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

RE: Comment on the Tracking and Monitoring of Antimicrobial Use in Food-Producing Animals Preliminary Summary Report (Docket FDA-2022-N-0824-0001)

To Whom It May Concern,

The Center for Science in the Public Interest (CSPI)[1] submits these comments to the United States Food and Drug Administration (FDA) on the above-referenced Reagan-Udall Foundation report ("the report") that addresses data collection regarding antimicrobial use on farms through a public-private partnership (PPP).

CSPI supports the FDA objective of developing an antimicrobial use monitoring system for food-producing animals, as such a system is the foundation for efforts to promote antimicrobial stewardship and limit the development of antimicrobial resistance in the food animal production industry. In general, we agree with the data collection principles the report enunciates. In particular, we agree with the report's findings that the system should gather data with adequate context to understand how and why antimicrobials are used on farms and to track trends over time. We also encourage the FDA to ensure proper usage data are collected by considering conclusions from the pilot studies the agency funded in 2016, which we detail further below. These data will be essential for future science-based antimicrobial policy and regulations.

CSPI requests that the FDA require producers to record and maintain usage data and make it available for representative sampling by the agency, requesting new authority from Congress if necessary to authorize this. Mandatory data collection and sampling by the agency will help ensure that data are representative of industry and allow the agency and industry to fully assess antimicrobial usage and create accurate baselines, both for national data and important subsets of industry. The purposes of this data collection effort can be realized without surveying all producers, provided those surveyed are representative of the broader population of producers. But high compliance with collection and sampling is necessary to assure representativeness. In addition, such a requirement to record antimicrobial use data in a uniform manner will have benefits independent of the data repository.

Finally, regardless of whether FDA adopts a mandatory or voluntary system to collect data, we urge the agency to develop a method of effectively sharing representative data in an aggregated and anonymous manner that easily allows for producers to compare their own detailed usage

[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.

information to anonymized aggregate data from similar segments of the industry, providing further motivation to improve stewardship.

We believe that the data collection and sharing system described in this comment would yield substantial benefits to public health agencies, producers, and prescribers alike

I. Background

A rising level of antimicrobial resistance is one of the most concerning public health issues of our time. The Centers for Disease Control and Prevention (CDC) estimates that 35,000 people in the United States already die each year as a result of antimicrobial-resistant infections.[2] 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 US dollars between 2016 and 2050 and the annual death total will exceed 10 million globally by 2050.[3]

Antimicrobial use is one of the most important factors leading to increased levels of resistance in microbial populations, and their use in food animal production can lead to increased antimicrobial resistance in human pathogens.[4] As such, animal use could affect human health.

Antimicrobial stewardship refers to the practice of judicious antibiotic use to limit the emergence of antimicrobial resistance.[5,6] The FDA conducts activities to limit antimicrobial resistance development due to antimicrobial use in animals based on antimicrobial stewardship principles. The FDA's Center for Veterinary Medicine, which regulates animal drugs, identified "aligning antimicrobial drug product use with the principles of antimicrobial stewardship" as a goal for fiscal years 2019-2023.[7]

The FDA monitors the amount of antimicrobials sold each year by drug sponsors for food animal usage (an estimated 10,449,476 kg in 2020) and publishes an annual summary of these sales data.[8] The summary stratifies antimicrobials sales by drug class, their importance to human medicine, and estimates of how much of each class is sold for major food-producing species.

Antimicrobial sales are a proxy for on-farm antimicrobial use, which is a key measure of the antimicrobial stewardship on farms. As the report notes, however, sales data do not provide the necessary context to fully understand how and why antimicrobials are being used on farms that purchase them. For example, the exact indications for the antimicrobial use, the dosage, and the age of the animals receiving antimicrobials are not collected. On-farm antimicrobial usage data,

