



## FDA Must Establish Limits for All Animal Antibiotics

Defined durations are important for animal and public health, key to combating resistant bacteria

### Overview

Antibiotic use in any setting—including animal agriculture—contributes to the emergence of drug-resistant bacteria, a dangerous and growing global health threat.<sup>1</sup> Of particular concern is the overuse of medically important antibiotics—those that are also essential to human health care—in food animals, which accelerates the development of resistance to these critical drugs. Despite widespread agreement among animal and public health experts and clear guidance from the Food and Drug Administration that antibiotic use without limits is not judicious, 1 in 3 of such drugs approved for use in agriculture can be administered for excessively long or undefined periods of time.<sup>2</sup> In fact, available evidence suggests that time frames for antibiotics use can exceed five consecutive months in some food-producing animals.<sup>3</sup> According to FDA's guiding principles, injudicious use of medically important antibiotics is any use beyond that necessary to assure animal health—which includes, but is not limited to, inappropriate long-term use of antibiotics. Such injudicious use presents a clear and serious public health risk, and federal action is long overdue.

In 2018, FDA announced a five-year plan to curb the spread of antibiotic-resistant bacteria, which included a commitment to ensuring that medically important antibiotics used in animals have limited and defined durations of use. Subsequently, FDA identified a list of animal antibiotics that lack duration limits and released a preliminary proposal outlining how the agency would work with drug sponsors—the companies responsible for drug marketing and compliance with FDA regulations—to establish defined durations for these drugs. The proposed process, however, is insufficient because it allows drugmakers to use a range of standards in place of clear and

specific duration limits; lacks clear guidance for medically complex diseases that frequently lead to prolonged or indefinite antibiotic use; and gives drug sponsors too lengthy a timeline to update their products.<sup>4</sup>

An analysis by The Pew Charitable Trusts identified several actions that FDA should incorporate in order to establish duration limits in a clear, comprehensive, and timely manner. By leveraging existing data from clinical studies for approved drugs, working with drug sponsors to identify data gaps, and supporting targeted new research to establish effective minimum durations of treatment, FDA can still achieve its goal of establishing duration limits before the close of the five-year plan in 2023.

## What Are Duration Limits, and Why Are They Important?

Duration limits provide veterinarians with science-based guidance on how long a given drug is allowed to be used, which ensures optimal clinical outcomes and reduces unnecessary antibiotic use in animal care. Such limits are part of a broader set of label instructions, established as part of the FDA approval process, that accompany all drugs available for use in veterinary medicine and include which health problems the drug can be used to address, route of administration, dosage, and dosing frequency. Although new drug applications are required to include duration of use information on their label instructions, a number of FDA-approved products lack this information, largely because they were approved before FDA required it.

Antibiotics should be used in animals, as in human medicine, for the shortest period of time needed to resolve an underlying bacterial infection. A too-long course of treatment unnecessarily raises the risk of antibiotic resistance, while one that's too short can fail to fix the health problem that prompted the use of the drugs. Veterinarians rely on FDA-approved instructions to determine the appropriate type of drug and length of treatment for affected animals, the same way human medical practitioners do. Antibiotic instructions that lack a duration limit validated through well-designed clinical research or field trials put both animal welfare and public health at risk.

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## How to Address a Lack of Duration Limits

For this analysis, the authors defined a drug indication as the FDA-approved use of an active ingredient (or combination of ingredients) in a specific animal species for a defined purpose of use. To provide targeted recommendations for how FDA should pursue solutions, Pew examined 59 animal antibiotic indications that lack an appropriate duration of use (see methodology for details). Approximately one-third of the animal antibiotics currently on the market can be prescribed for at least one of these 59 indications.<sup>5</sup>

Pew divides the 59 indications without duration limits into three categories:

- For 15 (about 1 in 4), information from other drug applications can be used to establish duration limits.
- For 19 (about one-third), either drug sponsors will need to provide FDA with the new data necessary to establish duration limits or different antibiotics with equivalent indications and defined durations of use can be substituted to achieve comparable clinical outcomes.

- For the remaining 25, there are no available antibiotics with duration limits that address the same animal health problem, and FDA should work with sponsors to ensure that any necessary clinical research is conducted to establish appropriate duration limits.

## **When existing information can establish a duration limit**

Over the years, FDA has granted multiple antibiotic approvals for identical or closely related indications. For instance, different drug companies may have obtained FDA approvals to sell the same active ingredient to address the same animal health problem. In several instances, some of these approved indications specify defined durations of use, while others do not.

