



National Cattlemen's  
Beef Association



January 5, 2024

Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2023-D-2925, Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals**

***Submitted via Regulations.gov***

The American Association of Bovine Practitioners (AABP), the Academy of Veterinary Consultants (AVC), the National Cattlemen's Beef Association (NCBA), and the National Milk Producers Federation (NMPF), appreciate the opportunity to provide comments to the Food and Drug Administration's (FDA) draft guidance for industry (GFI) #273, Docket No. FDA-2023-D-2925. These organizations of cattle veterinarians, and beef and dairy cattle producers, continue to work toward improving antimicrobial stewardship while maintaining the health, welfare and productivity of our beef and dairy cattle. We support the use of antimicrobial drugs in cattle for disease treatment, prevention, and control, under the oversight of the Veterinarian of Record and working within a valid Veterinarian-Client-Patient Relationship (VCPR).

As organizations that represent cattle veterinarians and the beef and dairy industry, our comments will address the potential effects of implementing the proposed changes to the labels of medically important antimicrobials fed to food-producing animals on the health and welfare of cattle as well as the potential implications for veterinarians, who provide the oversight on the use of these medications for their patients.

In reviewing the document, we have several substantive concerns. Additionally, we want to reference the agency back to our extensive evidence-based comments previously submitted to earlier requests by the agency for public comments on this topic and specifically, the joint comments from AABP, AVC, NMPF and NCBA in 2017 and 2021, to include a request for information document with over 80 scientific references submitted by the NCBA.

**GFI #273 Should Provide the Necessary Flexibility for Veterinarians to Provide Effective Treatments**

The agency states that "The Directions section of the labeling should be clear that the veterinarian is to determine the actual duration that the drug will be used in a specific group of animals." We remind the agency that this is already the case when a veterinarian authorizes the duration of use on a veterinary feed directive. The process established in this guidance is not necessary to establish the guidance of a veterinarian in the Veterinary Feed Directive (VFD) process. We are concerned that the process outlined in the draft guidance will result in needless

constraints on the ability of a veterinarian to authorize appropriate antimicrobial therapy through the feed under the VFD.

Lacking sufficient flexibility for duration of antimicrobial use with these new labels, the Veterinarian of Record may not be able to effectively control anaplasmosis in cattle or reduce the incidence of liver abscesses due to differences that exist in climate-based vector ranges, geographical differences, and variation in the feeding and finishing phases. Even after years of extensive research, our current understanding of the pathogenesis of liver abscesses in cattle remains incomplete, hampering efforts to completely define the periods of risk for the disease and limiting the ability to design effective alternative interventions. Assigning durations of use for the reduction of the incidence of liver abscesses outside of a science-based approach poses unnecessary risk to both animal and human health.

Defining durations of use on a label should not restrict the veterinarian's ability to adapt treatment protocols to changing management practices and changes in the epidemiology of infectious cattle diseases. Replacing the current clear pathway of veterinary oversight with the overly restrictive duration of use labels for the medically important antimicrobial drugs used in and on feed will most likely impact the ability of veterinarians to protect cattle health and welfare against all risk factors for disease. Does the FDA believe that an established defined duration of use label is better positioned than the Veterinarian of Record, who is familiar with the specific cattle production system, to make the most appropriate treatment decisions for the required length of the antimicrobial therapy? Treatment practices should be consistent with the veterinarian's oversight authority for medically important antimicrobial drugs. If the veterinarian is identified by the FDA as the professional charged with appropriate oversight for antimicrobial use, then the draft GFI #273 should provide the veterinarian with the necessary flexibility of labeling authority to implement such oversight.

For treatment indications, the requirement of the phrase "Feed only to animals that are diagnosed with the disease" would appear to require the removal of animals not currently displaying disease signs if the drug is labeled for treatment and is to be fed to a group of animals. Requiring 100% of the animals to be diseased to meet the requirements for a VFD drug labeled for treatment is unreasonable and will result in suffering and loss of livestock resources. This lack of understanding of disease population dynamics creates concern for the entire process of establishing defined durations of use under this guidance.

### **Defining Durations of Antimicrobial Use Requires Science-Based Decision-Making**

In veterinary medicine, the literature to support optimal duration of antimicrobial exposure is scarce. The absence of data for specific, science-based durations of use for antimicrobial therapy for cattle diseases, such as anaplasmosis and liver abscesses, suggests that any established durations would be speculative.

The agency includes suggested antimicrobial mitigation statements in the draft guidance, for example, "Using an antimicrobial of the same drug class in the same group of animals immediately following use of this drug may increase the risk of antimicrobial resistance development. Consider using a drug from a different class if available." Selection for resistance is based on two main components. One is the antimicrobial. The second component is the nature of resistance, both expressed and unexpressed, in exposed pathogen populations (i.e., populations composed of multiple isolates with different resistance characteristics). Without knowing the resistance status of

subpopulations, making dogmatic blanket statements as to continued use of the same drug class is irresponsible. A recent article, “Systematic review of the effects of antimicrobial cycling on bacterial resistance rates within hospital settings”, acknowledged the lack of robust designs and standardized protocols. However, their overall conclusion, based on 15 studies, was “Nonetheless, in view of the available data, we find no reason to believe that cycling should be expected to improve antibiotic resistance rates within hospitals.”<sup>1</sup> Does the agency have information to support the cautionary statement included in the draft guidance in relation to the affected approvals? Regardless of inclusion of cautionary words such as “may” and “consider”, this statement implies that a veterinarian should be rotating antimicrobial classes in a series of therapeutic interventions. We ask the agency to remove dogmatic statements based on general assumptions from the document, and to return to evidence-based label inclusions.

