U.S. FOOD & DRUG ADMINISTRATION

September 17, 2024

The Honorable Cory Booker
United States Senate
Washington, D.C. 20510

Dear Senator Booker:

Thank you for your July 9, 2024, letter to the Food and Drug Administration (FDA or the Agency) expressing concerns related to two draft FDA guidances for industry (dGFIs): dGFI #152, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*[1,2] and dGFI #273, *Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals*.[3] When finalized, these draft guidances will provide information to sponsors of new animal drug applications, which contain antimicrobial drugs important to human medicine and are intended for food-producing animals.

FDA's role in preserving the effectiveness of antimicrobials for human and animal use is critical, and the Agency has been successful in removing all non-therapeutic uses of medically important antimicrobials in food-producing animals and bringing the remaining uses under the supervision of licensed veterinarians. Your letter, in part, raises questions regarding FDA's approach to establishing recommended durations for use of antimicrobial new animal drugs. The principles of antimicrobial stewardship, including judicious use, emphasize that medically important antimicrobial drugs should only be used to treat, control, or prevent a disease and should be administered for an appropriate period (that is, have a defined duration of use). Our primary objective in dGFI #273 is to facilitate voluntary updates of certain product dosage regimens to define when and for how long the animal drug may be used. Defining durations of use for approved animal drugs that currently lack this information is one example of ongoing efforts by FDA's Center for Veterinary Medicine (CVM) to slow the development of antimicrobial resistance.

Since 2003, CVM has required all new indications for pioneer new animal drug approvals to include a defined duration of use. As a result, roughly 65% of all currently approved medically

[1] https://www.fda.gov/media/69949/download
[2] The current GFI # 152, which was originally issued in 2003, outlines a qualitative risk assessment method for evaluating foodborne antimicrobial resistance concerns related to the use of an antimicrobial drug in food-producing animals. GFI #152 also contains an appendix, commonly referred to as "Appendix A," in which FDA ranks antimicrobial drugs according to their relative importance in human medicine: "critically important," "highly important," or "important." Draft GFI #152 proposes to revise sections in the risk assessment framework, including updating tables and figures and revising Appendix A, based on new ranking criteria of antimicrobials according to their importance in human medicine.
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-273-defining-durations-use-approved-medically-important-antimicrobial-drugs-fed-food

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important antimicrobial drugs administered in the feed or water of food-producing animals already have a defined duration of use.

There are approximately 97 approved animal drug applications[4] that lack a defined duration of use. FDA intends to work with sponsors over the next several years to define durations of use for these products so that veterinarians will have clear labeling indications and instructions on how long to use a medically important antimicrobial drug.

In September 2018, CVM released a multi-pronged, five-year strategy designed to slow the emergence of resistance arising from the use of antibiotics in animals while continuing to ensure the availability of safe and effective antibiotics for use in animals and humans. This strategy, entitled, "Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019 - 2023,"[5] served as CVM's initial action plan for guiding its activities.

In September 2023, CVM released its second five-year plan, "Supporting Antimicrobial Stewardship in Veterinary Settings, Goals for Fiscal Years 2024-2028," which builds upon the progress of the previous plan. The five-year plans provide stakeholders with a transparent roadmap of the actions that correspond to FDA's three main veterinary stewardship goals: 1) Align antimicrobial drug product use with the principles of antimicrobial stewardship; 2) Foster stewardship of antimicrobials in veterinary settings; and 3) Enhance monitoring of antimicrobial resistance (AMR) and antimicrobial drug use in animals. FDA developed FDA-TRACK: Progress on FDA's Support of Antimicrobial Stewardship in Veterinary Settings,[6] a publicly available dashboard showing FDA's progress in achieving these goals.

Your letter also asks specific questions. We have restated these questions below in bold type, followed by our responses.

1. **Does the FDA believe it is appropriate to make human safety decisions based on animal health needs--as it has done in its revisions to GFI#152 and GFI#273--for durations of use intended to protect human health?**

   FDA takes human safety into account when evaluating products for animal health needs. CVM's mission is to protect both human and animal health. To achieve this broad mission, CVM ensures that animal drugs are safe and effective prior to approving them. With respect to antimicrobial new animal drug applications, the risk assessment process outlined in GFI #152 is specifically designed to address antimicrobial resistance risks to human health resulting from antimicrobial use in food-producing animals. As stated in GFI #152, FDA considers an antimicrobial new animal drug to be "safe" with regards to human health if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals. This safety standard remains unchanged in both the original and draft revised GFI #152.

