for which it is intended, the drug is restricted to use under veterinary oversight as an Rx or VFD product.

FDA believes it is important to include veterinary oversight in the use of antimicrobial new animal drugs to assure their appropriate and judicious use. Veterinarians play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. As discussed in more detail below, FDA believes that the judicious use of medically important antimicrobial new animal drugs in the feed or water of food-producing animals needs the scientific and clinical training of a licensed veterinarian.

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III. Medically Important Antimicrobial Drugs

FDA uses the concepts set out in its Guidance for Industry (GFI) #152, “*Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*,” in reviewing the human food safety component of new animal drug applications for medically important antimicrobial new animal drugs for use in food-producing animals. Guidance #152 includes an appendix that ranks antimicrobial drugs into three tiers, “critically important,” “highly important,” or “important,” in regard to their human medical importance. At this time, FDA considers all antimicrobial drugs listed in Appendix A to GFI #152 (Appendix A) to be “medically important” in the context of implementing the recommendations outlined in GFI #209 and further discussed in this draft guidance document (Draft GFI #213). We believe that the policy in GFI #209 and draft GFI #213 applies to all three tiers of medically important antimicrobial drugs at this time because each tier (and thus all of the drugs listed in Appendix A) contains drugs that have been previously assessed through the public processes used to develop GFI#152 and determined to be important for treating bacterial infections in people. We request comment on this issue.

FDA recognizes that the list of drugs in Appendix A is not static and should be periodically reassessed and updated as necessary. Such reassessment is necessary to take into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices in the United States. FDA will update Appendix A, as necessary, through a separate process that will also be subject to public comment. However, because Appendix A identifies those antimicrobials that have been determined to be medically important to human medicine, FDA believes the existing Appendix A provides adequate clarity for purposes of moving forward with the recommendations outlined in GFI #209.

IV. Voluntary Adoption of Judicious Use Principles

As discussed in the following section, FDA intends to work with affected drug sponsors to help them to voluntarily implement the principles described above through modifications to the approved conditions of use of their new animal drug products. However, FDA recognizes that it is equally important that the Agency also work with the veterinary and animal producer communities, the end users of these products, to ensure that their concerns are taken into consideration as these changes are implemented. With this in mind, FDA is very interested in receiving comments on the practical implications of these changes for animal producers, particularly those with smaller operations in remote locations. The Agency is also interested in receiving input on how impacts or disruption to animal producers could be minimized. Further, we solicit comment on the economic effects that may result from the adoption of the practices set out in this Guidance.

FDA acknowledges that one issue of concern is the ability of producers, particularly those with smaller operations in remote locations, to have adequate access to veterinary services. Therefore, as steps are taken to phase in the voluntary changes discussed in this document, FDA recognizes the need to concurrently engage key stakeholders on this broader issue. Therefore,

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FDA intends to work collaboratively with United States Department of Agriculture (USDA) to engage the veterinary community and other stakeholders to explore strategic approaches (e.g., new models, pilot programs) to address this issue. We request further comment on this issue.

FDA encourages the submission of comments on these draft documents so that practical concerns are adequately considered. However, FDA is also exploring other venues for seeking and obtaining input, particularly from animal producers, such as through listening sessions held in various parts of the country. FDA is working closely with USDA to identify mechanisms for obtaining this critical input.

A. Voluntarily Phasing out Production Uses

FDA is concerned about the risk that antimicrobial resistance poses to public health from the use of medically important antimicrobial drugs in food-producing animals for production purposes. As a consequence of this concern, FDA will be working with affected drug sponsors who notify us of their intent to voluntarily withdraw approved production uses of their medically important antimicrobial new animal drugs and combination new animal drug products.