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[2] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.
[3] Background. Review on Antimicrobial Resistance. https://amr-review.org/background.html. Published 2016. Accessed July 22, 2022.
[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
[5] Antimicrobial Stewardship Definition and Core Principles. American Veterinary Medical Association. https://www.avma.org/resources-tools/avma-policies/antimicrobial-stewardship-definition-and-core-principles. Accessed July 22, 2022.
[6] FDA's CVM Key Initiative for Antimicrobial Stewardship. U.S. Food & Drug Administration. https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/fdas-cvm-key-initiatives-antimicrobial-stewardship. Updated April 29, 2022. Accessed July 22, 2022.
[7] Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023. U.S. Food & Drug Administration. https://www.fda.gov/media/115776/download. Published Sep 2018. Accessed Aug 11, 2022.
[8] 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. U.S. Food & Drug Administration. https://www.fda.gov/media/144427/download#:~:text=Each%20year%2C%20every%20sponsor%20of%20an%20approved%20or,sold%20or%20distributed%20for%20use%20in%20food-producing%20animals. Published December 2020. Accessed July 22, 2022.

which could include those details, is critical to assessing the level of antimicrobial stewardship that occurs on farms and where resistance development could best be mitigated.

Consequently, the FDA has explored various means of collecting on-farm antimicrobial usage data. In 2016, the agency funded pilot studies to collect baseline information on antimicrobial use in the major food animal species production systems.[9] The pilot studies demonstrated methods for collecting antimicrobial usage data on-farm and illustrated methods by which the data could be aggregated.[10]

In 2021, the FDA commissioned the Reagan-Udall Foundation to "assess the feasibility of creating a public-private partnership to develop an antimicrobial drug use data repository to foster antimicrobial stewardship in food-producing animals."[11] The results of the initial assessment are compiled in the report.

II. The FDA Should Ensure the Proper Components of Antimicrobial Use Data be Recorded on Farms

CSPI urges the FDA to develop a food animal antimicrobial use monitoring system that fully captures the nuances detailed by both the Reagan-Udall report and the pilot studies.

We agree with the report's finding that antimicrobial use data needs to provide context such as number, size, species of animals, and indication to fully understand antimicrobial use in food animals and associated resistance development. The agency has made some first steps in this regard by developing its biomass adjustment for sales data, a development not reflected in the report. In addition, we agree with the report's determination that each species requires capture and analysis of different data elements, and that data capture and compilation should recognize the varying structure and stages of development for each species sector.

The FDA-funded pilot studies further detail data collection and analysis needs. The agency should consider the following recommendations drawn from the pilot studies as it develops the proposed antimicrobial use monitoring system:

- Analyze the usage data collected beyond total active weight of the drug, as the nature of usage can vary due to differences in animal weight and drug potency/dose.[12]
- Consider whether calculating the number of regimens per animal-year may be more useful for predicting antimicrobial resistance than grams of antimicrobial per animal year.[13]

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[9] Exploring the Potential for A Public-Private Partnership to Support the Tracking and Monitoring of Antimicrobial Use in Food-Producing Animals: Preliminary Summary Report. Reagan-Udall Foundation for the FDA. https://reaganudall.org/sites/default/files/2022-05/Report_%20Tracking%20and%20Monitoring%20Antimicrobial_Final.pdf?eType=EmailBlastContent&eId=3edead79-9297-46b6-8442-14ca4445a76b. Published May 2022. Accessed Aug 11, 2022.

[10] Ibid.

[11] Ibid.

[12] Singer, RS, Porter, LJ, Schrag, NFD, Davies, PR, Apley, MD, Bjork, K. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013–2017. *Zoonoses Public Health*. 2020; 67(Suppl. 1): 36– 50. https://doi.org/10.1111/zph.12763

[13] Schrag, NFD, Godden, SM, Apley, MD, Singer, RS, Lubbers, BV. Antimicrobial use quantification in adult dairy cows – Part 3 – Use measured by standardized regimens and grams on 29 dairies in the United States. *Zoonoses Public Health*. 2020; 67(Suppl. 1): 82– 93. https://doi.org/10.1111/zph.12773

- Include the therapeutic outcome of the antimicrobial use, such as illness resolution, additional antimicrobial treatment, or death, when possible.[14]

III. The FDA Should Require that Every Farm Record its Usage Data and that These Data be Made Available to the Agency for Sampling

The report describes a data repository that could be composed of data submitted voluntarily, but this raises concerns about the prospect of an inadequate number of producers participating in data collection, potentially resulting in a non-representative sample of producers. Distinct segments of industry could be omitted or under-sampled, or there could be bias toward including farms with self-perceived adequate stewardship. A preferable system would require that every farm's usage data be recorded and be available for representative sampling by the agency. With mandatory data availability, the agency could predetermine the most important relevant characteristics of industries and ensure that collected data will accurately capture these characteristics, while retaining the necessary statistical characteristics. We expect that a decided minority of farms would be sampled on an annual basis.

