CENTER FOR Science IN THE Public Interest
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Food And Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: Comment on Draft Guidance for Industry #273: Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals (Docket FDA-2023-D-2925)

To Whom It May Concern,

The Center for Science in the Public Interest (CSPI)[1] submits these comments on Draft Guidance for Industry (GFI) 273,[2] to the United States Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM). The draft guidance addresses voluntarily establishing durations of use for approved medically important antimicrobial animal drugs with indications that currently lack a defined duration of use.

CSPI supports the CVM objective of defining durations of use for these antimicrobials, as such durations could lead to decreased unnecessary antimicrobial use in food animal production and thus limit the antimicrobial resistance fostered by such use.

We have substantial concerns, however, regarding key aspects of CVM's proposal. The draft GFI instructs manufacturers to provide an indefinite, unbounded expected duration of use and provides a definite, time-bound duration of use only for the maximum duration of use, a timeframe that is established to accommodate rarer clinical circumstances. This approach will likely nudge veterinarians toward the maximum duration of use, in some cases potentially leading to longer durations of use than is currently the case. Furthermore, CVM does not request any antimicrobial resistance data or analyses drug sponsors may have or ask sponsors to consider resistance risks in establishing the duration of use, even though such information could be critical to understanding whether the benefits of certain durations of use outweigh the associated risk of resistance development.

We expand on these concerns below and urge CVM to adequately address them in the final guidance.

[1] CSPI is your food and health watchdog. Since 1971, CSPI has worked to improve the public's health through better nutrition and food safety. The organization's work is supported by subscribers to its Nutrition Action Healthletter, one of the nation's leading health newsletters. CSPI is an independent organization that does not accept government donations or corporate funding.
[2] Draft Guidance for Industry #273: Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals. U.S. Food and Drug Administration Center for Veterinary Medicine. September 2023. Accessed November 15, 2023. https://www.fda.gov/media/172362/download

Background

Antimicrobial use in food animals is a public health issue because it can foster the development of resistance to antimicrobials in pathogenic bacterial populations.[3] This resistance limits the available treatments for microbial infections in humans and animals. The Centers for Disease Control and Prevention estimates that 35,000 people in the United States die each year as a result of antibiotic-resistant infections.[4] The Review on Antimicrobial Resistance, a project commissioned by the United Kingdom to explore this public health problem in depth, predicted that, if resistance control measures fail, antimicrobial-resistant pathogens will cost 100 trillion U.S. dollars globally between 2016 and 2050 and the annual death total will exceed 10 million by 2050.[5]

Drugs used in animal feed could contribute substantially to antimicrobial resistance development, as they are approximately 64% of the annual total weight of medically important food animal antimicrobials sold in the United States.[6] CVM has acknowledged the role of feed antimicrobials in resistance development and taken previous actions to mitigate this harm. Most notably, the agency issued GFI 213, which offered guidance on voluntarily removing growth promotion uses from labels of medically important antimicrobials used in animal feed and drinking water.[7] For such feed antimicrobials, the guidance also advised manufacturers to require a Veterinary Feed Directive (VFD), which necessitates veterinary supervision and precludes off-label use. This GFI, while voluntary, resulted in full compliance by 2017, effectively eliminating labeled growth promotion uses and ensuring veterinary involvement in decisions to use these drugs.[8] GFI 213 was associated with a 33% decrease in the weight of medically important feed antimicrobials sold in the U.S. in 2017 compared to 2016, indicating that voluntary label changes can have a substantial impact on unnecessary antibiotics use.[9]

Another long-standing problem with feed antimicrobials is that the labels lack an explicit duration of use in many instances, which may contribute to antimicrobials being fed for longer than medically necessary, raising the risk of resistance development. CVM has indicated that approximately 40% of approved medically important antimicrobial feed drug applications include at least one indication that does not have a defined duration of use.[10]

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[3] Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence?.*BMC Vet Res*. 2017;13(1):211. Published 2017 Jul 4. doi:10.1186/s12917-017-1131-3

[4] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

[5] Background. Review on Antimicrobial Resistance. Published 2016. Accessed July 22, 2022. https://amr-review.org/background.html

[6] 2021 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. U.S. Food and Drug Administration Center for Veterinary Medicine. December 2022. Accessed November 15, 2023. https://www.fda.gov/media/163739/download?attachment

[7] 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: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209. U.S. Food and Drug Administration Center for Veterinary Medicine. December 2013. Accessed November 15, 2023. https://www.fda.gov/media/83488/download

[8] FDA-TRACK: Progress on FDA's Support of Antimicrobial Stewardship in Veterinary Settings. U.S. Food and Drug Administration. Updated August 18, 2023. Accessed November 15, 2023. https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-progress-fdas-support-antimicrobial-stewardship-veterinary-settings#Vet%20Oversight