One of our greatest concerns is that the agency applies “arbitrary” non-transparent criteria for acceptance or rejection of materials included in the white paper approach to establishing a defined duration of treatment. This especially applies to submission contents such as “expert consensus”. The result of this approach may be that current approvals are withdrawn or are severely limited in the ability of a veterinarian to appropriately treat animals under their care because of an agency default to a severely limited duration of treatment in the interest of maintaining an external appearance of aggressively pursuing antimicrobial stewardship. We urge the agency to be especially transparent in this process through the timely release of Freedom of Information Act documents. If the optimal duration of use represents a compromise between clinical efficacy and mitigation of antimicrobial resistance, what does the agency deem is an acceptable decrease in clinical efficacy to justify a decrease in duration of use therapy to mitigate antimicrobial resistance? Not all clinical trials support the use of shorter durations of therapy. Hoberman, et al demonstrated that treating otitis media in young children for five days vs. 10 days resulted in higher rates of clinical failure with no significant reduction on the emergence of antimicrobial resistance.<sup>2</sup> Does the agency really believe that the perception of taking steps to reduce antimicrobial resistance outweighs the current clinically determined targeted oversight by veterinary professionals? The disadvantage to imposing a label-defined duration of use for medically important antimicrobials in feed is that there is very little scientific evidence to support specific durations of therapy that minimize the development of antimicrobial resistance in either veterinary or human medical literature.

### **Implementation of GFI #273 Presents Increased Risk for Loss of Existing Products**

We believe that the changes to labels to reflect defined durations of use of medically important antimicrobials in feed requires special consideration by the agency for allowing flexibility in the process and guarding against the potential for any resulting unintended consequences. A significant and damaging unintended consequence would be the loss of existing products from the marketplace. While all newly defined durations of use should be based on scientific data for safety and efficacy, requiring extensive animal studies by the drug sponsors may present a financial burden for a historical product that could easily lead to removing the product from the

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<sup>1</sup> Chatzopoulou M, Reynolds L. Systematic review of the effects of antimicrobial cycling on bacterial resistance rates within hospital settings. *Br J Clin Pharmacology* 88(3):897-910, 2022.

<sup>2</sup> Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, Martin JM, Kurs-Lasky M, Green JD, Shaikh N. 2016. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med* 375: 2446-2456.

market as the most economically viable alternative. Withdrawing a product from the marketplace decreases the antimicrobial tools available for veterinarians and cattle producers to treat, prevent, and control infectious diseases in cattle. The unintended loss of valuable antimicrobial drugs would most certainly jeopardize animal health and subsequently, food safety. Additionally, the loss of antimicrobial products for use in animal agriculture would result in increasing the pressure for use on a smaller number of antimicrobial drugs and perhaps adversely impact the chances for developing antimicrobial resistance.

## **Conclusions**

We uphold and endorse actions to support antimicrobial stewardship, as evidenced by our multiple positions and policies on this subject within our individual organizations and the quality assurance programs that stress antimicrobial stewardship and responsible antimicrobial use in the beef and dairy industries. At the same time, we also stand in support of preserving the ability to treat animals under our care and to preserve livestock resources. Alterations in the availability and flexibility of approved products based on anything less than clearly defined evidence criteria threaten the practice of veterinary medicine. We remain skeptical that hard scientific evidence exists to establish many of the proposed durations of use for the required antimicrobial drugs in feed for the associated diseases for use in cattle. The lack of science-based decision making for all indications and uses in cattle could easily result in the unintended consequences of establishing arbitrary and unreasonable durations of use, compromising the ability of bovine veterinarians to effectively address infectious diseases in cattle, and the withdrawing of medically important antimicrobial approvals by drug sponsors.

Finally, we remain frustrated by the process at the FDA which has resulted in numerous opportunities for public comment on this issue to include: initial information from stakeholders on the affected diseases in cattle; comments on a concept paper; and comments on draft GFI #273; and yet, the agency refuses to honor stakeholders a requested 30-60-day extension to the comment period that initially originally ended during the Christmas holiday on December 26, 2023. The agency responded to a 60-day comment extension from multiple stakeholders with a 10-day extension until January 5, 2024. Given the lack of any substantive extension to the comment period by the agency, our comments should be viewed as preliminary, and we would request the opportunity to present to the agency any pending research findings on the diseases of concern for establishing durations of use, such as liver abscesses. We appreciate the opportunity to provide our joint comments and look forward to working with the agency on this issue and addressing any questions raised by our comments.

Respectfully submitted,



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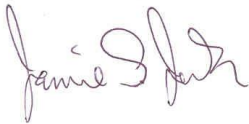
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