B. Need for Veterinary Oversight of Medically Important Antimicrobial Drugs Used in the Feed or Water of Food-Producing Animals

Prior to 1993, most feed and water use antimicrobial drugs were approved for over-the-counter use in food-producing animals. At that time, the methods used by FDA to assess the microbial food safety aspects of new animal drug applications for antimicrobials intended for use in food-producing animals were not as rigorous as those used today, in part because less scientific data about the public health ramifications of antimicrobial resistance existed at that time. In addition, FDA's recommended approach for conducting pre-approval microbial food safety assessments has evolved over time as the quantity and quality of epidemiologic and other data bearing on antimicrobial resistance has improved. As a result, all antimicrobial new animal drugs for use in food-producing animals approved by CVM since 1993 have been labeled with Rx or VFD marketing status, with the exception of approvals of generic copies of existing OTC products and approvals of combination medicated feeds using existing OTC antimicrobial Type A medicated articles. This shift to a marketing status requiring veterinary oversight was viewed as an important step to mitigate the microbial food safety risks of antimicrobial new animal drugs, particularly for those drugs considered to be medically important.

Based on the available scientific evidence concerning antimicrobial resistance, including information about resistance trends associated with the use of medically important antimicrobial drugs in food-producing animals, FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals should involve the scientific and clinical training of a licensed veterinarian. This is because judicious use involves accurately identifying bacterial disease that is present or likely to be present and selecting the suitable antimicrobial drug. In the case of prevention, judicious use includes a consideration of relevant factors for determining the risk of a specific bacterial disease.

In order to ensure judicious use, we believe that veterinary expertise is required to determine whether the use of medically important antimicrobials for prevention purposes is

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appropriate in a particular situation. We also believe that veterinarians are uniquely qualified to determine which specific etiologic agents are likely to be present and to determine appropriately timed administration relative to the disease. The decision to use a specific approved drug or combination drug is based on factors such as the mode of antibacterial action, drug distribution in specific tissues, and the duration of effective drug levels at the site of infection. From FDA's standpoint, the administration of a drug to animals when a veterinarian determines that there is a risk of a specific disease, based on the presence of risk factors such as the stress of transport or environmental factors, could be considered judicious prevention use. For example, if a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use. Another example would be the prevention of necrotic enteritis in broiler chickens. In this case, the prevention use of an antimicrobial is important to manage this disease in certain flocks in the face of concurrent coccidiosis, a significant parasitic disease in chickens. On the other hand, FDA would not consider to be judicious use the administration of a drug to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease.

For these reasons, in FDA's 1999 proposed rule on veterinary feed directives (64 FR 35966; July 2, 1999), the Agency gave antimicrobial resistance as a key example of a reason it can be important for medicated feed to be administered under a veterinarian's supervision. FDA stated, "control of the usage of certain antimicrobials is critical to reducing unnecessary use of such drugs in animals and to slowing or preventing the development of bacterial resistance to antimicrobial drugs."

Accordingly, FDA recommends that affected drug sponsors voluntarily revise the conditions of use of their medically important antimicrobial new animal drugs and combination new animal drug products to reflect the need for the professional oversight of a licensed veterinarian. This would mean a change from OTC to VFD status for medicated feed products and from OTC to Rx status for medicated drinking water products. A proposed timeline for making such changes is discussed in more detail below. FDA acknowledges that in order to facilitate the OTC to VFD change in marketing status, existing requirements related to the distribution and use of VFD drugs must be updated and streamlined. Therefore, concurrent with the development of this guidance, FDA is actively pursuing revisions to the VFD regulations (in 21 CFR part 558) through the rulemaking process. Some of the key changes being considered include: 1) providing for alignment between the criteria for appropriate veterinary supervision or oversight and those established as part of veterinary licensing and practice requirements; 2) providing veterinarians greater flexibility to exercise their professional discretion to authorize producer access to appropriate VFD drugs; and 3) streamlining administrative procedures. To facilitate the transition from OTC to VFD status, FDA believes it is critically important that changes such as these be implemented to minimize impacts on veterinarians, the animal feed industry, and animal producers.

While FDA believes that all medically important antimicrobial new animal drug products should be marketed with the appropriate professional oversight restriction, at this time FDA is most concerned with medically important antimicrobial new animal drugs and combination new

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animal drug products intended for use in or on the feed or water of food-producing animals. As discussed in GFI#209, FDA's current methodology for assessing antimicrobial risks associated with the use of antimicrobial new animal drugs in food-producing animals is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Because feed or water use antimicrobial drugs are typically administered to entire herds or flocks of food-producing animals (e.g., for production purposes), such uses pose qualitatively higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals (e.g., to prevent, control, or treat specific diseases). For that reason, this guidance is focused on those medically important antimicrobial new animal drugs that are approved for use in the feed or water of food-producing animals.

