November 13, 2017

Dockets Management Staff
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **FDA-2017-N-1197: FDA's Proposed Method for Adjusting Data on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Using a Biomass Denominator**

To Whom it May Concern:

On behalf of the consumer, public health, environment, animal welfare, food safety and sustainable agriculture organizations indicated below, please accept these comments on the *FDA's Proposed Method for Adjusting Data on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Using a Biomass Denominator* (e.g. FDA Proposal). How the FDA reports on antibiotic[1] sales/use is of obvious importance to public health, given broad consensus that the extent of antibiotic use is among the most important drivers of antibiotic resistance. FDA data also underscore that approximately 70% of all medically important antibiotics are sold for use in food-producing animals.[2] Since these antibiotics are provided to a variety of animals that vary greatly in number and size, the idea of a biomass adjuster is welcome.

Our organizations are advocates for the public interest, and in particular for policy and market changes that will improve antibiotic stewardship by reducing the unnecessary use of antibiotics in livestock production. By doing so, we hope to curb antibiotic resistance and thereby, help ensure that antibiotics—particularly antibiotics that are used in both human medicine and in livestock production—remain effective for longer in treating the sick people and animals who most need them.

Overview. We support FDA's efforts to improve reporting on how antibiotics are used in food animals as addressed in this proposal but view this effort as part of the Agency's broader mandate to protect public health and promote antibiotic stewardship. We therefore aim the following comments both to address the technical issues relevant to the proposed method, and to urge the FDA to consider other steps needed to meet its broader public health goal(s).

For example, the FDA has not set either a goal for concrete reductions in the use of medically important antibiotics, or a timeline for achieving that goal. In terms of bringing about better antibiotic stewardship, this is an important step that has been recommended by the World Health

[1] In these comments, the term "antibiotics" is used in place of "antimicrobials." The former term is commonly used, including by the Centers for Disease Control and Prevention, to refer to antimicrobial agents used to treat bacterial infections in both people and animals.
[2] FDA Annual Summary Report on Antimicrobials Sold or Distributed in 2015 for Use in Food-Producing Animals. Accessed at https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm534244.htm.

Organization[3], the O'Neill Global Review on Antimicrobial Resistance,[4] and the Expert Commission Addressing the Contribution to Antibiotic Resistance from Livestock Antibiotics.[5] It also is a step that was implemented and shown to be highly effective in the Netherlands and Germany.

1) ***Is the proposed mg/TAB formula appropriate for adjusting estimates of antibiotic sales relative to the size of the animal population potentially being treated with those drugs?***

We agree that the FDA's goal of reporting antibiotic sales on a biomass-adjusted basis could help to better characterize antibiotic use in the U.S. livestock sector. The FDA proposal is to develop estimates that rely substantially for the numerator on drug makers' estimates of the amount of antibiotics sold and distributed for four major animal species. The proposal is to further combine these sales estimates with demographic data on major food animal species to create a U.S. specific, biomass-adjusted measure, mg/TAB. While imperfect, the FDA proposal has potential to provide important data to inform policy and public health decisions, and represents a step forward in terms of transparency. We therefore urge the FDA to move forward with implementation of its proposal.

Nevertheless, it is important for the public to be made aware of various sources of uncertainty, bias and potential error in deriving the mg/TAB estimate, which will enable the information to be contextualized and interpreted with appropriate caution. **We recommend generally, therefore, that the FDA take great care to characterize sources of real or perceived error, or factors that may introduce bias or uncertainty into the data, both in its own methodology and in public reporting of the estimates. This is essential for providing the level of transparency needed for appropriately interpreting the data and subsequent estimates.**

a) Numerator: As the FDA proposal pertains to the use of species-specific sales estimates, and their use in calculating the numerator of the mg/TAB equation, there are several sources of uncertainty, bias and potential error described below, along with recommendations on how to be more transparent.

i) ***Recommend*: The FDA should require drug makers to report their methodology in estimating species-specific sales of their products, and report those methodologies in turn to the public.** This is not currently the case. The FDA Rule[6] requires drug makers to provide estimates of sales by species. However it does not specify how drug makers should derive those estimates, nor require drug makers to

[3] WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

[4] O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.The Review on Antimicrobial Resistance:May 2016. Accessed at : https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

[5] Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C. Available at http://battlesuperbugs.com/sites/battlesuperbugs.com/files/Final%20Report%208.25.17.pdf

[6] 81 C.F.R 29129. Accessed at https://www.gpo.gov/fdsys/pkg/FR-2016-05-11/pdf/2016-11082.pdf.

