CENTER FOR
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Docket Clerk
United States Food and Drug Administration
Division of Dockets Management, HFA-305
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket FDA-1998-D-0038 on draft GFI 152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"

To Whom it May Concern:

The Center for Science in the Public Interest (CSPI)[1] respectfully submits these comments on the Food and Drug Administration's (FDA) new draft of Guidance for Industry (GFI) 152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern."[2] We appreciate the general approach FDA has taken to this guidance are supportive of FDA updating the guidance to better incorporate public health considerations for animal antimicrobial drugs. We request, though, that the agency follow their own criteria and rank the polypeptide class of antimicrobials as medically important. We also ask that the agency more clearly and consistently emphasize that in addition to medical importance and foodborne disease considerations, other antimicrobial resistance factors like drug class novelty, cross-resistance, and antimicrobial treatment of non-enteric disease could carry substantial weight in the risk assessment and risk management decisions. Finally, we also request that the agency specify a regular cadence at which it will update GFI 152.

Background

GFI 152 provides an important building block in FDA's plan to combat antibiotic resistance. The Centers for Disease Control and Prevention estimates that each year 2.8 million people in the U.S. get antimicrobial-resistant infections and that 35,000 people die from these infections.[3]

It is well established that the use of antimicrobials in animals raised for food production contributes to the development of resistance in human pathogens.[4] The procedures outlined in

[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[2] *Draft Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*. Food and Drug Administration. January 2023. Accessed April 27, 2023. https://www.fda.gov/media/69949/download
[3] About Antimicrobial Resistance. Centers for Disease Control and Prevention. Updated October 5, 2022. Accessed April 27, 2023. https://www.cdc.gov/drugresistance/about.html
[4] 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

GFI 152 can help mitigate the risk these drugs pose to public health by ensuring they undergo thorough antimicrobial risk assessment and risk management prior to marketing.

Initially published in 2003,[5] GFI 152 describes the risk assessment method that FDA recommends new drug sponsors use to evaluate the human health risks of a potential new animal antimicrobial drug as they relate to antimicrobial resistance. As part of this assessment, the guidance ranks antimicrobial drug classes according to their medical importance to human medicine. Depending on the ranking, FDA either recommends or requires specific risk management actions for "medically important" drugs, such as veterinary supervision if they are administered in feed or water.[6] By contrast, use of "not medically important" drugs may be less restricted. Other findings from the risk assessment, such as duration of use and drug class novelty, can also carry weight in determining risk management actions.

FDA has not updated GFI 152 since 2003. Meanwhile, the science of antimicrobial resistance has advanced and new drugs were approved for human medicine, which may have affected the risk management actions that should have been taken for animal drugs. For example, in 2019 lefamulin was approved for treating community-acquired bacterial pneumonia in humans, decades after other drugs in its class were approved in animals.[7,8] This marked the first systemic human use approval for a drug from the "not medically important" pleuromutilin class of antibiotics. The medical importance ranking criteria in GFI 152 also primarily focused on foodborne antimicrobial resistance risks and placed less value on broader issues that could affect the importance of antimicrobials to human medicine, such as cross-resistance and the use of antimicrobials to treat non-enteric bacterial infections.

Concept Paper

In 2020, FDA released a concept paper that described a potential revised approach for ranking antimicrobial drugs according to their importance to human medicine, a key part of the original GFI 152.[9] The new approach addressed weaknesses in the original guidance by better considering broader risks to human health from antimicrobial resistance, beyond the risk from antimicrobial-resistant foodborne pathogens. Under this approach, the pleuromutilin class of antimicrobials would have been newly ranked as medically important.

The concept paper articulated a more complex and confusing categorization system, introducing a category of drugs approved for human medicine but nonetheless considered "not medically important. This was a contradiction, as the "medically important" group included a least-concerning sub-category that seemed to encompass all drugs approved in human medicine even

[5] *Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*. Food and Drug Administration. October 2003. Accessed April 27, 2023. https://downloads.regulations.gov/EPA-HQ-OPP-2015-0820-0016/content.pdf

[6] 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. Food and Drug Administration. Published December 2013. Accessed April 27, 2023. https://www.fda.gov/media/83488/download

[7] FDA Approves New Antibiotic to Treat Community-Acquired Bacterial Pneumonia. Food and Drug Administration. Updated August 19, 2019. Accessed April 27, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia

[8] New Animal Drugs for Use in Animal Feeds; Tiamulin. 52 Fed. Reg. 26955 (July 17, 1987). https://archives.federalregister.gov/issue_slice/1987/7/17/26954-26956.pdf

[9] Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs. Food and Drug Administration. October 9, 2020. Accessed April 27, 2023. https://www.fda.gov/media/142846/download

for non-serious infections (i.e. "drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans."). The polypeptide class of antimicrobials, which includes the human drug bacitracin, fell into the ranking of "not medically important."