[9] 2017 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. U.S. Food and Drug Administration Center for Veterinary Medicine. December 2018. Accessed November 15, 2023. https://www.fda.gov/media/119332/download?attachment

[10] Supporting Antimicrobial Stewardship in Veterinary Settings Goals for Fiscal Year 2109-2023. U.S. Food and Drug Administration Center for Veterinary Medicine. September 2018. Accessed November 15, 2023. https://www.fda.gov/media/115776/download?attachment

Establishing definite, time-bound durations of use in a drug label not only provides guidance for veterinarians, but it also creates legally enforceable limits on the length of time the drug can be administered under a single VFD. This is because a duration that falls outside of the labeled indication would be considered an "off-label" use, and such issuances are not allowed for antibiotics administered in animal feed. In other words, if an indication states "administer daily for 2 to 4 days," the veterinarian cannot write a VFD for less than 2 days or more than 4 days. Nevertheless, longer periods still may be achieved by issuing multiple VFDs with the same indication, provided the veterinarian determines additional time on the medication is warranted.

To assist in the development of this draft GFI, in 2021, CVM released a concept paper describing a potential approach to defining durations of use.[11] CSPI provided comments[12] on the concept paper, critiquing the long implementation timeline (four to six years at the earliest) and the lack of sufficient emphasis on antimicrobial resistance development potential when establishing duration limits.

Draft GFI 273 Summary

The draft GFI proposes to establish duration limits by having drug sponsors include both an "expected" and a "maximum permitted" duration of use on label revisions. The expected duration of use is meant to capture more routine uses. The maximum permitted duration of use is meant to enable flexibility for the rarer times when longer durations of use are called for.

The GFI does not advise sponsors to provide an expected duration of use that is definite and time-bound. Instead, the draft GFI advises sponsors to utilize standardized language provided by CVM, offering a menu of different boilerplate paragraphs depending on whether the indication is for treatment, control, or prevention. For example, the suggested boilerplate paragraph for the expected duration of most "treatment" indications is, "Feed only to animals that are diagnosed with the disease. Begin feeding after the disease is diagnosed and continue until the animals no longer require this medication, as determined by the veterinarian."

The guidance also includes "alternative" boilerplate paragraph options that do allow companies to include limited quantitative information, but nevertheless fail to create a definite, time-bound period for the duration of use. Examples of such language includes setting a minimum number of days, e.g., "...continue for at least [describe minimum duration] until the animals no longer require this medication…," or setting a number of days following resolution of symptoms, e.g. "continue until [X] days after resolution of clinical signs..."

The draft GFI states that sponsors do not need to provide scientific justification supporting the expected duration should they use the standardized boilerplate statement. However, if sponsors include any of the alternative boilerplate statements with the limited quantitative information, or if sponsors wish to deviate from any of the provided boilerplate statements, for example by

[11] Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed: A Concept Paper. U.S. Food and Drug Administration Center for Veterinary Medicine. January 2021. Accessed November 15, 2023. https://www.fda.gov/media/144927/download?attachment

[12] Docket No. FDA-2016-D-2635: Concept Paper: Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed Comment. Center for Science in the Public Interest. June 11, 2021. https://www.regulations.gov/comment/FDA-2016-D-2635-32019

including definite, time-bound expected durations, they are asked to provide scientific justification.

The maximum permitted duration of use provisions, on the other hand, suggest the inclusion of definite, time-bound information such as "Do not feed for more than X days" or similar statements on labels, preventing a veterinarian from issuing a VFD for longer than that duration unless they renew the VFD. This time frame is designed to capture the most extreme upper end of legitimate clinical use: CVM emphasizes that "the maximum permitted duration of use on the labeling should not be the duration veterinarians would routinely order," but should provide veterinarians with adequate flexibility to use the drug in a range of legitimate circumstances. The agency requests that a boilerplate statement reflecting this sentiment be included on the label in an "Additional Recommendations" section.

In contrast to the expected duration of use, CVM requests that drug sponsors support the maximum permitted duration of use with scientific justification. However, the standard of evidence for such justification is very permissive. Whereas the indication in a new animal drug application typically must be supported by efficacy data from adequate and well controlled investigations,[13] the draft guidance proposes that the maximum permitted duration of use can be justified by "peer-reviewed scientific literature, recognized standards of veterinary practice, a consensus of expert opinions, and other such information."

The agency does not provide a specific standard for how it will evaluate the scientific justification for maximum durations of use or determine that the duration of use requested is inappropriate, though it specifies that a maximum permitted duration of use approaching either the production lifespan of the target animal or the maximum VFD expiration date (i.e., six months) will be "difficult to justify." The agency implies, though, that such a maximum permitted duration of use may be "necessary" and "consistent" with good antimicrobial use principles in some cases.