A requirement for farms to record and maintain usage data could be analogous to regulations already in place for Veterinary Feed Directive (VFD) drugs, drugs used in animal feed. Pursuant to FDA rules, VFD records must be maintained by involved parties, including farms, for 2 years.[15] Such data could then be at the agency's disposal for sampling for the repository. If FDA determines that it does not have authority to require that usage records be kept and made available for sampling, the agency should request that authority from Congress.

Required antimicrobial usage data recording by farms and mandatory sampling compliance can spur antimicrobial stewardship advances and other potential benefits for all the primary stakeholder groups in animal production.

For the FDA and other agencies, representative data, enabled by mandatory data availability, will allow for better-targeted public health interventions. For example, the nature of an antimicrobial use in a particular segment of industry may warrant specific outreach or other action.

For producers, this data-recording requirement could provide various monetary benefits that would help drive antimicrobial stewardship. With detailed antimicrobial use monitoring on their farms, producers would be better able to track antimicrobial use and to recognize their associated costs. They may then be more motivated to minimize costs and more critically evaluate the number of uses and duration of use of antimicrobials, among other factors associated with antimicrobial stewardship.

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[14] Singer, RS, Porter, LJ, Schrag, NFD, Davies, PR, Apley, MD, Bjork, K. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013–2017. *Zoonoses Public Health*. 2020; 67(Suppl. 1): 36– 50. https://doi.org/10.1111/zph.12763

[15] Veterinary Feed Directive Requirements for Distributors (Who Manufacture VFD Feed). U.S. Food & Drug Administration. https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-feed-directive-requirements-distributors-who-manufacture-vfd-feed. Updated Feb 11, 2021. Accessed Aug 11, 2022.

For example, tylosin, an antibiotic, is commonly used in feed to reduce liver abscesses in cattle.[16] There is no limitation on the duration of use for this drug [17]A VFD is required for drugs administered to animals in feed, including tylosin.[18] Though the VFD record requires information such as species, level of drug in the feed, duration of use, indication for use, and approximate number of animals fed, it does not require therapeutic outcome, age, and weight ranges to be recorded, which are needed to provide sufficient context on how the antimicrobial is used.[19] If farms were required by FDA to systematically collect more detailed usage data for lots of animals fed antimicrobials, they would be better prepared to continuously monitor within their herd how much they could reduce the use and subsequently the cost of tylosin, while still having the desired therapeutic effect.

Davedow et al (2020) demonstrated what individual farms could accomplish if they were required to record sufficiently detailed antimicrobial use data. In their study, yearling cattle were randomly assigned to groups receiving tylosin either days 0-125, 41-161 or 0-161 during a 161-day feeding period. The proportion of erythromycin-resistant enterococci in the cattle fecal samples increased significantly over the feeding period for all 3 treatment groups. There was no difference, however, in the number of liver abscesses and associated mortality between the treatments, suggesting that all 3 groups obtained the desired therapeutic outcome.[20] If producers were required to monitor use of antibiotics on farms, they would each possess datasets that would lower the barrier to conducting similar trials or otherwise evaluate antimicrobial usage on their farms, even if on a smaller and more informal scale than this study.

Because they will be required to adequately record antimicrobial usage, producers will also have a better indication of disease burden on their farms and where to target interventions. Poor welfare is generally associated with higher antimicrobial use. For example, one study examined data on medicine usage, animal welfare, and the condition of farm buildings in the pig health and welfare classification system in Finland, which covers over 95% of pig production in the country. The study found that problems with air quality, poor cleanliness, and the poor condition of farms were associated with a higher number of antimicrobial treatments due to respiratory diseases in swine production.[21] (This study leaves open the possibility that farms with lower resistance rates were also the kinds of farms that tended to address on-farm conditions.) Usage records would highlight areas of substantial antimicrobial use to producers, which could be a sign of underlying problems that could be prevented or mitigated through improving management practices. Resulting better management could provide a financial benefit from improved production in addition to decreasing the need for antimicrobials (and their cost).