Finally, FDA stated in the concept paper that the medical importance rankings would be periodically updated but did not specify a timeline for such updates.

CSPI gave feedback to the agency on the concept paper in a public meeting presentation.[10] We supported the agency classifying pleuromutilin antimicrobials as medically important. The sponsoring company was also working at the time towards having the drug approved to treat other human infections.[11]

We expressed concern, however, that the described system allowed some human antimicrobial drugs and seemingly all novel animal antimicrobial drug classes not yet approved in humans to be ranked as "not medically important." Though under the system in the concept paper these drugs were to be explicitly elevated over strictly animal drugs with "an extensive history and experience of use in animals" for their potential to impact human health, the concept paper did not clarify what risk management steps would be tied to this elevated standing. We asked FDA to take a more aggressive approach in ranking drugs as "medically important," as risk management actions would then be required for them. We also noted that ranking such drugs as "medically important" would not necessarily restrict antimicrobials from animal usage.

We also suggested that FDA set a timeframe (we believed five years could be appropriate) for updating the rankings. That would have ensured a timely review of risk assessment and risk management approaches as new antimicrobials enter the market and scientific knowledge and surveillance data develop.

Draft Guidance

We applaud FDA for adopting two modifications in the new draft of GFI 152 that we supported in the concept paper. First, the agency is officially proposing to classify pleuromutilin antimicrobials as medically important. Second, the agency describes a system under which all antimicrobial classes used to treat infections in humans would be classified as "medically important," removing the explicit category presented in the concept paper that allowed for certain human drugs to be classified as "not medically important."

We have some remaining concerns about the new draft of GFI 152, though, which we urge the agency to address in the final version.

First, the draft guidance continues to classify polypeptides as "not medically important," even though bacitracin (a polypeptide) is approved for use in human medicine. This contradicts the described system of classifying antimicrobials which, as noted above for the concept paper,

[10] FDA Public Meeting: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs. November 16, 2023. https://downloads.regulations.gov/FDA-2020-N-1736-0017/attachment_1.pdf

[11] Pipeline and Research. Nabriva Therapeutics. Accessed April 27, 2023. https://www.nabriva.com/pipeline-research

includes a broad sub-category ranking even drugs used in non-serious infections as medically important. The ranking could also cause confusion for future classifications.

This classification may also be particularly important because there is emerging is emerging evidence of a bacitracin-resistance gene being located on a novel mobile colistin (a critical "medically important" antibiotic in GFI 152) resistance gene, *mcr-1*, identified in domestic food animal bacteria[12] and cited by CDC as threatening last-resort antibiotics such as colistin. [13,14] As colistin use in food animals is proposed to be a major driving force behind *mcr-1* resistance,[15] cross-resistance with bacitracin could mean that bacitracin use could also propagate this resistance.

Second, we agree that the distinction between medically important/not medically important is not the only factor that should be considered by the agency in determining antimicrobial risk. For example, there may be "not medically important" drugs that warrant elevated risk management steps, such as those conferring cross-resistance to a "medically important" antimicrobial class, or those from a novel class. While the draft guidance acknowledges this, for example by mentioning cross-resistance in the "release" section, it could be woven more fully into the rubric by clarifying that risk assessment findings such as cross-resistance potential and drug class novelty can also carry substantial weight when determining what appropriate risk management actions should be (see below).

In some cases, the use of additional risk management actions for animal antimicrobials could be impactful especially if there is limited history and experience of their use in animals, even if there is no approved human use. Considering the slow pace at which antimicrobials are developed and approved, there could be a substantial time delay before a new antimicrobial's full potential for human health is realized. In the interim between animal and human drug approval, animal use could increase the risk of resistance to the antimicrobial.