Importantly, while mitigating antimicrobial resistance is a key objective for the guidance, FDA offers no instructions to industry regarding considering resistance risks in establishing the duration of use. Sponsors are also not advised to submit or consider information pertaining to antibiotic resistance to the drug, even where such information may be publicly available or in the possession of the sponsor. While the guidance offers sponsors the option to include boilerplate "resistance mitigation statements," such as "Feed this drug only to the number of animals necessary to treat, control, or prevent the indicated disease in accordance with the approved conditions of use," the agency does not suggest that the risk of resistance should be considered in establishing an expected or maximum duration of use.

Lastly, CVM has accelerated the timeline for implementation from that described in the 2021 concept paper, expecting industry compliance three years from the GFI's finalization, one to three years earlier than originally contemplated.

[13] 21 U.S.C. § 360b(d)(3) https://www.govinfo.gov/content/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360b.htm

In summary, GFI 273 encourages industry to establish a boilerplate expected duration of use language with generally no definite, time-bound duration and no scientific support. It also would establish a definite, time-bound maximum permitted duration of use intended to capture the extreme, non-routine cases, but these durations may be supported by potentially weak scientific evidence. Companies need not consider the risk of antimicrobial resistance in setting such durations of use.

Concerns with GFI 273

CSPI's primary concerns with the draft GFI are the recommended indefinite, non-time-bound language for the expected duration of use and the resultant lack of a request for scientific justification for the expected duration of use. This approach, combined with the request for establishing a maximum duration of use that is definite, time-bound, and supported by scientific evidence (albeit potentially weak), will likely encourage veterinarians to utilize the maximum permitted duration of use rather than opting for a shorter expected duration of use.

As described above, the guidance encourages sponsors to take an approach that will leave the maximum duration as the only definite, time-bound duration of use on labels, even though CVM acknowledges that this duration "should not be the duration veterinarians would routinely order." Failing to provide a definite, time-bound duration of use for the expected course of treatment, which is what most veterinarians will expect in a drug label, in effect transfers the burden of determining an expected duration onto clinical veterinarians, who may have little evidence or sufficient resources to make such a determination. Thus, they may be inclined to default to the maximum, presumably longer duration of use.

Moreover, if veterinarians appreciate that the maximum duration of use is better substantiated by scientific evidence than the expected duration of use, which is merely a standardized boilerplate, this, too could nudge them toward employing the maximum duration.

Veterinarians may be accustomed to following FDA-approved, evidence-supported quantitative expected durations of use on a label as a default, unless there is overriding evidence that a provided duration of use should not be followed. The draft GFI describes a reversed approach to labeling (i.e., the evidence-supported duration is meant to be the rare exception, not the expected approach). Veterinarians' lack of familiarity with this counter-intuitive approach will likely again tend to nudge them toward the only definite, time-bound duration of use on the label, the maximum permitted duration of use.

Even without this guidance, antimicrobial drug sponsors and salespersons are financially motivated to promote the drug to veterinarians and producers at the longest duration of use approved in the label, creating additional encouragement for the maximum duration of use.

CVM does not provide adequate rationale for taking the approach it has to setting durations of use. It is possible that the agency is concerned about establishing a duration of use that unnecessarily restricts veterinarians from addressing rare clinical circumstances, particularly where sufficient clinical trial data are lacking for an indication. Unfortunately, the approach the agency has taken to resolving this concern over-emphasizes the rare cases over the typical ones.

If an expected duration of use fails to deliver the desired clinical outcome, a reassessment by a veterinarian would generally be warranted before another VFD is issued. This GFI, however, appears to foreground inconvenience to veterinarians over the wisdom of requiring clinical reassessment or the dangers of unnecessarily promoting antimicrobial resistance. Moreover, even if rare circumstances warrant a longer duration than would be routinely recommended, this does not preclude a definite, time-bound expected duration for routine circumstances.

Our second concern with the draft GFI is that CVM does not indicate that drug sponsors should provide available data or analysis on their drug's antimicrobial resistance development potential. In order to ensure that the benefits of a duration of use of a drug outweigh its risks, the drug sponsor and FDA should consider all of the safety risks, including antibiotic resistance risks. Resistance data and analysis could be especially useful, for example, in determining durations of use in cases where the animal health data indicate that the drug has substantially diminishing efficacy benefits at longer durations of use, even as antimicrobial resistance risk rises.

