

June 11, 2021

Dockets Management Staff
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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

Introduction

The undersigned members of Keep Antibiotics Working (KAW)¹ and colleague organizations are writing to express our serious concerns about the Food and Drug Administration's (FDA's) flawed approach to addressing antibiotic overuse as described in the [Concept Paper](#), "Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed".

The Concept Paper wrongly prioritizes the narrow economic interests of the animal drug industry and livestock producers over the FDA's mission and the broader public's interest in protecting public health. The Concept Paper dangerously legitimizes the routine use of medically important antibiotics in large numbers of food animals for long durations by not requiring concrete limits on how long a drug can be used and by explicitly supporting the routine use of medically important antibiotics in healthy animals for disease prevention. Finally, the proposed timelines for transitioning to limited durations are too long. FDA first accepted comments on setting duration limits over four years ago and has proposed a timeline for implementation of four to six years after final guidance is released in the future. Under the FDA's current timeline, the agency

¹ Keep Antibiotics Working, a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups, is dedicated to eliminating the inappropriate use of antibiotics in farm animals, a significant contributor to the rise in antibiotic resistant disease.

will have spent at least fourteen years implementing this modest step to restrict the overuse of antibiotics on farms. This is unacceptable for an agency with a mission to protect public health.

Antibiotic resistance continues to grow as a public health threat leading to tens of thousands of deaths each year and putting common medical treatments at risk. The events of this previous year have proven that federal agencies can drastically reduce the impacts of public health threats if they choose to act. Sadly, we have also seen how federal inaction can lead to unnecessary death and disease. FDA has been stalled on addressing the threat of antibiotic resistance that results from the overuse of antibiotics on farms over the last four years. Now is the time for FDA to swiftly move forward to act to stop the overuse of antibiotics on farms.

Prohibit the use of medically important antibiotics to prevent disease

The overuse of antibiotics in food animals is not limited to using antibiotics for extended periods of time. One major area of overuse is the use of antibiotics for disease prevention. FDA defines prevention in the Concept Paper (page 6) as the administration of a drug “to a group of animals, none of which have been diagnosed with the indicated disease, when transmission of existing undiagnosed infections, or the introduction of pathogens, is anticipated based on history, clinical judgment, or epidemiological knowledge.” So, in the Concept Paper “prevention” refers to administering antibiotics to animals when none of them are showing signs of illness. The FDA then lists the type of information which could be used to determine whether preventive administration of antibiotics could be initiated: “Environmental risk factors for the indicated disease (e.g., related to temperature, ventilation) and Host risk factors for the indicated disease (e.g., related to age, production class or production stage, nutrition, breed or genetics, stressors, immune status).” These host and environmental risk factors have nothing to do with disease but instead are related to the conditions under which animals are raised. Using these as determinants of antibiotic use is an invitation to overuse and is contrary to any principles of antibiotic stewardship.

Rather than administering antibiotics to all animals at a certain production stage under conditions related to poor ventilation, or type of nutrition, livestock producers should provide healthier living conditions, improved ventilation, and proper nutrition. FDA’s explicit allowance for antibiotics to be used to compensate for unhealthy conditions on farms where animal illness is

commonly anticipated under normal operating conditions as proposed in the Concept Paper is contrary to any principles of judicious use and also contrary to FDA's mission to improve animal health.

Arguably, the most clear and egregious use of antibiotics in this way is the use of tylosin in cattle feedlots to prevent liver abscesses. Liver abscesses occur in feedlot cattle because of inappropriate high energy diets with inadequate roughage. The cattle industry's response to this problem is not to provide healthy diets, but instead to feed a critically important antibiotic, tylosin, in the feed of cattle for the whole time they are at the feedlot. This does not eliminate the health problems caused by the inappropriate diet but instead reduces it to an economically acceptable level. The long duration of use of antibiotics for liver abscesses is a significant issue, but so is the more general problem of using a critically important antibiotic to prevent an animal health problem created by farm management decisions. FDA's approval of tylosin for this purpose is a direct contributor to the unhealthy feeding practice and to the associated overuse of medically important antibiotics affiliated with the practice.

