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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2016-D-2635: Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed: A Concept Paper

Dear Dr. Solomon:

The Pew Charitable Trusts (Pew) appreciates the opportunity to comment on the U.S. Food and Drug Administration's (FDA, the Agency) proposed framework to establish durations of use for medically important antibiotics approved for use in food-producing animals. Pew is an independent non-partisan research organization which applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life. In our work on antibiotic resistance, we seek to reduce the inappropriate use of antibiotics in human healthcare and animal agriculture and to foster innovation in drug development. Overuse of antibiotics – including use for unnecessarily long periods of time or indiscriminate use in instances not supported by clinically validated prescribing guidelines – promotes the emergence of antibiotic resistance, diminishing the effectiveness of antibiotics and placing both animal and human lives at risk. In 2018, FDA outlined its laudable objective to establish appropriately targeted durations of use for animal antibiotics that lack this essential label information, as part of its goal of bringing antibiotic use into alignment with principles of antimicrobial stewardship. While we appreciate the Agency's commitment to continue to advance antibiotic stewardship in production agriculture, FDA's concept paper misses the mark in several ways.

The Agency's proposed standards for targeted durations of use are poorly defined and unbounded.

FDA's Guidance for Industry (GFI) #213 states that new animal antibiotics are expected to "have an explicitly defined duration of dosing."[1] The framework put forth in the concept paper

[1] U.S. Food and Drug Administration, "Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals:

represents a significant departure from this standard, potentially allowing drug sponsors to avoid assigning fixed duration limitations in favor of less specific terms and conditions such as animal age, body weight, or to simply allow a veterinarian to decide the length of treatment. Because FDA already requires veterinary oversight for the administration of feed and water drugs, allowing sponsors to defer the identification of clinically appropriate duration limits for medically important antibiotics used in food animals to veterinary discretion severely limits the potential benefits of label updates in assisting prescribers to make informed veterinary and animal management decisions necessary to promote antimicrobial stewardship. Further, the framework allows sponsors to define a duration of use as a range, without requiring drug sponsors to demonstrate that the maximum of that range is necessary to protect animal health and, crucially, that the specified duration or range will avoid the induction of pathogenic resistance through prolonged or inappropriate use, to the extent possible.

The FDA should, at a minimum, adopt an updating process for animal antibiotic drug labels that ensures that sponsors are held to FDA's own judicious use standards for new animal drugs, including the stipulation that sponsors must explicitly define evidence-based use limitations for the shortest duration necessary to resolve the underlying condition and avoid the induction of resistance to the extent possible. In cases where a sponsor deems it necessary to define multiple durations or a duration range, the sponsor should be required to provide empirical data demonstrating the necessity of the longest proposed duration.

The framework fails to provide the guidance necessary to curb long-term antibiotic use.

Lengthy antibiotic treatment using agents that lack defined durations of use has become routine for producers in certain production settings. A study of 22 beef feedlots published in November 2020 found that cattle were treated for an average of 134 consecutive days, and in some cases in excess of 350 days, with in-feed macrolides.[2] This information is consistent with data from a 2011 USDA study,[3] confirming that long-term treatment reflects ongoing practices in the US agriculture industry. It is therefore alarming that the 2018 update from the National Antimicrobial Resistance Monitoring System reported that rates of resistance to the critically important macrolide erythromycin had increased from 2.1% in 2013 to 11.4% in 2018 among *Enterococcus* species sampled from beef cattle.[4] A recent meta-analysis of studies investigating the relationship between tylosin treatment and antimicrobial resistance concluded that long-duration treatment of cattle with tylosin was correlated with increased resistance among fecal

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Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209" (2013), https://www.fda.gov/media/83488/download

[2] Hope et al., "Antimicrobial Use in 22 U.S. Beef Feedyards: 2016–2017," *Zoonoses and Public Health* 67, no. S1 (2020): 94-110, https://onlinelibrary.wiley.com/doi/10.1111/zph.12775.

[3] U.S. Department of Agriculture, "Feedlot 2011 Part IV: Health and Health Management on U.S. Feedlots With a Capacity of 1,000 or More Head" (2011), https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV_1.pdf.

[4] National Antimicrobial Resistance Monitoring System, "2018 NARMS Update: Integrated Report Summary," https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2018-narms-update-integrated-report-summary.

enterococci.[5] Bacteria in the genus *Enterococcus* can act as reservoirs for antimicrobial resistance genes, and are capable of facilitating the transfer of plasmids carrying resistance genes from food animals into the human gut microbiota.[6,7] Genes that confer resistance to tylosin, such as *ermB*, can confer resistance to all clinical macrolides, as well as lincosamides and streptogramin B. It is essential that the Agency take immediate steps to reduce the overuse of these antibiotics so that the trends of resistance can be reversed.