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[16] FDA Clarifies Use of Tylosin Phosphate in Beef Cattle – Veterinarians. U.S. Food & Drug Administration. https://www.fda.gov/animal-veterinary/product-safety-information/fda-clarifies-use-tylosin-phosphate-beef-cattle-veterinarians. Updated Dec 19, 2018. Accessed July 22, 2022.

[17] Ibid.

[18] Drugs with Veterinary Feed Directive (VFD) Marketing Status. U.S. Food & Drug Administration. https://www.fda.gov/animal-veterinary/development-approval-process/drugs-veterinary-feed-directive-vfd-marketing-status.Updated Feb 2, 2022. Accessed Aug 11, 2022.

[19] Veterinary Feed Directive Requirements for Veterinarians. U.S. Food & Drug Administration. https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-feed-directive-requirements-veterinarians. Updated Feb 11, 2021. Accessed July 22, 2022.

[20] Davedow T, Narvaez-Bravo C, Zaheer R, Sanderson H, Rodas-Gonzalez A, Klima C, Booker CW, Hannon SJ, Bras AL, Gow S, McAllister T. Investigation of a reduction in tylosin on the prevalence of liver abscesses and antimicrobial resistance in enterococci in feedlot cattle. *Front Vet Sci.* 2020. https://doi.org/10.3389/fvets.2020.00090.

[21] Stygar AH, Chantziaras I, Toppari I, Maes D, Niemi JK. High biosecurity and welfare standards in fattening pig farms are associated with reduced antimicrobial use. Animal. 2020;14(10):2178-2186. doi:10.1017/S1751731120000828

Purchasers could also create further incentives for stewardship by building on required uniform antimicrobial use recording, as they would be better enabled to require antimicrobial use data as a condition of sale and make more informed purchasing decisions. Processors and other businesses could pay premiums (and market more expensive products) for food animals from farms perceived to have sufficient or superior antimicrobial stewardship. The meat and food production industry has already demonstrated interest in buying products from producers with better antimicrobial use practices, like McDonald's announcing an antibiotic policy for beef and Costco including antibiotics in its animal welfare policies.[22,23]

An analogous situation exists in the dairy industry in the United States. Somatic cell counts in milk are representative of cow health and milk quality, and each bulk tank of milk purchased by processors can be sampled for its somatic cell count.[24] Certain processors will pay premiums for milk that has a somatic cell count significantly lower than the legal limit of 750,000 cells/mL or penalize those who have higher than average somatic cell count milk, whether that penalty is the result of the government or of market forces. In Minnesota, for example, farmers may get a penalty of $2.00 per hundredweight of milk with high SCC levels.[25] As a result, farmers are motivated to produce milk with the lowest SCC and may change their practices to improve herd health.

For veterinarians, uniform antimicrobial use recording will also better describe antimicrobial prescribing practices and allow them to compare how antimicrobials are prescribed on individual farms over time and compare a farm's usage to different client farms. Veterinarians can then more closely monitor and critically evaluate their prescribing practices and improve stewardship.

Given the benefits to public health, producers, retailers, and veterinarians, we urge the FDA to develop a system to require uniform antimicrobial use recording and sample to provide representative aggregate estimates.

IV. The FDA Should Develop a Data Collection System that Enables Farm Comparison

Regardless of whether FDA adopts a mandatory or voluntary system to collect data, we urge the agency to develop a method of data collection and publication that allows for producers to easily compare their own detailed usage information to anonymized aggregate data from similar segments of the industry. Producers and other industry members could then more easily compare their usage to industry baselines and be more motivated to improve stewardship.

Although private industries may eventually develop systems to analyze industry-wide and farm-specific antimicrobial use data, an FDA-sponsored system could set an important benchmark for how these data should be compiled to best encourage antimicrobial stewardship. Such a system