V. Timeline for Voluntarily Implementing Changes

The Agency recognizes the significance of the proposed changes and the potential impacts such changes will have on the animal pharmaceutical industry, animal producers, the animal feed industry, and the veterinary profession. For this reason, FDA is currently pursuing a strategy for the voluntary adoption of these changes in an effort to minimize the impacts and provide for an orderly transition. FDA encourages all sponsors of affected new animal drugs and new animal drug combination products to contact the Agency and initiate steps to change product labeling and approved conditions of use through the process outlined in this draft guidance.

FDA also believes it is critical to see meaningful progress toward eliminating production uses of medically important antimicrobial drugs and bringing the remaining therapeutic uses of such drugs in or on the feed or water of food-producing animals under the oversight of veterinarians. In order to ensure progress under the cooperative framework outlined in this draft guidance, FDA will monitor progress to assess whether these changes are being adopted along the timelines discussed below. FDA is confident that the objective of phasing in these changes can be met through the cooperative process discussed in this draft guidance, which is why we are initially pursuing this voluntary approach. To assist FDA in effectively monitoring rates of adoption in the industry, we request that sponsors of affected products (i.e., those products containing antimicrobial new animal drugs of importance to human medicine that are administered in medicated feed or drinking water of food-producing animals) notify the Agency of their intentions to engage in the voluntary process to modify their product labeling within 3 months from the date of publication of the final version of this guidance. FDA anticipates that sponsors of affected products should be able to complete implementation of the changes discussed in this draft guidance within 3 years from the date of publication of the final version of this guidance. Upon issuance of final guidance, the Agency will monitor the progress of its strategy for the voluntary adoption of the changes outlined, including the progress of measures intended to facilitate an orderly and minimally disruptive transition. In addition, 3 years from the date of publication of the final version of this guidance, FDA intends to evaluate the rate of adoption of the proposed changes across affected products. The agency will consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved new animal drugs.

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FDA recognizes that the proposed changes in the use of these antimicrobial drugs have significant practical implications for animal producers, veterinary practitioners, animal drug sponsors, and feed mills. In particular, as mentioned previously, implementing changes to streamline existing VFD requirements is pivotal to facilitating the transition to greater veterinary oversight (i.e., from OTC to VFD marketing status) for many of these products. Therefore, the 3-year timeframe for voluntary phase-in noted above is intended to provide sufficient time for the necessary changes to the existing VFD requirements to be developed and implemented through notice and comment rulemaking. Although FDA is committed to completing this rulemaking process within the 3-year timeframe for implementing the changes discussed in this draft guidance, FDA is prepared to extend the timeframe, as necessary, to ensure that it coincides with the implementation of the revised VFD requirements.

The 3-year timeframe for voluntary phase-in is also intended to provide time for animal drug sponsors to make these changes in an efficient and practical manner, and for other stakeholders to prepare for the resulting changes in management/business practices. When several approved products are involved (e.g., combination drug approvals containing the same active ingredients; same active ingredient in different dosage forms), sponsors are encouraged to coordinate implementation when practicable.

FDA requests comments on this proposed 3-year timeframe for implementation, including impacts on the animal pharmaceutical industry, the feed industry, and producers.

VI. Supplemental New Animal Drug Applications

A. Removing Production Uses/Changing Marketing Status

The procedures in this section (VI.A) apply to the situation where no new indications are being proposed. In the limited circumstances where a sponsor would be proposing that a new therapeutic indication be added, the procedures set forth at section VI.B below for submitting a supplemental application should be followed instead. As always, FDA encourages sponsors to consult with FDA prior to submitting supplemental applications to ensure that sponsors are targeting their submissions to answer questions that are relevant to the particular drug. The recommendations below, which, as guidance, establish no legally enforceable requirements, apply when sponsors who wish to voluntarily pursue judicious use changes are submitting supplemental new animal drug applications under 21 CFR 514.8.