Requested Changes to GFI 273

Considering the aforementioned issues with the draft GFI, we recommend the following changes be made:

First, the section "Defining the Expected Duration of Use" should be amended to advise manufacturers to provide a definite, time-bound expected duration of use for each indication in the label, supported by evidence. If necessary, labels can provide flexibility within these quantitative expected durations of use (e.g., feed for 2 to 4 days), provided such range has a definite upper bound and is supported by evidence.

CVM should define what level of evidence should be submitted to support the expected durations of use. Where substantial evidence is lacking, companies should be advised to explain to the agency that current evidence is insufficient to justify an expected duration of use. The agency should then give sponsors a reasonable timeline to develop such data and should also direct its own resources towards clinical studies designed to fill the most critical evidence gaps, if necessary. The agency has already funded several studies to help determine durations of use for some common feed antimicrobials lacking durations of use.[14] In the interim period before such data is available, CVM could consider advising sponsors to utilize existing evidence to establish a tentative definite, time-bound expected duration of use, which could be amended when better data become available. While generating such data may take time, it is preferable to take this approach if it results in a duration of use that is evidence-based and protective of public health, in contrast to an approach that undermines public health by nudging veterinarians towards unnecessarily long durations of use.

Second, the section on "Defining the Maximum Permitted Duration of Use" should be revised to make clear that a duration aimed at capturing rare, non-routine clinical circumstances is not required. We recommend the title of this section be amended to reflect these changes (e.g.,

[14] FDA Funded Grants and Contracts Related to Antimicrobial Use and Resistance in Animals. U.S. Food and Drug Administration. Updated August 11, 2023. Accessed December 6, 2023. https://www.fda.gov/animal-veterinary/antimicrobial-resistance/fda-funded-grants-and-contracts-related-antimicrobial-use-and-resistance-animals

"Defining Durations for Rare Circumstances"). Manufacturers should be advised that language describing durations of use to be used in rare clinical circumstances may be included in the label only if the manufacturer submits evidence justifying such use. CVM should describe a high evidence burden for such uses that demonstrate that 1) clear clinical circumstances exist under which the benefits of an extended duration outweigh the risks 2) veterinarians can identify, at the point of writing the initial VFD, that such circumstances exist (i.e., no additional assessment by the veterinarian would be required to diagnose the need for such extended use). The labeling for such extended durations of use, if included, should instruct the veterinarian how to distinguish these rare circumstances from the expected circumstances (e.g., diagnostic testing necessary, specific clinical signs present). Such rare uses, if longer than the expected duration, should be definite and time-bound in order to avoid leaving an open-ended duration.

Finally, in setting duration limits, CVM should request that drug sponsors consider antimicrobial resistance development due to the usage of their antimicrobials in feed. In doing so, sponsors may reference the agency's draft Guidance 152 ("Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern").[15] Manufacturers should be advised to characterize the effects of duration of use on selection pressure for antimicrobial resistance and to provide adequate information supporting the overall safety of the drug under the proposed duration of use. This includes considering any antibiotic resistance data or analysis that are available to the manufacturer and demonstrating how such data have been integrated into the proposed duration language.

Such a population-based approach to drug regulation would be consistent with the direction in which the agency appears to be moving. In a recent guidance related to the evaluation of new drug and biological products for humans, FDA states, "For example, in the review of drugs, including vaccines, to diagnose, prevent, or treat communicable diseases, risks related to disease transmission are important considerations."[16] In a JAMA Viewpoint, we noted that, "With respect to veterinary products, FDA already considers the effects of regulatory decisions on the human population, not just animals,"[17] citing language in CVM's GFI 213 that "concerns regarding the development of antimicrobial resistance in human and animal bacterial pathogens."[18] For these reasons, we believe that including antimicrobial resistance data in duration setting is appropriate and consistent with current agency practice.

Conclusion

Thank you for providing an opportunity to comment on the draft GFI. We emphasize the need for the agency to require drug sponsors to include evidence-supported, definite, time bound

[15] Draft Guidance for Industry 152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern. U.S. Food and Drug Administration Center for Veterinary Medicine. January 2023. Accessed December 6, 2023. https://www.fda.gov/media/69949/download

[16] Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products. U.S. Food and Drug Administration Center for Drug Evaluation and Research. October 2023. Accessed January 5, 2024. https://www.fda.gov/media/152544/download

[17] Lurie P, Sharfstein JM. Product Approval and Public Health at the US Food and Drug Administration. JAMA. 2021;326(24):2469-2470. doi:10.1001/jama.2021.22354

[18] 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: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209. U.S. Food and Drug Administration Center for Veterinary Medicine. December 2013. Accessed November 15, 2023. https://www.fda.gov/media/83488/download

expected durations of use. We look forward to working more with CVM as the agency finalizes GFI 273.

Sincerely,

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