The World Health Organization has recommended that medically important antibiotics not be used for disease prevention except under exceptional circumstances² and legislation consistent with these recommendations will take effect in the European Union in 2022.³ The Codex Alimentarius Ad hoc Task Force on Antimicrobial Resistance, with the participation of the U.S. has agreed to language stating that medically important antibiotics for disease prevention should only be used under "exceptional circumstances".⁴

We ask that FDA, while requiring changes to antibiotic drug labels for use in food-producing animals, put limits on how long antibiotics can be used and also remove claims for disease prevention except in "exceptional circumstances." If FDA chooses to not address the overuse of

² World Health Organization. "WHO guidelines on use of medically important antimicrobials in food-producing animals". Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

³ EUR-lex | Access to European Union Law. "Authorisation, Import and Manufacture of Veterinary Medicines," June 7, 2021. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM%3A4381220>.

⁴ Joint FAO/WHO Food Standards Programme and Codex Alimentarius Commission. "Report of the Sixth Session of the Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance." Codex Alimentarius Commission, December 10, 2018.

http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-804-06%252FREPORT%252FFINAL%252520REPORT%252520FREP19_AMRe.pdf

antibiotics for disease prevention it should make clear that age and stage of production should not be the basis for decisions to use medically important antibiotics but instead cite other exceptional circumstances before use.

Limit durations of use for medically important antibiotics to under 21 days

FDA's stated goal in releasing this paper is to, "mitigate the development of antimicrobial resistance" in order "to protect public health" (Concept Paper page 1). Despite this, the Concept Paper does not require drug makers to take any steps to identify a safe duration of use as they would for a new drug approval. Instead the Concept Paper (page 9) asks the drug makers to identify durations based on drug efficacy. By setting durations of use based on efficacy data alone rather than taking into consideration human health, FDA is prioritizing in the Concept Paper the interests of drug makers to maintain sales of their products and livestock producers to maintain productivity of their flocks or herds rather than the interests of the broader public to maintain the efficacy of antibiotic drugs for disease treatment.

Instead of a single duration, the Concept Paper (page 9) allows drug makers to create a range of durations (e.g. feed for 7 to 14 days) for a single indication, but only requires efficacy data for the shortest allowed duration. Based on the efficacy data from the shortest duration, the sponsor would choose a duration that "generally would be significantly less than the animals' typical production lifespan and slaughter weight, unless otherwise justified." Alternatively, a sponsor could allow a veterinarian to decide when to stop administration. Given that feedlot cattle live several years and pigs live on average half a year, significantly less than the whole life of an animal could be months of antibiotic use and FDA would allow, if "otherwise justified," use for the whole life of the animal (Concept Paper page 11). Similarly, there is no evidence that all veterinarians will make decisions that limit the duration of use of an animal antibiotic to a duration that is safe. In fact, there is overwhelming evidence that medical professionals, both veterinarians and physicians, consistently make prescribing decisions that are contrary to judicious antibiotic use.

The efficacy only approach in the Concept Paper is in contrast to the safety assessment for new animal drugs put in place by the FDA in 2003 as described in [Guidance for Industry #152](#) (GFI#152). GFI#152 (page 25) recommends that drug applications that are at a high or medium

risk for antimicrobial resistance not be approved for “high extent of use,” which is defined as use in a group of animals for more than 21 days (GFI#152, page 23). Most medically important antibiotics used in food animals have been found to be at high or medium risk for antibiotic resistance when evaluated during the drug approval process. Consistent with GFI#152 we recommend that FDA set 21 days as the maximum duration of use for all medically important antibiotics used in food animals. If an antibiotic is to be used for longer than 21 days in a group of food-producing animals, the animals should be examined by a veterinarian to determine whether an additional prescription or veterinary feed directive is needed.

This 21 days default maximum duration limit will also provide a clear guidance to drug makers, something which is absent from the current Concept Paper. The Concept Paper does not actually provide guidance on how to determine durations beyond stating that it should be “significantly less than the animals’ typical production lifespan and slaughter weight, unless otherwise justified.” The FDA has not described what is to be done if the data shows that a drug is effective for the whole life of an animal and as we discussed above, the Concept Paper does not require drug makers to provide data showing that the chosen durations reduce the risk of antibiotic resistance. Setting a default duration of 21 days consistent with existing guidance would resolve the question over how to determine a safe duration. If there is evidence that a duration shorter than 21 days is effective, then that duration should be used.