share with FDA any information as to how those estimates were derived. The absence of this information leaves many questions about the accuracy of individual estimates unanswered, and means that estimates by different companies could be based on different methods and vary in their accuracy, but without sufficient information to characterize the degree of that variability.[7] Ideally, drug makers would follow a common FDA-recommended methodology, which would help ensure a measure of transparency and consistency between drug makers' estimates.

ii) ***Recommend:*** **The FDA should require that drug makers use a consistent methodology for making estimates from year to year.** The corollary to the problem of undisclosed estimation methodology addressed above is that a drug maker could use a different estimation methodology each year, and yet never disclose that fact to the FDA. Without this information, meaningful analysis of

iii) trends in the sales or distribution of antibiotics would be compromised. The lack of this information also compounds the uncertainty discussed above.

iv) ***Recommend:*** **The FDA adds further imprecision by combining categories that need not be combined; therefore, the FDA should disaggregate the data for "other species" and "unknown" species.** The more finely-grained the data collected and reported, the better able the Agency will be to assess the impact upon public health. The FDA Rule currently requires drug makers to combine estimates of product sales for pets and for minor food-animal species with estimates of sales for which the companies have zero information. By doing so, this Rule ensures that the FDA itself cannot know the proportion of estimated antibiotic sales for which the drug makers simply have no information. For example, if a company reports that 40% of its sales of a particular antibiotic are for "other species/ unknown", there in fact will be no way for either FDA or the public to differentiate whether this means that the company has zero information concerning that 40% of sales, or alternatively, that the company DOES have specific information that indicates the 40% of sales in question is for species other than cattle, swine, chickens, or turkeys. In short, the FDA's Rule obscures the uncertainty around estimates; which will impair the usefulness of the information in making good policy decisions. If public reporting requires that data be aggregated to protect the identity of manufacturers, then the FDA can always do that if it begins with disaggregated data in the first place. Wherever possible, however, the FDA should also report disaggregated data to the public.

v) ***Recommend:*** **The FDA should explicitly acknowledge the effect of combining sales estimates of antibiotics with different potencies.** The FDA currently requires species specific estimates of sales only down to the level of antibiotic class. This

[7] In 80 FR 28866, the FDA has previously noted significant variability between drug makers in their reporting accuracy on sales of their antibiotic products, especially after the companies were asked to do a simple unit conversion so that the reports reflected sales and distribution by antibiotic active ingredient rather than by total product. FDA as a result no longer expects drug makers to make such calculations.This experience reinforces the concern that drug makers estimates by species could be highly variable.

approach will allow for a rough analysis of sales trends of that class over time, but it also carries the potential to obscure transitions from a high-volume, low potency antibiotic to another, higher potency antibiotic used at lower volumes but which may actually provide the same or greater degree of selection pressure (or vice versa). Such movements may occur between antibiotic classes, but also between low potency and high potency antibiotics within an antibiotic class. Therefore, transformation into measures that take differences in potency into account should be performed before summarizing the antibiotic use on class level. Ideally, the FDA would first make mg calculations for each antibiotic product specific to each major species, even if those calculations could not be publicly reported due to concerns about confidential business information.

Denmark, as well the Netherlands and other countries, now report their antibiotic sales/use in food-producing animals in terms of Defined Animal Daily Dosages (DADD, DDDvet eg.). These defined animal daily doses are constructs, or technical units of measurement, solely intended for the reporting of antibiotic use data. They don't reflect the daily doses of particular products as recommended or prescribed. Instead the defined daily doses are typically determined by experts, and the values chosen often represent a compromise. With the collection of sufficient data, defined daily doses can be determined for each antibiotic agent, administration route and animal species, as does Denmark, for example. In the U.S., as in most member countries of the European Union (EU), there are insufficient data on antibiotic use by animal species to calculate defined daily doses. However, the EU is moving in that direction. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), a project of the European Medicines Agency (EMA), has begun creating a system for collecting data on antibiotic use, by animal species, that is standardized and harmonized across the 28 EU member countries. As a first step, the ESVAC established the defined daily dose, or DDDvet, as a standardized unit of measurement for reporting antibiotic use in animals.[8] The proposed DDDvet is defined by species, and represents a quantitative measure of amounts of antibiotics, taking into account the potency of the active compound. Transforming the antibiotic use into number of DDDvet before summarizing an antibiotic class (eg. tetracyclines), will enable the evaluation of trends in use of antibiotic classes.