1. Administrative Procedures

Sponsors who wish to voluntarily remove production use claims and change the marketing status for the remaining approved feed or water uses of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Such supplemental applications do not need to include additional safety or effectiveness data. Sponsors of such applications would either (1) propose to change the marketing status to VFD or Rx and voluntarily withdraw the approval for all production uses or (2) for those applications without approved production uses, such sponsors would only propose a change in marketing

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status to VFD or Rx. No new indications would be proposed by the sponsors and in most cases the sponsors would only be required to submit revised labeling.

2. Applicable Supplemental New Animal Drug Application Technical Sections

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s).

B. Adding New Therapeutic Indications

In some cases, it has been suggested that there could be a therapeutic benefit associated with the production use of a drug. In situations where this could be the case, concerns have been raised that removing production uses from approved conditions of use will have negative animal health impacts. In those cases, where scientific evidence demonstrates a therapeutic benefit associated with the use of the drug for treating, controlling, or preventing a particular disease, sponsors could wish to seek new therapeutic indications to fill the therapeutic needs of animals.

FDA stresses that such new indications must be based on scientific evidence that such drug is safe and effective for the intended therapeutic use. Such new therapeutic indications should be directed at specifically identified diseases and should involve dosage regimens that provide the desired therapeutic effect while minimizing overall extent of use.

1. Administrative Procedures

Sponsors who wish to seek new therapeutic indications for use of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Because new therapeutic indications are being proposed, these supplemental applications require the inclusion of additional safety and effectiveness data. These supplemental applications would need to include specific information as follows:

2. Applicable Supplemental New Animal Drug Application Technical Sections

a. Labeling

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water

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products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s). In both cases, the labeling would need to reflect the new therapeutic indications for use.

b. Chemistry, Manufacturing, and Controls

The recommendations in this section assume there is no change in the chemistry, manufacturing and controls (CMC) information for the Type A medicated article or medicated drinking water products, including the product formulation, raw materials, manufacturing process, controls and packaging. If there are changes to the CMC information for the Type A medicated article or medicated drinking water product associated with the new therapeutic indication, the sponsor should provide a description of such changes in the supplemental application, along with appropriate documentation and data to support the changes. See 21 CFR 514.8(b).

Medicated Drinking Water Product

If the new indication provides for use of the medicated drinking water product at the same concentration or concentration range as currently approved, no additional chemistry, manufacturing and controls (CMC) information is required. If the medicated drinking water product will be used to prepare medicated water at a different concentration than currently approved, the sponsor should address stability of the medicated drinking water at the new concentration (Ref. 1).

Type A Medicated Article

If the new indication is for a currently approved species and provides for a medicated feed inclusion rate currently approved for that species, no additional CMC information is required.

If the new indication is for a medicated feed inclusion rate outside of the currently approved inclusion rate or range (i.e., lower than the lowest currently approved inclusion rate or higher than the highest currently approved inclusion rate for that species), the sponsor should address homogeneity, non-segregation, and stability of the drug in representative medicated feeds at the higher/lower inclusion rate (Ref. 1). In addition, the sponsor should demonstrate that the approved medicated feed assay method is valid for assay of feeds manufactured at the higher/lower inclusion rate or provide a new method that is capable of assaying the feed (Refs. 2, 3, and 4).

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If the new indication is for a species not currently approved, the sponsor should address homogeneity, non-segregation, stability, and medicated feed assay methodology in representative medicated feeds at the highest and lowest proposed medicated feed inclusion rates.

c. Human Food Safety

Toxicology/Residue Chemistry

Toxicology information associated with the original approval was considered for currently approved antimicrobial new animal drugs, and that information was the basis of the acceptable daily intake (ADI) that drove the residue chemistry conclusions (target tissue, tolerance, withdrawal times, etc.) for those approvals. The toxicological assessment is not expected to be reconsidered under proposed therapeutic indications with similar conditions of use to those corresponding to the production use (see Impact on Human Intestinal Flora below). If a new, proposed therapeutic indication has corresponding conditions of use (same species, with dose/duration/formulation/route of administration) that fit within existing residue chemistry parameters and are covered by previous residue chemistry evaluations, we do not anticipate that the sponsor will need to provide additional data or information.