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[22] Using our Scale for Good: McDonald's New Antibiotic Policy for Beef. McDonald's. https://corporate.mcdonalds.com/corpmcd/en-us/our-stories/article/ourstories.beef_antibiotics.html. Accessed Aug 11, 2022.
[23] Animal Welfare. Costco. https://www.costco.com/sustainability-animal-welfare.html. Updated June 2022. Accessed Aug 11, 2022.
[24] Alhussien MN, Dang AK. Milk somatic cells, factors influencing their release, future prospects, and practical utility in dairy animals: An overview. Vet World. 2018 May;11(5):562-577. doi:10.14202/vetworld.2018.562-577. Epub 2018 May 2. PMID: 29915493; PMCID: PMC5993762.
[25] Wilmes E. Lowering somatic cell counts in milk. University of Minnesota Extension. https://extension.umn.edu/dairy-milking-cows/dairy-somatic-cell-counts#:~:text=Processors%20also%20pay%20a%20premium%20for%20milk%20with,to%20%242.00%20per%20hundredweight%20for%20high%20cell%20counts. Published 2019. Accessed July 22, 2022.

should enable detailed antimicrobial use comparisons between farms with similar characteristics. For example, veterinarians and producers would likely find a tool that allows searches for aggregate usage data by farm location and type, month, and animal characteristics such as species and weight to be extremely useful when making management decisions regarding antimicrobial use.

An example of the benefits of such a system can be found in the efforts of the Dairy Herd Improvement Association (DHIA), a voluntary association constituted of members that include 39% of the herds and 46% of the cows in licensed herds in the U.S.[26] The association collects standardized records including production parameters like the pounds and fat in the milk produced, the total value of product, total feed cost, and other reproductive and health data for individual cows.[27] By collecting data through DHIA, producers can compare their production parameters to other member herds, providing motivation to improve parameters.[28,29]

Veterinarians would also greatly benefit from such a system, as they would be able to compare the antimicrobial usage of their farms to other farms and adjust prescribing behavior. A similar system exists in human medicine. The CDC's National Healthcare Safety Network (NHSN) allows medical facilities to compare their antimicrobial use rates over time and to a baseline for similar facilities.[30] Healthcare facilities have reported quantitatively evaluating their prescribing, establishing interventions where they identified high usage, and decreasing usage after joining the network.[31,32]

While such comparison systems could be useful even when managed by private industry on a voluntary basis, a system based on uniform national data recording and mandatory data availability, as we have recommended in the prior section, would be more valuable. Indeed, the limitations of the voluntary DHIA system are reflected in the limited participation in that system, raising questions of representativeness that will not exist in mandatory systems. The owner of a beef feedlot with 1,000 head capacity in the Southwest would likely prioritize comparing their feedlot's antimicrobial usage to like operations and not 10,000 head feedlots in the Midwest.

Conclusion

Thank you for providing an opportunity to comment on the report and on potential plans for an antimicrobial use data repository. We generally agree with the report's findings, but we believe that the FDA should make antimicrobial usage data recording and availability for collection mandatory, even though data may only be collected from a representative subset. We look

[26] DHIA: What is it? Who is it? Dairy One. https://dairyone.com/dairy-herd-improvement-association-what-is-it-who-is-it/. Accessed Aug 11, 2022.
[27] Ferris T. 1106 PD: History of a national dairy record system. Progressive Dairy. https://www.progressivedairy.com/topics/a-i-breeding/1106-pd-history-of-a-national-dairy-record-system. Published Nov 10, 2006. Accessed July 22, 2022.
[28] Ibid.
[29] DairyMetrics. DHI Cooperative, Inc. https://dhicoop.com/dairymetrics.html. Accessed Aug 11, 2022.
[30] CDC. 2020 National Healthcare Safety Network Antimicrobial Use Option Report. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2021. https://www.cdc.gov/nhsn/pdfs/datastat/2020-au-report-508.pdf
[31] Decreasing Aztreonam Use in a Veterans Affairs Hospital. CDC. https://www.cdc.gov/nhsn/au-case-examples/reducing-aztreonam-use.html. Published Jun 17, 2019. Accessed Aug 11, 2022.
[32] Targeting a Reduction in Fluoroquinolone Use within a Community Hospital. CDC. https://www.cdc.gov/nhsn/au-case-examples/reduce-fluoroquinolone-use.html. Published Jan 30, 2019. Accessed Aug 11, 2022.

forward to working with the FDA as the agency further develops an antimicrobial use monitoring system.

Sincerely,

James Kincheloe, DVM, MPH
Food Safety Campaign Manager

Peter Lurie, MD, MPH
President and Executive Director

Sarah Sorscher, JD, MPH
Deputy Director for Regulatory Affairs

Laila Tabatabai
Food Safety and Public Health Intern