Since ESVAC already is harmonizing antibiotic use reporting by animal species across so many countries, among them several major food animal producers, we urge that the FDA consider eventually harmonizing its approach to this same set of practices.

b) **Denominator:** The denominator used to adjust the antibiotic sales data is equivalent to the biomass of the animal population. There are additional concerns around how the FDA proposes to determine the denominator in its mg/TAB calculation, and the FDA should

[8] European Medicines Agency website. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Accessed November 9, 2017 at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001493.jsp&mid=WC0b01ac0580a2fcf5.

explicitly acknowledge these concerns in its transparent discussion around sources of uncertainty, potential bias and error.

i) ***Recommend:*** **The FDA should be consistent across animal species and antibiotic classes in terms of how it determines the biomass of animals used in calculating the TAB.** On page 6 of its proposal, the FDA signals its intent to use USDA-collected data on average animal slaughter weights rather than the alternative approach of estimating average weights of animals at the age of treatment. Elsewhere, in the proposal, the Agency describes more of an "apples-and-oranges" approach that at times mixes slaughter weights with live animal weight, e.g. on page 9, the FDA discusses mixing slaughter weight of feedlot cattle with census data (live weights) of dairy cattle. We feel strongly that FDA should choose just one method and apply it consistently, across different animal species as well as across different antibiotic classes.

ii) ***We also recommend:*** **The FDA in its calculations should harmonize the denominator with the European Surveillance of Veterinary Antimicrobial Consumption, or ESVAC.** To adjust antibiotic sales data, ESVAC uses as a denominator the "Population Correction Unit", or "PCU". Both Canada[9], and the UK [10] in their most recent reports on antibiotic use surveillance have also employed mg/PCU. Presumably, annual weights of animals will tend to be larger than treatment weights, which in turn will result in FDA estimates of mg/TAB that are lower than they might be if treatment weights were used instead. To the undersigned organizations, it seems desirable for the FDA to try and harmonize with this denominator to facilitate comparison with antibiotic use in Canada, the UK and the EU member countries. That was also a recommendations earlier this year of the independent Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis, comprised of 12 infectious disease physicians, microbiologists, pediatricians, as well as five veterinarians.[11]

2. ***Does the proposal provide an appropriate way to look for sales trends of antibiotics to be used in major food-producing animals? Are there other methods the FDA should employ?***

The proposed method could provide FDA with some useful data on overall sales trends of antibiotics intended for use in major food-producing animals, especially if the methodology were more transparent and consistent. For more meaningful antibiotic use information, however, FDA should undertake additional steps to improve antibiotic use surveillance.

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[9] Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System (CARSS) Report, 2016. September 2016. Accessed November 9, 2017 at https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/drugs-health-products/antibiotic-resistance-antibiotique/antibiotic-resistance-antibiotique-2016-eng.pdf.

[10] https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2016.

[11] Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C.Accessed at http://battlesuperbugs.com/sites/battlesuperbugs.com/files/Final%20Report%208.25.17.pdf.

Many of the undersigned groups are members of Keep Antibiotics Working, which has long noted the critical need for an on-farm data collection program that is robust and transparent. No such system currently exists. Neither FDA nor the USDA has publicly requested funds from Congress to build such a system. The failure to establish such a system or to attempt to establish such a system is particularly troubling given the fact that, over nearly two decades, various government advisory bodies and others have strongly urged it:

- In the 2001 Interagency Task Force on Antimicrobial Resistance, collection of data on actual antibiotic use was a top priority recommendation.[12]
- In a 2007 review of the National Antimicrobial Resistance Monitoring System (NARMS), the FDA's Science Advisory Board recommended that drug use data be integrated with microbiological data, and stated that the lack of drug use data "represents a critical barrier for NARMS to achieve its objectives and further utility."[13]
- Another 2017 review of NARMS, for FDA's Science Board, echoes the 2007 recommendation, again identifying the need for actual antibiotic use data.[14]
- The 2015 National Action Plan on Combating Antibiotics Resistant bacteria directs the FDA and USDA to "initiate collection of drug use and resistance data on farms."**[15]**
- In 2017[16], the United States Government Accountability Office (GAO) again identified the need for the collection of actual antibiotic use data as it had in earlier reports in 2004[17], and again in 2011.[18]
- Also in 2017, the aforementioned Expert Commission on Addressing the Contribution of Livestock made the development of a data collection system a key recommendation of its policy roadmap.[19]

Our organizations agree with these recommendations. While we recognize that federal agencies are constrained to act within their statutory authority, the FDA does have existing authority to collect data on feed distributed under veterinary feed directives. For example, an audit of VFDs from a selection of representative, sentinel farms could provide valuable complementary information to sales/distribution and on-farm data. This would offer a transparent and consistent methodology for collecting species-specific data on antibiotic

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[12] See page 3, at https://www.cdc.gov/drugresistance/pdf/aractionplan-archived.pdf.