FDA should prioritize reducing the risk of antimicrobial resistance and promoting judicious use in production settings where high-volume antibiotic use is common. Although effective management of some animal diseases can be complex, FDA's concept paper provides little to no specific guidance in cases where current use practices are per se injudicious. FDA should provide clear and specific definitions and guidelines governing the conditions under which any duration of use could be considered injudicious, and give sponsors unambiguous direction as to the Agency's expectations on the balance that sponsors should attempt to strike in order to appropriately weigh a product's proposed duration of use against the risk of promoting antimicrobial resistance. FDA-funded research is already underway to help establish more targeted durations of use for certain antibiotics, and the Agency's guidance should provide instruction to sponsors on the use of the results of this research.[8] Ultimately the Agency's review should acknowledge and take full account of common veterinary applications in feedlots and other production agriculture settings that drive antibiotic use and approach the label updating process for macrolides and other medically important drugs with an explicit goal of identifying and eliminating indiscriminate use. Furthermore, FDA should work closely with USDA and other federal One Health stakeholders to advance a more comprehensive strategy to help producers and veterinarians transition away from reliance on long-term antibiotic use and toward improved disease prevention and animal health management. A healthy, well-managed animal may never need an antibiotic. Substantially reducing antibiotic use in food animal production is an attainable outcome, but FDA must identify this goal as part of its broader stewardship objectives in order to make progress at protecting these vital drugs for human medicine.

The proposed timeline for implementation is too long.

The timeline described in the concept paper provides all sponsors up to six years or longer to provide updated duration of use information. This timeline is inconsistent with the urgency of the threat of antimicrobial resistance—the process should be allowed to take no more than three years for the overwhelming majority of drugs currently in the marketplace. Although the label

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[5] Cazer et al., "The effect of tylosin on antimicrobial resistance in beef cattle enteric bacteria: A systematic review and meta-analysis," *Preventive Veterinary Medicine* 176, (2020): https://www.sciencedirect.com/science/article/abs/pii/S0167587719304593?via%3Dihub.

[6] Angulo et al., "Human Health Hazard from Antimicrobial-Resistant Enterococci in Animals and Food," *Clinical Infectious Diseases* 43, no. 7 (2006): 911-916, https://doi.org/10.1086/507534.

[7] Sparo, Delpech, and Allende, "Impact on Public Health of the Spread of High-Level Resistance to Gentamicin and Vancomycin in Enterococci," *Frontiers in Microbiology* 9 (2018), https://doi.org/10.3389/fmicb.2018.03073.

[8] U.S. Food and Drug Administration, "FDA Announces Funding Opportunity to Help Define Durations of Use for Certain Medically Important Antimicrobial Drugs for Food Animals," news release, April 1, 2019.

updates may require sponsors to conduct new research in order to update their labels, much of this research can be performed swiftly and concurrently. An investigation by Pew of animal antibiotics without duration limits concluded that many labels should be able to be updated without new clinical research by referencing data already submitted to FDA for approval of similar drug products.[9] Cases that involve complex diseases that may necessitate more extensive research to establish durations of use should be the exceptions, not the rule. Other labels describe uses that are intrinsically injudicious, such as maintenance of weight gain or nonspecific prophylaxis, and sponsors should be required to withdraw such labels. FDA should revise its timelines and implement a tiered approach to help sponsors triage label updates according to the complexity of new studies they will need to conduct and their relative contribution to total antibiotic use among food animals. Additionally, FDA should add enforcement language to the guidance for sponsors that do not meet the deadline.

Overuse of medically important antibiotics in any setting—including animal production settings—poses a risk to public health, and FDA must ensure that these critical drugs are used responsibly. Well-defined and appropriately targeted durations of use can help producers keep treatments to the minimum durations necessary to keep animals healthy. However, limiting prescription durations is not sufficient by itself to support judicious use. FDA should carefully and skeptically review data supporting the use of combination antibiotics, especially where single-antibiotic products can be used to treat the same disease while maintaining a lower selective pressure for organisms to develop resistance. Furthermore, data supporting the use of products intended for use in disease prevention should be carefully examined and weighed against the risk posed by potentially widespread use of the antibiotic in the absence of disease. In all cases, the responsibility lies with the drug sponsor to demonstrate the necessity, safety, and judiciousness of their products under conditions specified on the label.

Pew strongly supports the implementation of science-based duration limits on medically important antibiotics. However, the initial proposal FDA has outlined in its concept paper is substantially flawed and will require significant revision. We urge FDA to carefully consider the comments and feedback it receives, and suggest that FDA considers hosting a public meeting to give stakeholders a platform to continue the dialogue. We look forward to continuing to work with FDA on this important issue.

Sincerely,

David Hyun
Project Director, Antibiotic Resistance Project
The Pew Charitable Trusts

[9] The Pew Charitable Trusts, "FDA Must Establish Limits for All Animal Antibiotics" (2021), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/04/fda-must-establish-limits-for-all-animal-antibiotics.