Because there are approved medically important antibiotics with defined durations that are longer than 21 days, FDA should expand the list of affected products to include these drugs. Some of these drugs with long durations are approved for use in water so FDA should expand the scope of the guidance to include all drugs that have durations longer than 21 days, not just medicated feeds.

Clarify that duration limits should actually be followed

In order to have the desired impact and protect public health, the new duration limits made through the process laid out by the Concept Paper and the subsequent guidance or regulation must be followed. If a veterinarian can write an order to use an antibiotic drug for multiple instances of the same duration in the same group of animals, this completely undermines the impact of this effort to set limited durations of use. This currently occurs with the practice of

pulse feeding chlortetracycline in the feedlot industry. Chlortetracycline has a clear duration limit of five days when used at a treatment dose in cattle. In the common industry practice of pulse feeding, a veterinarian writes an order to feed chlortetracycline for five days, followed by a two day pause in the drug, which is then followed by another five-day administration of the antibiotic. Additional pulses may be added extending the duration of feeding chlortetracycline at the treatment dose. In effect, veterinarians and livestock producers are ignoring the duration limit when pulse feeding. FDA must make clear that durations should be followed and that durations cannot be legally stacked on one another as they are during pulse feeding.

Implement label changes by the end of 2025

FDA first requested comments on setting duration limits for medically important antibiotics in 2016 and took no further public action for over 4 years when it released the Concept Paper in January 2021. FDA has indicated that it does not anticipate a final rule until June 2024⁵ and the Concept Paper (page 7) then includes an implementation timeline of an additional 4 to 6 years. This establishes a potential completion of implementation in the year 2030, 14 years after FDA first accepted comments. Fourteen years is too long to wait to protect public health. With this timeline, FDA is once again prioritizing the interests of the regulated industry over public health. We ask that FDA issue final guidance by the end of FY 2022 and complete the implementation by 2025. The simplification that we have proposed to limit durations to no more than 21 days, consistent with protecting public health, makes the transition much simpler allowing for a shorter timeline for implementation.

Update existing labels so that they are consistent with definitions of treatment, control, and prevention in the Concept Paper

The Concept Paper (pages 5-7) provides clear definitions for the terms “treatment”, “control”, and “prevention” that are often used to describe approved indications for antibiotic drugs in food producing animals. We support these definitions and ask that the FDA use them consistently when approving indications for the use of antibiotics. We also ask that the FDA review existing

⁵ Center for Veterinary Medicine | FDA. “FDA-TRACK: Progress on FDA’s Support of Antimicrobial Stewardship in Veterinary Settings.” *FDA*, May 26, 2021. <https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-progress-fdas-support-antimicrobial-stewardship-veterinary-settings>.

indications to identify ones that are not consistent with these definitions and seek changes from the drug makers to make sure they are used consistently. For example, lincomycin is approved to control swine dysentery but the label instructions state that it is to be used “on premises with a history of swine dysentery but where symptoms have not yet occurred” (21 CFR 555.325). Under the Concept Paper’s definition, use of an antibiotic before clinical signs are present is prevention not control.

Conclusion

FDA has delayed too long in acting to address the overuse of antibiotics in food animals and has prioritized too often the interests of the regulated industry over the interests of the broader public. This must stop. FDA must prioritize protecting public health and require drug makers to set durations that are short enough to reduce antibiotic resistance. FDA should also considerably expedite the timeline for implementation and make it clear that durations limits are not to be ignored. Finally, FDA should not only limit how long antibiotics can be used in animals but also prohibit the routine use of antibiotics for disease prevention.

Sincerely,

Antibiotic Resistance Action Center, George Washington University

Center for Food Safety

Center for Biological Diversity

Food Animal Concerns Trust

Health Care Without Harm

Johns Hopkins Center for a Livable Future

Natural Resources Defense Council

World Animal Protection