[13] See page 7, at https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_06_NARMS%20Review%20Update.pdf.

[14] See page 7, at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM564273.pdf.

[15] https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM564273.pdf

[16] Antibiotic Resistance:. More Information Needed to Oversee Use of Medically Important Drugs in Food Animals, GAO-17-192 (Washington, D.C.: March 2, 2017). Accessed at http://www.gao.gov/assets/690/683130.pdf.

[17] Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals, GAO-04-490 (Washington, D.C.: Apr. 22, 2004).

[18] Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals, GAO-11-801 (Washington, D.C.: Sept. 7, 2011)

[19] Expert Commission. Combating Antibiotic Resistance: A Policy Roadmap. 2017.

usage, as feed is specific to an animal species and feed distributors are already required to maintain and make available to the FDA records of distributed feed (although this would need to be supplemented by other data on antibiotics administered through other routes on farm because VFDs relate to feed administration only).

The World Health Organization (WHO) and the World Animal Health Organization (OIE) provide guidance on how more antibiotic use data closer to farm-level could be collected; additionally, Denmark[20] and the Netherlands[21] are two countries that have been particularly thorough in documenting the construction of systems for collecting data with a higher degree of granularity than what is currently available in the U.S..

3) ***Should FDA consider additional methods besides biomass to adjust antimicrobial sales data relative to the U.S. livestock population that are not referenced here? Please provide examples.***

With the caveats above**,** we support the FDA's proposed method as a step forward, but suggest the following improvements:

Recommend: **The FDA should calculate mg/PCU along with its proposed mg/TAB calculations, and publicly report both sets of calculations side-by-side, so anyone can see how they differ, if at all and to allow for a rough comparison with other countries.**

As the FDA notes in its technical paper, the ESVAC project of the European Medicines Agency has a well-established methodology for calculating a biomass-adjusted calculation, called mg/PCU; The EMA uses the mg/PCU values to estimate temporal trends in the amount of antibiotics sold for food-producing animals within individual countries—the same as the FDA's stated goal—as well as across countries.[22] Several EU member states, including the UK and France, already have incorporated variations on the mg/PCU calculation and biomass denominator into their country-specific reports.[23,24] The FDA's proposed mg/TAB metric is similar, except that it uses annual weights instead of weights at treatment and produces species-specific estimates, whereas the European method produces a single metric for each country, depending on the particular animals raised there.

In explaining its choice of the mg/TAB indicator, the FDA states that "food producing animals in the U.S. are generally larger at similar points in the production cycle than in

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[20] Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) website.Accessed November 9, 2017 at https://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP%202016%20DADD%20description.ashx).

[21] http://www.rivm.nl/dsresource?objectid=f9799644-beb0-405b-b35f-c3db66dc153b&type=pdf&disposition=inline

[22] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf.

[23] Veterinary Medicines Directorate, *Veterinary Antimicrobial Resistance and Sales Surveillance 2014*; https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2014

[24] Veterinary Medicines Directorate, *Veterinary Antimicrobial Resistance and Sales Surveillance 2014*; https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2014.

Europe, and therefore, the standard average weights at treatment may be different." We ask that the FDA publicly document the data on which this claim is based.

We also urge the FDA to publish both the mg/TAB and the more widely used mg/PCU adjuster as well, as this will allow for a comparison of trends and practices in antibiotic sales/use across countries.[25] Moreover, since there are no species-specific sales data prior to 2016, the mg/PCU permits comparisons with earlier years, a comparison critical to the evaluation of the effectiveness of GFI #213.

Thank you for the opportunity to provide these comments.

Sincerely,

Antibiotic Resistance Action Center, the George Washington University

Consumers Union

Natural Resources Defense Council

U.S. PIRG (Public Interest Research Group)

Food Animal Concerns Trust

Center for Foodborne Illness Research & Prevention

Center for Food Safety

Consumer Federation of America

Johns Hopkins Center for a Livable Future

Center for Science in the Public Interest

[25] Public Health Agency of Canada, *Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) Annual Report*, http://www.phac-aspc.gc.ca/cipars-picra/2012/index-eng.php.