

August 28, 2019

Norman E. Sharpless, MD
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: FDA leadership in combating antibiotic-resistant bacteria

Dear Acting Commissioner Sharpless:

We the undersigned members and colleague groups of the Keep Antibiotics Working coalition write to ask that the Food and Drug Administration (FDA) quickly move forward with 5 additional steps to address the serious public health threat caused by the development and spread of resistance to antibiotics. Specifically, we ask that FDA strengthen and implement the Center for Veterinary Medicine's Five-Year Action Plan for Supporting Antimicrobial Stewardship in Veterinary Settings¹. Formed in 2001, Keep Antibiotics Working is a coalition of 16 advocacy organizations that joined together to ensure that untreatable superbugs resulting from the overuse of antibiotics on farms do not reverse the medical advances of the past century.

The Centers for Disease Control and Prevention (CDC) has estimated that 2 million people are infected, and over 23,000 die each year in the U.S. of antibiotic-resistant infections.² These estimates are highly conservative, with some infectious disease experts recently estimating an annual mortality up to 7 times higher.³ The toll on the economy each year from these deaths, plus the exorbitant expense of treating more than 2 million drug-resistant infections annually could be up to \$55 billion.⁴

The key factor driving the epidemic of antibiotic resistance is the overuse and misuse of antibiotics in both human medicine and agriculture. FDA, with the clear mission of protecting and promoting public health including assuring the safety of drugs both in human and veterinary medicine, must continue to play an essential role in addressing this overuse both by making sure that drugs are used only when needed and by monitoring use and setting goals for the reduction of overuse. We ask that FDA prioritize the following actions.

¹<https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-five-year-plan-supporting-antimicrobial-stewardship-veterinary-settings>

²https://www.cdc.gov/drugresistance/biggest_threats.html

³<https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/reestimating-annual-deaths-due-to-multidrugresistant-organism-infections/>

⁴<https://onlinelibrary.wiley.com/doi/pdf/10.1111/1469-0691.12798>

Reduce sales of medically important antibiotics for use in food-producing animals by at least 45% from 2009 levels by 2021 –

Goal setting is an essential part of protecting public health. FDA has a stated goal of improving the stewardship of antibiotics in food animals but has never indicated what the expected or desired outcomes of these efforts are. In contrast, the CDC has ambitious targets for reductions in antibiotic use both in inpatient⁵ and outpatient⁶ settings. We recommend a targeted reduction of sales of medically important antibiotics for use in livestock by at least 45% from 2009 levels by 2021. Additional targets should be set for critically important drugs. In 2018, the U.S. Food and Drug Administration reported a 28% drop in such sales from 2009 to 2017.⁷ Other countries have had success with including reduction targets as part of their efforts to improve antibiotic stewardship.⁸

Require all durations of use to be under 21 days for medically important antibiotics administered to food-producing animals –

In its five-year plan, FDA accepts the need for limited durations for the use of medically important antibiotics. We strongly support this and ask that FDA move forward with implementing regulation or guidance. The continuous use of medically important antibiotics in food animals clearly increases the risk of antibiotic resistance.⁹ In order to meet the goal of reducing resistance, durations need to be sufficiently short. We ask that FDA limit durations to no longer than 21 days, and require an additional veterinary order if the use needs to be extended. Durations longer than 21 days are considered to be high extent of use in FDA's Guidance for Industry #152 (GFI#152) and are not recommended for antibiotics considered at high or medium risk of resistance.¹⁰ While there is a lack of studies in veterinary settings, there is ample evidence from human medicine that shorter-course durations are just as effective as longer courses and create fewer side effects including antimicrobial resistance.¹¹ The evidence from human medicine indicates that for most infections 21 days is a longer than necessary duration.

Update FDA's list of medically important antimicrobials –

We support the goal in the five-year action plan to update the FDA's list of medically important antibiotics. FDA has not updated the list since it was published in 2003 as part of GFI#152. Since then, new science has emerged, resistance concerns have risen, and new drugs have been approved. FDA does not consider tiamulin, a pleuromutilin class drug, to be medically important because the first approval for human use was in 2007,¹² after FDA created its list. Another pleuromutilin class drug, lefamulin, has recently been approved for treatment of community-acquired pneumonia.¹³ Use of tiamulin in pigs has also been shown to select for resistance to medically important drugs in other

⁵ <https://www.cdc.gov/antibiotic-use/stewardship-report/outpatient.html>

⁶ <https://www.cdc.gov/antibiotic-use/stewardship-report/hospital.html>

⁷ <https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2017-use-food-producing>

⁸ https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac_en.pdf

⁹ <https://www.fda.gov/media/83488/download>

¹⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-152-evaluating-safety-antimicrobial-new-animal-drugs-regard-their-microbiological-effects>

¹¹ <https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy1134/5275222>

¹² https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022055s000TOC.cfm

¹³ <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia>

classes including linezolid.¹⁴ Another drug used in animals that FDA does not consider to be medically important is bacitracin, but recent studies have shown that bacitracin use can select for resistance to the last resort drug colistin.¹⁵ We call on FDA to promptly move forward with updating this list and commit to a schedule for updating the list at least every three years or more frequently when appropriate.