Pew's analysis identified 15 indications without a duration limit whose active ingredient exactly matched another product with a label that includes a science-based duration limit—and is approved for the same indication and species. In these cases, as long as the two products are valid substitutes that provide comparable clinical outcomes (see methodology), FDA should immediately require sponsors to update their labels with duration limits established by referencing the data from these comparable products.

## **When similar products with duration limits can be substituted**

For 19 of the 59 indications, FDA should direct drug sponsors to produce the data necessary to establish science-based durations of use and update their labels accordingly. If the drug sponsors are unable or unwilling to do so in a timely manner, FDA should consider withdrawing these drugs from the market. Such a move would not harm the ability of veterinarians to keep animals healthy because alternative antibiotics with similar though nonidentical claims and evidence-based duration limits are FDA-approved to treat the same animal health problems. Although these alternatives may require a different treatment regimen and some antibiotics may have certain advantages over others, veterinarians already use such alternative drugs to achieve the desired therapeutic results.

## **When FDA should work with drug sponsors to acquire the additional data needed**

For the remaining 25 indications, FDA will likely need additional data to support label revisions that establish an appropriate duration of use. In many cases, drug sponsors may already have the necessary data from the original research studies used to validate the pioneer drug application and should be able to provide it to FDA in a reasonable amount of time. In all cases, the responsibility rests with the drug sponsors to assess the data gaps associated with their products and promptly undertake any supplemental research necessary to support judicious label updates. If drug sponsors are unable or unwilling to submit the data needed, FDA should deem those products injudicious and require that sponsors withdraw them from the market.

## **Additional Considerations**

### **Complex animal diseases**

For particularly complex animal diseases, FDA should work with the Department of Agriculture, veterinarians, and other stakeholders to advance targeted animal research that ensures judicious use.

For example, six indications concern anaplasmosis or liver abscesses in cattle, two complex diseases that are more appropriately resolved through improved management practices—which, as research has shown, can significantly reduce the need for antibiotics<sup>6</sup>—but are currently addressed by long-term antibiotic treatment that can exceed several months.<sup>7</sup> Because antibiotic treatment is not intended to cure these diseases, relying primarily on antibiotics is injudicious.

FDA has begun funding targeted research to help establish durations of use for two antibiotics commonly used for these conditions: chlortetracycline for anaplasmosis, and tylosin for liver abscesses.<sup>8</sup> Expanded research is warranted along these lines and should include additional field research to better understand the nexus between antibiotic use and resistance in feedlot settings where these drugs are widely used. Further studies could also identify animal husbandry and management practices that would help growers reduce the incidence of diseases that drive the need for antibiotic therapy.

In addition, FDA should pursue interagency initiatives with USDA and other stakeholders to advance a well-coordinated research agenda that optimizes animal management practices in feedlots and swine operations and supports producer efforts to transition away from extended antibiotic use.

## Withdrawal of approval

Of the 59 indications examined, 22 across all categories are likely to be injudicious for reasons in addition to their lack of a science-based duration limit. These products should be closely scrutinized by FDA to evaluate whether their drug sponsors should be required to withdraw them from the market. For instance, nine indications are for a combination of two antibiotics to address a health condition for which single antibiotic indications are available. Unless the combined antibiotics contribute defined and complementary roles to treatment, using a single antibiotic is preferable—because the risk of developing resistant bacteria increases with combined antibiotics.<sup>9</sup>

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Thirteen of the indications that lack duration limits are specified for preventive uses. Although antibiotics can sometimes offer protective benefits to animals during a specified period when they are vulnerable to infection, such preventive uses should be restricted to exceptional cases and should not be applied in a systematic or routine manner.<sup>10</sup> FDA must closely examine whether the scientific and clinical evidence associated with indications for preventive uses supports the conclusion that these products are truly necessary and judicious, and—if so—the agency should ensure that any such use be strictly limited to what is needed to protect animal health.

An additional four indications directly contradict FDA’s own judicious antibiotic use principles. These specify either “maintenance of weight gain” or “prophylaxis in times of stress” as their purpose of use. In its five-year plan, FDA states that it “believe[s] medically important antimicrobial drugs should only be used when necessary to treat, control, or prevent disease” and that use of antimicrobials should be linked to a specific etiologic agent.<sup>11</sup> Because these indications fail to meet these standards, FDA should work with drug sponsors to have them withdrawn.