[4] https://www.fda.gov/animal-veterinary/antimicrobial-resistance/list-approved-medically-important-antimicrobial-drugs-administered-feed-food-producing-animals-lack
[5] https://www.fda.gov/media/115776/download?attachment
[6] https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-progress-fdas-support-antimicrobial-stewardship-veterinary-settings

The draft revised GFI #152 states, "Duration of use will be revised on a case-by-case basis in light of, but not limited to, animal species, disease risk period, and animal management husbandry practices, etc." This language was added as a table note to address the varying differences across animal production systems and disease pressures over time and does not change the qualitative risk rankings outlined in Table 7 of draft GFI #152, nor does it limit the Agency from considering additional use restrictions. FDA received and is reviewing comments on the draft guidance, including comments on this added language. The Agency is currently preparing a final version of the guidance for release.

2. **How will the FDA's consideration of animal health concerns impact its ability to ensure human safety in the use of animal drugs? Will FDA now begin to consider animal health or economic benefit to the impacted industry when holding hearings on whether to withdraw drugs from the market for safety reasons?**

FDA considers a new animal drug to be "safe" with regards to human health if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals. Draft revised GFI #152 and draft GFI #273 would not change the way FDA evaluates the human food safety of an animal drug.

3. **Does the FDA believe it has the authority to ask drug sponsors to voluntarily adopt durations that are consistent with existing guidance (i.e. under 21 days as recommended by the original GFI#152)? If not, please explain why the FDA does not have authority for requesting this voluntary action.**

It is within FDA's authority to request that affected drug sponsors voluntarily update their applications to reflect more refined durations of use. FDA expects that individual products will need to be considered on a case-by-case basis, and changes requested to those applications will need to be supported by relevant scientific information. FDA has published draft GFI #273, which when finalized will guide the sponsor through that process.

The purpose of GFI #152 is to outline a qualitative risk assessment process that drug sponsors may use to evaluate antimicrobial resistance risks associated with a product for which they are seeking FDA approval. To incorporate a consideration of the proposed duration of use of the product into this qualitative assessment process, GFI#152 classifies durations of use that are longer than 21 days as *high extent of use*. Therefore, the reference to use durations in GFI#152 is intended to serve as guidance for conducting pre-approval qualitative risk assessments. This guidance is not intended to be a recommended maximum duration of use for all medically important antimicrobials.

4. **Given the slow pace of action to address the critical public health threat of antibiotic resistance, what additional resources or authorities does the FDA need to take prompt action to protect public health from antibiotic resistance?**

FDA has been diligently making progress to mitigate the spread of antimicrobial resistance. FDA has posted a Timeline of FDA Action on Antimicrobial Resistance,[7] which covers the 1980s through the present time. Many of the important changes that FDA has brought about, including eliminating growth promotion uses of medically important antimicrobials in feed or drinking water and bringing all medically important antimicrobials under veterinary oversight, were accomplished through a strategy that sought the cooperation of the animal pharmaceutical industry to voluntarily adopt change. This strategy has been successful in building consensus for change. However, it does have limitations, as the agency has limited post-market authorities related to animal drugs, including limited authority to require labeling changes after an animal drug product is approved.

FDA has included a legislative proposal in its FY 2025 budget request to amend the Federal Food, Drug, and Cosmetic Act (FD&C Act) to authorize the Center for Veterinary Medicine (CVM) to require animal drug sponsors to make safety-related labeling changes based on new safety information that becomes available after approval of an animal drug; to require animal drug sponsors to develop and implement a Risk Evaluation and Mitigation Strategy (REMS), a drug safety program for drugs with serious safety concerns and for which interventions beyond FDA-approved labeling are necessary to ensure the safe use of the drug; and to require animal drug sponsors to conduct post-approval studies of animal drugs to assess a known or potential serious safety risk. We'd be happy to further discuss this proposal with you.

5. It has been over 20 years since the Interagency Task Force on Antimicrobial resistance identified collection of antibiotic use data as a priority.

a. When does the FDA anticipate creating "functional and efficient systems for collecting antimicrobial use (AMU) data in animals" as described in the FDA's 2019-2023 plan for antimicrobial stewardship in veterinary settings? When does the FDA expect the data collection plan to be finalized, and when will it be implemented?

Collecting data to monitor AMU in humans and animals is a key element of the FDA's strategy to support antimicrobial stewardship in veterinary settings. FDA recognizes and continues to support the need for additional scientifically sound data on antimicrobial use in veterinary settings.