Microbial Food Safety

Antimicrobial Resistance

It should be noted that microbial food safety for older antimicrobial new animal drug application approvals was most likely not considered at the time of the original approval in the same way or to the same extent as is currently the case. The Agency is concerned, consistent with the general elements of judicious use discussed in section II above and GFI#152, that giving antimicrobial drugs to food-producing animals at low levels for long periods of time and in large numbers of animals may contribute to antibiotic resistance. We expect any new indication(s) to (1) have an explicitly defined duration of dosing, (2) specify a therapeutic dose level, most likely a higher dose than that approved for the current weight gain/feed efficiency indications, and (3) be available only to those animals that need the drug for the new indication, rather than the entire flock or herd when such use is not necessary.

Generally, these changes are expected to remove injudicious use indications, and to result only in the therapeutic use of medically important antimicrobial drugs in or on the feed or water of food-producing animals. In addition, such indications for use should include risk mitigations intended to reduce antimicrobial resistance when these drugs are used in or on the feed or water of food-producing animals as discussed further below in this section.

To address the Agency's antimicrobial resistance concerns and in lieu of a complete, qualitative, microbial food safety risk assessment, firms should discuss with CVM the type of information to submit with their application. This information may include, but is not limited to:

- (1) Basic information on the subject antimicrobial new animal drug, including information on mechanisms of action, spectrum of activity, resistance mechanisms, transfer of resistance, pharmacokinetics and/or pharmacodynamics if known, proposed conditions of use and how these could influence resistance development, and information on susceptibility among bacteria of human health concern;

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- (2) Information on the use of the subject antimicrobial new animal drug in or on the feed or water of food-producing animals, focusing on numbers of animals treated, class, consumption rates for food products from treated animals, and rates of contamination by bacteria of human health importance;
- (3) Information on the use of the subject antimicrobial drug or drugs similar to it in human medicine, including a discussion on how loss of susceptibility of organisms of human health concern to the subject antimicrobial drug or drugs could impact human clinical medicine;
- (4) Information detailing how FDA's general elements of judicious use discussed in section II have been addressed. Specifically, all approved indications should be for therapeutic and/or preventive use only, require veterinary oversight, and restrict use to an explicitly defined duration of dosing. FDA considers these measures to be significant risk mitigations consistent with the goals of GFI #152.

We request comment on the practical utility and burden of providing this information. Upon review of this information, the Agency should be able to: 1) determine appropriate risk mitigations to match proposed conditions of use with an acceptable level of risk from emergence or selection of antimicrobial-resistant bacteria of human health concern in or on treated animals; and 2) advise on the types of information or data needed to address any existing data gaps associated with the new, proposed use of the subject antimicrobial new animal drug.

Impact on Human Intestinal Flora

Based on the expected changes in use patterns for new indications described in the previous section, which are expected to reduce overall human exposure to residues of antimicrobial new animal drugs in animal-derived food products, we do not anticipate that this issue will need to be addressed by sponsors. However, if changes in conditions of use (dose/duration/formulation/route of administration) are proposed that are expected to increase overall human exposure to residues of antimicrobial new animal drugs in animal-derived food products, then sponsors could be asked to address the safety of their proposed use with respect to impact of residues or metabolites of antimicrobial new animal drugs and compounds with antimicrobial activity on the intestinal flora of human consumers.

d. Target Animal Safety

Regarding previously approved antimicrobial new animal drugs, target animal safety information associated with the original approval has already been considered. As long as any new, proposed therapeutic indication has conditions of use that are covered by previous target animal safety evaluations (same species, a dose within the approved dosage range, same or shorter duration, same route of administration, same formulation), we do not anticipate that the sponsor will need to provide additional data or information, unless the Agency becomes aware of human or animal health concerns that were not apparent at the time of the original target animal safety evaluation.