FDA should carefully consider how essential each indication is to animal health. When the agency is evaluating data to establish durations of use, it should hold indications for prevention uses, as well as those for combination products, to a high standard of evidence.

## Next Steps

Although the problem of undefined duration limits for animal antibiotics is significant, the evidence supports FDA's assertion that this challenge is manageable. As outlined in this brief, FDA has a clear path to ensure that all antibiotics used in animals have a valid and science-based duration limit by the completion of its five-year plan, ending in 2023. It is critical that the agency acts with urgency to establish a concrete plan with detailed timelines to achieve that goal.

Ultimately, FDA must clearly communicate to drug sponsors, veterinarians, and producers that label updates are expected to meet its judicious use standards and that any label revisions must incorporate specific and time-limited usage indications for any course of treatment. If drug companies are unwilling to swiftly provide sufficient data, FDA should move to require them to withdraw these antibiotics from the market.

## Methodology

**Data source:** FDA provided a dataset to Pew in March 2016 consisting of drug label information for all medically important animal antibiotics approved for use in food-producing species in the U.S., including drugs currently marketed and those not being marketed. The data was sourced from the [animaldrugsatfda.fda.gov](http://animaldrugsatfda.fda.gov) website. Additionally, the analysis incorporated supplemental data, also sourced from FDA's animal drug database, queried in January 2020. Notably, there can be a delay between when changes, including withdrawals, are made to labels and when they are reflected in relevant databases. Therefore, data searches in other databases (e.g., Food Animal Residue Avoidance Databank) may yield slightly different results.

**Data coding and analysis:** For consistency with FDA's approach, this analysis focused on medically important antibiotic drug labels approved for use in feed. Data analysis was complicated by the fact that the same product label, as defined by FDA's New Animal Drug Application (NADA) numbers for pioneer drugs or Abbreviated New Animal Drugs Application (ANADA) numbers for "generic" products, may be approved for a variety of indications in several species. To standardize the analysis, each unique combination of active ingredient(s), indications (reason for use, which includes disease or condition to be addressed, and intention of use—prevention, control, reduction, or treatment of that disease or condition), and species was counted as an indication. To account for inconsistencies in terminology on the approved labels, indications specifying disease as swine dysentery or porcine proliferative enteropathies were combined, as were all indications specifying a respiratory disease in cattle. "Duplicate" indications found on multiple NADAs and/or ANADAs were removed from the analysis. Numbers of indications for the various categories displayed in this analysis were counted manually using Microsoft Excel.

**Durations of use:** Indications that do not mention a duration of use, had a poorly defined duration of use such as "until symptoms improve," or had a duration of use longer than 21 days were considered not to have a defined duration limit. To ensure consistency, this analysis was cross-referenced with FDA's list of NADAs and ANADAs that the agency considers not to specify duration limits.<sup>12</sup>

**Multiple ingredients:** If a product included one or more secondary ingredients that are not medically important antibiotics—such as coccidiostats, growth hormones, or anthelmintics—indications specific to those secondary ingredients were excluded from the analysis. Indications that included two or more medically important antibiotics were considered to be distinct from those that included only one of the medically important antibiotics and treated separately in the analysis.

### **Specific label considerations:**

- Feed drugs are those labeled “Medicated feed” or “Type A medicated feed.”
- Withdrawn drugs. Drugs voluntarily withdrawn by sponsors were identified using FDA’s Section 6.0: Voluntary Withdrawal list (May 2020) from Approved Animal Drug Products (Green Book).
- Quality control. Pew staff duplicated all steps of data coding and analysis to ensure quality control. After the data was coded, values were compared and discrepancies resolved. Data analysis was cross-checked by a third Pew staff member. The dataset was cross-checked with [animaldrugsatfda.fda.gov](http://animaldrugsatfda.fda.gov).<sup>13</sup>

## **About this report**

This report was researched and written by senior associate Mark Eichelberg of The Pew Charitable Trusts’ antibiotic resistance project. It was edited by David Hyun, project director, along with Helene Sherburne, Kyle Kinner, Heather Cable, Sara Miller, and Demetra Aposporos.

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## Endnotes

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**For further information, please visit:**

**[pewtrusts.org/en/projects/antibiotic-resistance-project](https://pewtrusts.org/en/projects/antibiotic-resistance-project)**

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