KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.org

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RE: Draft Guidance for Industry Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals, Docket Number: FDA-2023-D-2925

We, the undersigned member and colleague organizations of Keep Antibiotics Working (KAW), appreciate the opportunity to comment upon Draft Guidance for Industry #273 (*Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals* (draft GFI#273)).

Introduction:

The Food and Drug Administration (FDA) has for decades recognized the dire nature of the public health threat from antibiotic resistance which leads to over 2 million illnesses and over 35,000 deaths in the U.S. each year. Yet, there is a disconnect between the seriousness of the problem and the FDA's actions to respond to it. This is clear in draft GFI#273 where the stated goal is to "mitigate the development of antimicrobial resistance" but mitigation of resistance is not included as a criterion in defining appropriate durations, it is not included as a consideration for veterinary decision making, and any specific labeling aimed at mitigating resistance (such as not using drugs from the same class right after a previous use) are entirely optional "not required conditions of use" and are not even required to be included on the veterinarian's order given to the client.

The FDA has in the past used "mitigating resistance" as a criterion for setting durations in New Animal Drug Approvals; as early as the 1970s when sponsors of antibiotics for use in feed for more than 14 days had to submit data from studies showing they did not lead to resistance,[1] as well as in 2003 in Guidance for Industry #152, which recommends against use of antibiotics for more than 21 days when there is a high or medium risk of resistance for the proposed use.[2] The

[1] Gilbert. A review of studies submitted to CVM assessing the effects of sub-therapeutic use of antimicrobial drugs on the Salmonella reservoir in food producing animals. December 5, 2001. https://wayback.archive-it.org/7993/20170114062719/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM127720.pdf

[2] The FDA has added additional language related to animal health criteria in the current draft of Guidance For Industry #152 (Draft GFI#152) with relation to durations which was not included in the original guidance published in 2003. It is inappropriate for animal health criteria to be included in a human safety review of new animal drugs. FDA regulations do not allow balancing human safety against animal health benefits, yet the agency is doing this in draft GFI#152 and in draft GFI#273.This undermines the FDA's authority to regulate animal drugs with respect to microbial safety. The irrelevance of animal health criteria to human safety decision in the context of antibiotic resistance is extensively discussed in the 2005 Final Decision of the [FDA] Commissioner on Withdrawal of the New Drug Application for Enrofloxacin in Poultry, Docket 2000N-1571: https://www.regulations.gov/document/FDA-2000-N-0109-0137. The irrelevance of animal health factors to decisions on human safety criteria was also reiterated by the FDA in the recent order revoking the Approved Method for Carbadox in Medicated Swine Feed, 88 FR 76760-76770: https://www.federalregister.gov/documents/2023/11/07/2023-24548/phibro-animal-health-corp-carbadox-in-medicated-swine-feed-revocation-of-approved-method

FDA has chosen not to take this approach in draft GFI #273. We recommend that the FDA create a default, baseline maximum duration for the use of medically important antibiotics in animal feed consistent with the definition of "long duration of use" in GFI#152, i.e., 21 days. If drug sponsors propose a duration of use longer than 21 days, the FDA should require sponsors to submit data showing that the longer use does not lead to increased resistance and that such use is necessary. In addition, when the FDA has evidence that risk mitigations other than duration limits are effective, such as not using the same class of antibiotics immediately after a prior use, the FDA should require these additional risk mitigations as conditions of use.

We are concerned that allowing sponsors to create maximum durations based on the "range of legitimate circumstances or scenarios that might sometimes be encountered in the United States" (Draft GFI#273, p. 16) without any consideration of potential resistance might actually *increase both* overall use of medically important antibiotics, and antibiotic resistance. Our concern is that the maximum duration may be treated as the default, given that draft GFI #273 makes clear that the antibiotic resistance risk mitigation language, such as "use only when needed," is entirely optional. The FDA should not assume that this approach to setting durations will have the intended effect of minimizing the extent of antimicrobial drug exposure for the covered new animal drug applications.

As this is a guidance document that does not create any legal obligations for anyone, the FDA should affirmatively ask sponsors to make changes to the directions of use of the covered antibiotics that would in fact meet the intended goals of minimizing resistance development.

The final guidance should consider resistance development as a problem that should be taken into consideration when making antibiotic use decisions.

Draft GFI#273 (p.1) states that the goal of defining durations is "to mitigate the development of antimicrobial resistance" noting that "the development of resistance to medically important antimicrobial drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat." "A serious public health threat" clearly indicates the FDA understands there is a human safety issue related to the continued use of these products. Draft GFI#273 goes on to state that the products subject to the Draft GFI were approved before the problem with long durations were recognized (p. 2), and that the Draft GFI's aim is "minimizing the extent of antimicrobial drug exposure, thereby supporting efforts to mitigate the development of antimicrobial resistance (p.4)." To that end, sponsors are encouraged to include "Antimicrobial Resistance Mitigation Statements" that promote "practices that would minimize the development and spread of antimicrobial resistance (p.10)."