As part of its strategy to enhance monitoring of antimicrobial drug use data in animals, FDA CVM funded four cooperative agreements for antimicrobial use data collection: two in food-producing animals (funded since 2016) and two in companion animals (funded since 2020). These pilot data collection efforts provide baseline information on antimicrobial use practices in animals and important information on methodologies that may help optimize long-term strategies for collecting and reporting such data. The initial results from the projects were summarized in a series

[7] https://www.fda.gov/animal-veterinary/antimicrobial-resistance/timeline-fda-action-antimicrobial-resistance

of papers in 2020[8] describing the first few years of data collection in food producing animals (published in a supplemental issue of the journal *Zoonoses and Public Health*). Building on this initial work, the cooperative agreement projects continued to develop robust methodologies to collect AMU data and generate baseline information on AMU practices in the U.S. through 2021, and the methodologies for major food-producing species were recently summarized in an article in the Journal of the American Veterinary Medical Association.[9] It is also notable that certain data collection efforts in the poultry sector are ongoing, with continued support from associated industry groups. Progress on this ambitious action is further summarized in a report issued in June 2022, "Antimicrobial Use and Resistance in Animal Agriculture in the United States, 2016-2019."[10]

From 2021-2023, FDA CVM collaborated with the Reagan-Udall Foundation for the FDA (RUF) to seek input from a variety of affected stakeholders on a draft framework exploring public-private partnerships to track antimicrobial use data in food-producing animals in the United States. RUF conducted this outreach under a cooperative agreement with FDA, the results of which are summarized in a report outlining a draft framework.[11] The report includes information about antimicrobial use data standardization and protection of data confidentiality, as well as a summary of stakeholder input and public comments about potential objectives, membership, organizational structure, and financing for a public-private partnership. The report describes a potential framework, supported by public and private resources, that includes a Data Repository Coordinator, Data Partners, and a Steering Committee. The publication of that report concluded Action 3.1.3[12] from CVM's initial five-year plan.

In March 2024, FDA announced a new cooperative agreement funding opportunity for "Long Term Data Collection on Antimicrobial Use in Animals." The recipients are intended to be similar to the external data partners described in the RUF framework report. Funds from this program will support projects to:

1) collect antimicrobial use data from diverse animal sectors, including domestic livestock, poultry, companion animals (dogs, cats, and horses), and minor species (e.g., fish, sheep, goats), and
2) contribute to the development of data collection frameworks, including providing data and expertise as resources and public-private partnership frameworks are established.

FDA is in the process of reviewing and awarding proposals through this new program.

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[8] https://www.fda.gov/animal-veterinary/antimicrobial-resistance/timeline-fda-action-antimicrobial-resistance
[9] https://avmajournals.avma.org/view/journals/javma/262/8/javma.24.03.0180.xml
[10] https://www.fda.gov/animal-veterinary/cvm-updates/fda-delivers-progress-update-5-year-veterinary-stewardship-plan-publishes-report-about-antimicrobial
[11] https://reaganudall.org/programs/antimicrobial-use-data-food-animals
[12] Action 3.1.3: "Develop a long-term strategy for implementing a functional and efficient systems for collecting antimicrobial use data in animals."

> The National Action Plan for Combatting Anti-microbial Resistant Bacteria (CARB), 2020-2025, presents coordinated, strategic actions that the United States Government has planned for the five-year period to improve the health and wellbeing of all Americans by changing the course of antibiotic resistance. Goal 2 of the CARB National Action Plan is to strengthen national One Health surveillance efforts to combat resistance, which includes the objective to "Develop new or expand the number of sources for and quantity of surveillance data on the use of antibiotics collected from animals, farms, and production facilities to improve understanding and implementation of responsible use of antibiotics."

For this objective, FDA and USDA APHIS are tasked with reporting progress towards increasing published reports and dashboards on antibiotic use in animals. However, FDA notes that the pace of development for key infrastructure such as database repositories that would hold such information will depend on available resources and the degree of support and collaboration from involved public and private partners.

b. So far, the FDA has only publicly discussed a public-private partnership.

i. Why has the FDA not collected feed distribution data from feed mills as recommended by public health advocates?

Medicated feed records represent potential, not actual, use of medicated feed by the producer. They are not an indicator of antimicrobial use, but rather sales and distribution data. As required, veterinary feed directives (VFDs) specify the potential number of animals that will be fed the VFD feed, but VFDs do not represent the amount of medicated feed that is ultimately administered to animals by the animal producer. For instance, there may be medicated feed authorized or distributed that is then not used, which could be discarded or used under a future VFD. Therefore, if the Agency were to collect feed distribution data from feed manufacturing facilities, the data would not be representative of actual antimicrobial use trends at the national level. Furthermore, this data collection approach is limited as it would not yield information on antimicrobials administered via nonfeed routes.

ii. What resources would be needed to collect drug distribution data from feed mills?