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e. Evidence of Effectiveness

Sponsors seeking approval of a new therapeutic indication should provide substantial evidence (as defined in this agency's regulations at 21 CFR 514.4) in support of the effectiveness of the new animal drug for the proposed new therapeutic indication. When replacing certain production indications, a sponsor could be able to show substantial evidence in a variety of ways. For example, the sponsor can provide data or subsets of data from previously conducted studies (including studies previously used for approval of other uses in the United States or in other countries in and outside of North America). Alternatively, the sponsor can cite public data and/or relevant published scientific literature. As further evidence of effectiveness, the sponsor can point to any other sources of information that will allow the Agency to determine that:

- parameters selected for measurement and the measured responses reliably reflect effectiveness;
- the results obtained are likely to be repeatable;
- valid inferences can be drawn from these sources to the use of the new animal drug in the target population; and
- the new animal drug is effective for the new therapeutic indication under the proposed conditions of use.

Previously approved therapeutic indications that are very similar or “related” to the new therapeutic indication could provide inferential value in support of the new indication (e.g., a new “control of bovine respiratory disease” indication added to an application that has a previously approved “treatment of bovine respiratory disease” indication with a similar dosage regimen). While *in vitro* data (e.g., minimum inhibitory concentration (MIC) data) can be used as part of the evidence of effectiveness for the new use, at least some data should come from studies conducted *in vivo* in the target species and production class.

If traditional clinical field effectiveness studies are not used in the demonstration of effectiveness, the sponsor should also provide information to establish that the approved dose levels for the new therapeutic use are within a therapeutic range and not at sub-therapeutic levels.

Sponsors are encouraged to discuss approaches to satisfying the requirements of substantial evidence of effectiveness with CVM.

f. Environmental Impact

By regulation (see 21 CFR 514.1(b)(14)), the Environmental Impact section must include either an environmental assessment (EA) (see 21 CFR 25.40), or a claim for categorical exclusion (see 21 CFR 25.30, 25.33). The agency expects that most sponsors submitting supplemental applications described in this draft guidance will be able to assert a claim of categorical exclusion. Under 21 CFR 25.15(a), a claim of categorical exclusion must include a statement of compliance with the categorical exclusion criteria and must state that to the sponsor's knowledge, no extraordinary circumstances exist. “Environmental Impact Considerations” and directions for preparing an EA can be found in 21 CFR Part 25.

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VII. Generic Drugs and Combinations

Revising the conditions of use in applications for a pioneer single ingredient new animal drug products may have an effect on abbreviated (generic) new animal drug applications and combination new animal drug applications that reference these single ingredient products. The effects that submission and approval of a supplement for the pioneer drug may have on these generic or combination drugs are discussed in this section. FDA intends to work expeditiously with the sponsors of affected generic and combination new animal drug applications to align their products with the revised conditions of use specified in the referenced (i.e., pioneer) applications for the single ingredient new animal drug products.

A. Generic Applications

If the approved conditions of use for a new animal drug application for a medically important antimicrobial new animal drug are revised under this draft guidance by voluntarily withdrawing a production use, the approved labeling for any currently approved generic application(s) that references the original new animal drug application must generally be revised in a similar fashion, as is now standard practice. In such cases, if the generic labeling is not revised accordingly, the generic application holder(s) faces the possibility of suspension of the generic application under section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G)). With regard to suspension, FDA intends to follow the procedures outlined in its regulations at 21 CFR 314.153(b) relating to human generic drug suspensions until generic new animal drug regulations implementing section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G) are finalized.

In addition, any future generic sponsor that wants to use such a drug as its referenced listed new animal drug cannot include the production use that was voluntarily withdrawn from the pioneer application in its generic application because under section 512(n)(1)(F) of the FD&C Act (21 U.S.C. 360b(n)(1)(F)) the generic sponsor must submit labeling that is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant here. Furthermore, under section 512(c)(2)(A)(vii) of the FD&C Act (21 U.S.C. 360(c)(2)(A)(vii)), the Agency cannot approve an abbreviated new animal drug application unless the labeling proposed for the generic product is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant for purposes of this draft guidance.

B. Combination New Animal Drugs

The term *Combination new animal drug* is defined in the substantial evidence provisions of 21 CFR Part 514 to mean a new animal drug that contains more than one active ingredient or an animal drug that is applied or administered simultaneously in a single dosage form or simultaneously in or on animal feed or drinking water (See 21 CFR 514.4(c)(1)(i)). Although the term combination new animal drug applies both to products intended for use in or on animal feed and products intended for use in the drinking water of animals, the majority of approved combination new animal drug products are feed use combination drug products.