We expect these changes to the guidance would assist in capturing FDA's current practices, rather than creating a new policy for the agency. FDA has already demonstrated prioritized public health considerations in developing a risk management approach for animal drugs that are "not medically important," an approach to product approval we have previously argued for FDA to take more generally in a Viewpoint in the Journal of the American Medical Association.[16] For example, avilamycin, a novel animal drug not yet licensed for use in humans in the United States, was approved by FDA for animal use under veterinary supervision in 2015 rather than for over-the-counter use as "not medically important" drugs can be, in part due to resistance concerns.[17] The drug was then put into the NARMS *Enterococcus* panel for post-approval monitoring in 2018, an additional risk management step not always taken for "not medically

[12] Meinersmann RJ, Ladely SR, Plumblee JR, Cook KL, Thacker E. Prevalence of mcr-1 in the Cecal Contents of Food Animals in the United States. *Antimicrob Agents Chemother*. 2017;61(2):e02244-16. Published 2017 Jan 24. doi:10.1128/AAC.02244-16

[13] Xu F, Zeng X, Hinenoya A, Lin J. MCR-1 Confers Cross-Resistance to Bacitracin, a Widely Used In-Feed Antibiotic. mSphere. 2018;3(5):e00411-18. Published 2018 Sep 5. doi:10.1128/mSphere.00411-18

[14] Newly Reported Gene, mcr-1, Threatens Last-Resort Antibiotics. Centers for Disease Control and Prevention. Updated November 30, 2023. Accessed May 12, 2023. https://www.cdc.gov/drugresistance/solutions-initiative/stories/gene-reported-mcr.html

[15] Sun J, Zeng X, Li XP, Liao XP, Liu YH, Lin J. Plasmid-mediated colistin resistance in animals: current status and future directions. *Anim Health Res Rev*. 2017;18(2):136-152. doi:10.1017/S1466252317000111

[16] 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.

[17] Freedom of Information Summary: Original New Drug Application NADA 141-438. Food and Drug Administration. May 8, 2015. https://downloads.regulations.gov/FDA-2015-N-0002-0039/content.pdf

important" drugs.[18]

One way to clarify that FDA will consider risk management more broadly in this way would be to modify the risk estimation section to explicitly discuss the risk estimation ranking of "not medically important" drugs. Currently, Table 6 (Possible Risk Estimation Outcomes for Medically Important Antimicrobials Based on the Integration of the RELEASE, EXPOSURE, and CONSEQUENCE Assessment) only has risk estimations of medically important antimicrobials, implying that no remediation is necessary for "not medically important" drugs. Changes could include modifying Table 6 to show some rankings of "not medically important" antimicrobials, which could then better be matched with risk management recommendations in Table 8 (Examples of Risk Management Actions Based on the Outcome of the Risk Estimation (Low, Medium, High)).

Third, in a related note, we commend FDA for expanding the focus beyond enteric pathogens, such as having the top ranking of medical importance be determined by the importance of drugs for the treatment of any condition rather than for foodborne disease like in the 2003 version. As we note above, the pleuromutilin ranking is evidence of this approach. However, the wording throughout GFI 152 does not consistently reflect this expanded focus. For example, the scope of the document section states that "although FDA's primary focus will be foodborne pathogens and their resistance determinants, other (enteric/gastrointestinal) bacteria may be considered when deemed necessary." Here, the parenthetical "enteric/gastrointestinal" could be removed to expand the scope of "other bacteria." We recommend FDA review the document for other references to foodborne or enteric illness in order to reconcile the language with the new expanded scope.

Finally, we are disappointed that FDA did not adopt our suggestion of publicly setting a minimum timeframe for revisiting rankings, and again ask the agency to do so. In this draft GFI 152, FDA only includes a section on "periodic reassessment of rankings," but does not specify a time frame. The lack of revision of GFI 152 since the original publication in 2003 highlights the need for a scheduled periodic reassessment. FDA should publish the rankings currently included in Appendix A in a separate document from GFI 152 to ease this periodic revision.

We recommend that FDA accepts public comments during ranking reassessments, to ensure new scientific evidence is highlighted. This will both encourage stakeholder engagement and boost confidence in the resultant list.

Conclusion

While the draft GFI 152 has areas that could be improved, we are optimistic that if these issues are addressed the document will enhance FDA efforts to prevent antimicrobial resistance.

Questions and communications related to these comments can be directed to jkincheloe@cspinet.org or (202) 777-8316.

[18] 2019 NARMS Update: Integrated Report Summary. Food and Drug Administration. Updated May 5, 2023. Accessed May 12, 2023. https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2019-narms-update-integrated-report-summary

Sincerely,

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