Provide guidance on product label information (e.g. define treat, control, and prevent) to strengthen stewardship –

The five-year plan includes an action (1.1.5) to address how product label information can better support antimicrobial stewardship. FDA approves medically important antibiotics to treat, control, and prevent bacterial infection but provides no guidance on what these terms mean. Instead, individual veterinarians or livestock owners determine when it is appropriate to use an antibiotic for these purposes. This can undermine efforts in antimicrobial stewardship. For example, some swine producers inject every pig in their facilities multiple times with the third generation cephalosporin ceftiofur as a “control” for respiratory disease.¹⁶ In the absence of guidance, these producers are using a drug approved for control in a manner consistent with disease prevention, not control. FDA explicitly prohibits the use of ceftiofur for disease prevention as part of extra-label restrictions published in 2012.¹⁷ This restriction is meaningless if there is no distinction between treatment, control, and prevention. The failure to define these terms also makes it easier for drug makers to inappropriately market drugs. In its marketing materials, the drug maker Elanco recommends “proactively” treating subclinical illness for a drug approved for disease treatment.¹⁸ In the absence of guidance, the drug maker effectively blurs the distinction between treatment and prevention. FDA must provide guidance on what it means by the terms treatment, control, and prevention on its labels. The guidance should also cover terms related to duration of use since these are also open to interpretation. For example, livestock producers may use drugs with a duration of 5 days for longer periods by skipping a few days of treatment between multiple 5-day periods,¹⁹ increasing the risk of adverse effects such as antibiotic resistance.

Strengthen data collection on both antimicrobial use and resistance –

The five-year plan includes goals related to data collection. Despite FDA’s recognition of the need for data on how antibiotics are used on farms for almost two decades,²⁰ there has been very limited progress on filling this data gap. FDA collects data on sales of antibiotics for use in food-producing animals as required by Section 105 of the Animal Drug User Fee Amendments of 2008.²¹ USDA, under the National Animal Health Monitoring System, collects data through periodic voluntary surveys of livestock producers. But neither of these provide a clear picture of the amount of antibiotics used and the reason for their use. The FDA sales data has recently improved with per species estimates, but there is no quantitative data at any level closer to the farm. The USDA surveys are at the farm level but are infrequent, rely on voluntary participation, and do not actually collect

¹⁴ <https://academic.oup.com/jac/article/69/8/2022/873861>

¹⁵ <https://msphere.asm.org/content/3/5/e00411-18>

¹⁶ <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0208430>

¹⁷ <https://www.govinfo.gov/content/pkg/FR-2012-01-06/html/2012-35.htm>

¹⁸ <https://www.nytimes.com/2019/06/07/health/drug-companies-antibiotics-resistance.html>

¹⁹ <https://academic.oup.com/tas/article/3/1/185/5235607>

²⁰ <https://www.cdc.gov/drugresistance/pdf/aractionplan-archived.pdf>

²¹ <https://www.fda.gov/industry/animal-drug-user-fee-act-adufa/adufa-reports>

data on the amount of antibiotics administered or detailed data on reason for use²². So far, these two data collection programs have operated in isolation and the two agencies have not reported any effort to compare and draw conclusions from the two separate data collection programs. We ask that FDA put in place a program to sample feed distribution records kept as required by the Veterinary Feed Directive regulations²³ as another source of data that would include information on both the amount of antibiotics administered in feed and reason for use. We also encourage FDA to strengthen the surveillance of antimicrobial resistance through the National Antimicrobial Resistance Monitoring System (NARMS) and to improve the speed of reporting. The latest NARMS data is from 2015.

Antibiotic resistance continues to be a major and growing threat to public health. FDA's five-year action plan includes important actions to help mitigate this threat but the plan needs to be strengthened and implemented. We ask that you show leadership to make sure that this is done.

Sincerely,



Steven Roach (sroach@foodanimalconcerns.org)

Food Safety Program Director, Food Animal Concerns Trust

On behalf of Keep Antibiotics Working and its undersigned member and colleague organizations

AllergyKids Foundation
Alliance for Humane Biotechnology
Alliance for Natural Health USA
Alliance to Save our Antibiotics
Antibiotic Resistance Action Center, GW
Milken Institute School of Public Health
Arizona PIRG
Association for Professionals in Infection
Control and Epidemiology
CalPIRG
Center for Biological Diversity
Center for Food Safety
Center For Foodborne Illness Research &
Prevention
Certified Naturally Grown
Clinician Champions In Comprehensive
Antibiotic Stewardship Collaborative
(CCCAS)
Colorado PIRG
ConnPIRG
Consumer Federation of America
Consumer Reports

Family Farm Defenders
FamilyFarmed
Farm Forward
Food Animal Concerns Trust (FACT)
Food Sleuth, LLC
Health Care Without Harm
Humane Society Legislative Fund
Humane Society of the United States
Humane Society Veterinary Medical
Association
Illinois PIRG
Johns Hopkins Center for a Livable Future
Maryland PIRG
MASSPIRG
Michigan Antibiotic Resistance Reduction
Coalition
National Center for Health Research
National Latino Farmers & Ranchers Trade
Association
Natural Resources Defense Council (NRDC)
NOFA-VT
Northeast Organic Dairy Producers Alliance

²² <https://www.gao.gov/assets/690/683130.pdf>

²³ 21 CFR 558.6 (c) (3)

Northeast Organic Farming Association of
New York (NOFA-NY)
OSPIRG
Prevention Institute
Roots of Change
San Francisco Marin Medical Society
Science and Environmental Health Network
Society of Infectious Diseases Pharmacists
The Food Voice
Third World Network
U.S. PIRG
WashPIRG
Waterkeeper Alliance
WISPIRG
Women's Voices for the Earth