FDA has not pursued obtaining formal cost estimates on collecting VFD feed distribution data due to the aforementioned reasons.

iii. How would the resource needs for collecting feed distribution data compare to resource needs for collecting data through a public-private partnership?

In 2023, FDA opened a docket to seek public comment on the RUF report outlining a potential framework for establishing a public-private partnership to collect and analyze data on antimicrobial use in food-producing animals. During this comment period, FDA requested specific input on cost estimates for External Data Partners to develop and sustain a mechanism for collection of data on AMU in animals – recognizing diversity of data sources across animal sectors – and cost estimates for the setup and maintenance of an AMU data repository under the public-private partnership framework described in the RUF report. Public comments offered a cost estimate in the millions of dollars; however, these estimates were not based on a formal economic analysis. As stated, FDA has not pursued obtaining formal cost estimates on collecting VFD feed distribution data.

iv. If the FDA does move forward with a public-private partnership how will the agency ensure that the collected data is representative i.e., how will it ensure that those facilities practicing poor antimicrobial stewardship (that will likely not be inclined to participate) are represented?

Given the limited infrastructure and legal authority for FDA to collect broad-based information on AMU in food-producing animals in the United States and the fact that FDA does not regulate the practice of veterinary medicine, FDA determined that a voluntary and collaborative approach to data collection that relies on support from public and private sectors is the most feasible approach.

FDA acknowledges that a limitation of voluntary data collection on AMU in animals is the reliance on convenience sampling of participating data providers. In the FDA-funded cooperative agreements that piloted data collection on antimicrobial use in cattle, swine, and poultry, all sectors faced unique limitations in collecting AMU data that were fully representative[13] of all animal production phases. For example, in all sectors, limited information was collected about breeding animals, young animals, or animals housed on smaller operations.

Despite its limitations, it is feasible to aggregate and contextualize data to create a representative picture of antimicrobial use in the United States by calculating relevant metrics. This approach allows for focused analysis and more meaningful reporting across sectors, veterinary care settings, or animal populations. Standard epidemiological methods are instrumental to quantifying and contextualizing antimicrobial use trends at the national level. For instance, in FDA-funded pilot projects aimed at collecting information on antimicrobial use in poultry, the data from all three sectors were characterized for representativeness of U.S. flock populations using the USDA poultry

[13] We use the term "representative" in this context to mean the degree to which a data sample collected is considered to be reflective of the target population, and whether study results can be generalized to that target population either in estimate or in interpretation.

production statistics. Data from participating companies from 2016 to 2022 were estimated to cover 45 percent of national egg production, 85 percent of broiler chicken production, and 70 percent of turkey production.[14] This approach allows for effective definition of target populations and data contextualization.

FDA has explored a variety of incentives to encourage participation in pilot cooperative agreements and outreach efforts. These incentives include monetary reimbursement schemes, value-added benchmarking information for producers, and participation in quality assurance programs such as check-off programs. Participation levels are expected to vary across sectors due to factors such as trust and working relationships between stakeholders, data source availability or access, and sector-specific characteristics such as vertical integration. Consequently, incentives required to engage participants may also differ based on unique sector-specific considerations.

6. **What is the FDA doing to measure its progress on combating antibiotic resistance? Has the FDA adopted any indicators of success such as a reduction in antibiotic use by livestock sectors and reductions in antibiotic resistance in food animal isolates?**

FDA's primary goal is to support the implementation of good antimicrobial stewardship practices to slow the development of antimicrobial resistance. Important actions in support of this goal include implementing GFI #213, the Veterinary Feed Directive Final Rule, GFI #263, and various outreach efforts to support antimicrobial stewardship. The significant reduction in the volume of sales of medically important antimicrobials reported since 2015, and a concomitant decline in resistance among indicator bacteria, are important indicators of change. FDA intends to continue to advance policies and actions to support continued improvement of antimicrobial stewardship in veterinary settings, including efforts to help establish systems for collecting antimicrobial use data at the farm level.

Thank you again for your interest in this issue. Please let us know if you have any further questions.

Sincerely,

Erin O'Quinn
Associate Commissioner for
Legislative Affairs

[14] https://mindwalkconsultinggroup.com/abu-interactive-figures/