Minimizing exposure to antibiotics and adopting practices that would minimize the development and spread of antimicrobial resistance are appropriate responses to the serious public health threat of antibiotic resistance. Yet the FDA throughout draft GFI#273 creates a process that requires consideration of animal health needs, however tenuous, over minimizing antibiotic exposure in setting durations while making the adoption of other minimization practices completely optional. For example, Draft GFI#273 (pgs. 12, 24) states that no safety information needs to be provided because the drugs have already been shown to be safe– completely undermining the whole purpose of the draft guidance, which is to address the serious public health threat of antibiotic resistance. Despite acknowledging that the affected antibiotics were approved and shown to be safe when antibiotic resistance was poorly understood and prior to

current requirements that resistance be considered during approval. As another example, Draft GFI#273 (pgs. 2,5,16) does not ask drug sponsors to consider antibiotic resistance when determining the expected duration of use or even to determine the maximum duration of use, but instead asks them to only consider factors related to animal health.

Moreover, while encouraging sponsors to include additional statements about practices to minimize resistance, Draft GFI#273 also makes clear that these practices are entirely voluntary for the sponsor (p. 19) and, if voluntarily included by the sponsor, voluntary for the veterinarian to follow (p.6,17), even to the extent that these additional resistance minimization practices do not need to be provided to the producer-client on the veterinary feed directive (VFD) (p. 18). The FDA believes that there are additional practices that would minimize the development and spread of resistance, but these practices do not need to be adopted. One of the practices that the FDA provides as an example of minimizing resistance is to not use the same class of drug immediately after it has been used.

Repeatedly using the same antibiotic clearly creates a risk for increased resistance, but existing labels actually *promote* this behavior. For example, under the current approved label, NADA #012-491 for the critically important macrolide class antibiotic tylosin can only legally be used to control swine dysentery after treating with tylosin at a high dose, followed by treating with a low dose for a lengthy period of time - "until market weight." Similarly, the label also includes a high dose followed by low dose claim for tylosin to control ileitis. Using a low antibiotic dose for a long duration after a treatment dose is likely to maintain the resistance selected for by the initial high dose. This is one of the labels that is affected by draft GFI#273. The FDA already appropriately states that "until market weight" should not be used as a duration (p. 5). In addition, the agency should ask the sponsor to change the existing label when adjusting the duration so that it does not require the drug to be used in a way that maximizes resistance – by requiring a shift in the class of the drug used for control after the initial treatment with a macrolide. Similarly, the FDA should ask sponsors to include labeling changes that prohibit the use of the macrolide tylosin to control liver abscesses after a macrolide is used for control of bovine respiratory disease in feedlot cattle. The FDA is already asking sponsors to change the conditions of use by changing durations. There is no reason not to ask for other changes such as this that are consistent with the goals of minimizing resistance selection.

While the FDA does not directly regulate the practice of veterinary medicine, draft GFI#273 places a high amount of emphasis on veterinary decision making and allowing the veterinarian to decide the appropriate use of an antibiotic. Draft GFI#273 describes factors that veterinarians should take into consideration when deciding on the use of an antibiotic (pgs. 6-7). Consistent with the rest of the document, this section does not even mention that the potential for the selection of antibiotic resistance should be one of the "types of information" provided on the label to inform the veterinarian's decisions around antibiotic use.

Throughout GFI#273, the FDA should require that all decisions related to antibiotic use consider the development of resistance including when setting maximum durations. It should require consideration of known resistance minimization practices as conditions for use, regardless of whether decisions are being made by drug sponsors, veterinarians, or antibiotic users.

The FDA should follow the precedent set in previous regulation and guidance and limit maximum durations based on the stated concern about minimizing the extent of antimicrobial drug exposure, by setting a baseline maximum duration of 21 days.

We recommend that the FDA follow the approach laid out in GFI#152, and ask the sponsors to voluntarily change labels to durations that do not represent "high extent of use" as defined in GFI#152– i.e. under 21 days. 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. Alternatively, the sponsor could provide data showing that these long durations are needed and do not select for increased resistance; only then should FDA allow longer durations.

The extent of antimicrobial exposure will not be minimized solely by creating a defined duration. As draft GFI#273 (p. 22) states, the drugs subject to the guidance were already assumed to "be used only for the duration needed in any given group of animals." If producers switch to routinely using the maximum labeled duration, this could potentially *increase* the extent of antimicrobial exposure, and the FDA has no authority to limit how much this is done. Setting a maximum duration of 21 days based on the need to minimize exposure will limit the risk from a switch to routinely using the maximum duration. In addition, draft GFI#273 should be modified to ask sponsors to provide a definite, time-bound expected duration of use for each indication in the label, supported by evidence in addition to the 21-day maximum duration.