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Most feed use combination new animal drugs are combinations of individual Type A medicated articles that have previously been separately approved. So, for example, a 3-way feed use combination actually involves four approved new animal drug applications, one for the combination and one for each of the three individual Type A medicated articles. The holder of an approved feed use combination new animal drug application is normally also the holder of an approved application for at least one of the individual type A medicated articles in the combination.

1. Production Uses.

As discussed above, FDA is requesting affected sponsors to voluntarily withdraw production uses of their medically important antimicrobial new animal drugs and combination new animal drug products. In those instances where an approved combination new animal drug product with a production claim includes a medically important antimicrobial new animal drug and the sponsor of the individually approved new animal drug application for a medically important antimicrobial new animal drug has voluntarily withdrawn the production use claims, FDA expects the sponsor of the affected combination new animal drug product will voluntarily follow suit and similarly withdraw the production use claim from the combination new animal drug application. If sponsors of these affected combination new animal drug products do not voluntarily withdraw the production use claim from the combination new animal drug application, FDA intends to consider its alternatives.

2. Remaining Therapeutic Uses.

As discussed at section IV above, based on a number of factors FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals needs the scientific and clinical training of a licensed veterinarian. This belief applies not only to individual medically important antimicrobial new animal drugs but also to combination new animal drug products incorporating such drugs. However, as previously discussed, in recognition of the significant practical implications of revising the marketing status for these products, FDA has expressed its intent to pursue a strategy for voluntarily phasing in these changes over time in an effort to minimize the impacts and provide for an orderly transition. As explained more fully in section V, FDA is proposing clear timelines for sponsors of the affected products to make these changes in order to ensure effective progress under the cooperative framework outlined in this draft guidance.

However, once a sponsor of an individual Type A medicated article that is also part of a combination new animal drug submits a supplement to switch the marketing status of the individual product to VFD or Rx, FDA expects the sponsor of the affected combination new animal drug product to voluntarily follow suit. Indeed, for a combination new animal drug product containing individual Type A medicated articles intended for use in or on animal feed, this outcome is essentially compelled since a voluntary switch to VFD marketing status by one or more of the sponsors of the individual Type A medicated articles will automatically trigger the requirement for a VFD to be issued before the affected combination new animal drug product can be used in or on animal feed. This is the case because under section 504(a)(1) of the FD&C

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Act, “[a]ny animal feed bearing or containing a veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian’s professional practice.” (21 USC 354(a)(1)). Thus, the requirement for a VFD to be issued applies whenever a VFD drug will be used in feed, regardless of whether the VFD drug is being used by itself or in combination with other drugs. Because a voluntary switch to VFD marketing status by one or more of the Type A medicated articles contained in a combination new animal drug product results, by operation of law, in the requirement for a VFD to be issued before a feed containing the combination new animal drug product can be fed to animals, in effect, the combination new animal drug product takes on VFD status also.

Therefore, we believe that in such instances the combination new animal drug product sponsors should also timely submit their own supplements to formally change the marketing status of the affected combination new animal drug products to VFD.

This outcome is consistent with the Agency’s policy, as expressed in the substantial evidence notice of proposed rulemaking (62 FR 59835; Nov. 5, 1997) which provides that a combination new animal drug should generally bear VFD or Rx marketing status if one or more of the new animal drugs that make up the combination product were individually approved with VFD or Rx marketing status for any of the intended uses or conditions of use that are also applicable to the combination product.

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VIII. References

1. FDA 2008. Guidance for Industry 5: Drug Stability Guidelines
2. FDA 2005. Guidance for Industry 135: Validation of Analytical Procedures for Type C Medicated Feeds
3. FDA 2007. Guidance for Industry #136: Protocols for the Conduct of Method Transfer Studies for Type C Medicated Feed Assay Methods
4. FDA 2007. Guidance for Industry #137: Analytical Methods Description for Type C Medicated Feeds