As the FDA has consistently recognized, an increased risk of resistance development is not created by whether or not a use has a defined duration, but instead by the period of exposure i.e. the length of duration. This was clearly understood in the 1970s when the FDA required studies for uses in feed for over 14 days, and is an important part of GFI#152. Long durations, regardless of whether they are defined or not, are associated with increased antimicrobial resistance. A defined duration that is long could potentially be worse for resistance than an undefined duration that is short in practice, if users and veterinarians start routinely selecting the longer, defined duration. The FDA should ensure that when sponsors create durations of use, they do not inadvertently encourage durations longer than those ordinarily used already.

The "duration of antimicrobial treatment can play a major role in the development of bacterial resistance" as both clinical and laboratory studies have shown that longer durations are associated with higher resistance, and farms using longer antibiotic treatments have shown higher levels of resistance.[3] Despite the clear connection between long durations and resistance, and despite the FDA's stated goal of minimizing exposure and selection for antibiotic resistance, draft GFI#273 allows for durations of use for an "extended period" (p. 16). Draft GFI#273 allows sponsors to set a maximum duration based on extremely limited data (p. 17) and allows the duration to be designed to cover any situation that "might sometimes be encountered in the United States (p.16)." In draft GFI#273 (p.13), the FDA acknowledges the weakness of the data the agency is asking sponsors to provide supporting durations, stating the data "may support a range of durations that would be appropriate for use to treat, control, or prevent a given disease."

[3] Guardabassi, L. Apley, M. Olsen, J. Toutain, P. Weese, S. Optimization of Antimicrobial Treatment to Minimize Resistance Selection. Microbiology Spectrum 2018, 6 (3), 10.1128/microbiolspec.arba-0018–2017. https://doi.org/10.1128/microbiolspec.arba-0018-2017.

If this is truly the case, the shortest duration of those supported would be the appropriate one. The disconnect between the stated goals and the proposed solution to the problem is glaring.

Setting a default maximum duration of 21 days also reduces the challenge created by multiple products for the same indication with unaligned durations.

Draft GFI#273 acknowledges that the data available is likely not sufficient to identify science-based durations creating the risk that "directions for use across products approved for the same or similar indications" will not be aligned. Draft GFI#273 states the FDA will not object to companies coordinating to address this problem. It is not clear that this coordination will ultimately be in the interest of public health and help with identifying the shortest duration among the range of possible durations, which should be the goal given the stated intent of draft GFI#273. If the FDA instead set a default maximum duration of 21 days, that would help with alignment.

Any final guidance should eliminate the current minimum durations on existing labels and allow veterinarians to discontinue ineffective treatment.

Draft GFI#273 (pgs. 14-16) repeatedly makes clear that the intent is not to limit a veterinarian's discretion on deciding how long an antibiotic should be used. The one exception to this is that draft GFI#273 does not recommend changes that would allow a veterinarian the discretion to *shorten* the duration of use when there is an existing minimum duration on the label (pgs. 14-16). In final GFI#273, the FDA should ask drug sponsors to remove these minimums and allow veterinarians to shorten the duration of use for all covered drug applications when appropriate.

Similarly, the recommended language (draft GFI#273, p. 14) that treatment should continue until "resolution of clinical signs" ignores the increasing likelihood that resistant animal pathogens may mean that the treatment is ineffective and clinical signs may not resolve. Labels must allow for veterinarians to stop ineffective treatments.

Summary of Recommendations:

- The FDA should set a default baseline maximum duration of 21 days for all covered antibiotics and require sponsors to provide microbial safety and efficacy data if they choose to seek longer maximum durations.
- The FDA should ask sponsors to provide a definite, time-bound expected duration of use for each indication in the label, supported by evidence, in addition to the 21-day maximum duration.
- The FDA should devise guidance related to the setting of durations of use, to avoid inadvertently incentivizing longer durations than are currently routine practice.
- The FDA should ask sponsors to include identified resistance minimization practices as conditions for use and remove instructions for use that increase the risk of resistance (e.g., eliminate usage of the same drug at low dosages for control after using a drug for treatment at high dosages).
- The FDA should ask sponsors to eliminate minimum durations.
- The FDA should remove and avoid new language that limits a veterinarian's ability to stop ineffective treatment.

The FDA's stated reason for creating this document is to minimize exposure of food-producing

animals to antibiotics in order to mitigate the development of resistance, but draft GFI#273 fails to ask sponsors to take into consideration resistance when making the proposed changes to durations of use on drug labels. This creates the real risk that after a decade of work on defining durations, exposure will not be reduced and potentially, could be increased. The FDA should ask for sponsors to make changes consistent with science and its own public health mission, and at least seek voluntary changes that will more fully meet the FDA's stated goals. It can do this by setting a default baseline 21-day maximum duration and by asking sponsors to make other changes that mitigate the development of antibiotic resistance.

Food Animal Concerns Trust

Antibiotic Resistance Action Center (ARAC) at the Milken Institute School of Public Health, George Washington University

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