KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.org

September 14, 2020

Dr. Stephen Hahn
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Hahn,

Public health and the need for coordinated government action are foremost in everyone's mind now. While dealing with the new viral pandemic, it is important to keep moving forward with actions to address other serious public health threats such as antibiotic resistance. The current difficulties in ensuring that all who need medical care receive it underscore how important it is to have antibiotics that are effective against bacterial infections. For that reason, we the undersigned members and colleague groups of the Keep Antibiotics Working coalition write to ask the Food and Drug Administration (FDA) to move forward with efforts to protect the efficacy of existing antibiotics by strengthening and implementing the Center for Veterinary Medicine's Five-Year Action Plan for Supporting Antimicrobial Stewardship in Veterinary Settings. [1]

The need to protect currently available antibiotics is even more important given the ongoing failures in the antibiotic pipeline. As evidenced by the recent bankruptcy of both Melinta Therapeutics and Achaogen, the antibiotic industry is faltering. While the development of new antibiotics and antibiotic alternatives is an important facet of the fight against antimicrobial

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

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resistance, there are long-term barriers to improving the antibiotics pipeline so there must be a much more deliberate focus on preserving the antibiotics we already have.

Each year, antibiotic-resistant bacteria kill at least 35,000 Americans and cause almost 3 million illnesses. The toll on the economy from these deaths plus the exorbitant expense of treating these types of infections could be up to $65 billion annually. [2]

The key factor driving the epidemic of antibiotic resistance is the overuse and misuse of antibiotics in both human medicine and agriculture. About two-thirds of the total of medically important antibiotics sold in the U.S. go to livestock and poultry, mostly for routine use to keep the animals from getting sick in overcrowded and often unsanitary industrial-scale facilities when better animal husbandry practices could avoid such use.[3] This overuse encourages the development and spread of antibiotic-resistant bacteria, which in turn increases the likelihood that these lifesaving drugs will be ineffective when needed for sick people and animals. FDA, with the clear mission of protecting and promoting public health including assuring the safety and efficacy of drugs in human and veterinary medicine, must continue to play an essential role in addressing this overuse by making sure that drugs are used only when needed and by monitoring use and setting goals for the reduction of overuse.

Setting Duration Limits:

In its five-year plan (section 1.1.2), FDA accepts the need for limited durations for the use of medically important antibiotics as an important step in improving antimicrobial stewardship. However, FDA has not adequately outlined definitive next steps for requiring duration limits and has so far only suggested that drug sponsors should set durations based on efficacy, not on the need to better protect human health.[4]

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[2] https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

[3] https://www.worldanimalprotection.us/sites/default/files/media/us_files/us_pork_superbugs_report.pdf ; http://www.saveourantibiotics.org/media/1777/asoa-report-real-farming-solutions-to-antibiotic-misues-what-farmers-and-supermarkets-must-do.pdf

[4] As indicated by FDA funding of studies on efficacy to support label changes not resistance and FDA not mentioning the need for extent of use limitations consistent with existing guidance. See https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-2020-funding-opportunity-help-define-durations-use-certain-medically-important

We ask that FDA move forward promptly with requiring drug sponsors to limit the duration of the use of medically important antibiotics and in doing so provide clear guidance to sponsors on how to prioritize human health over drug efficacy. This can be done by ensuring that duration limits are set in accordance with the risk assessment principles outlined in FDA's Guidance for Industry #152. Guidance for Industry #152 outlines a risk assessment approach in which extent of use is a key consideration, and proposes a process for ranking extent of use that considers both the method of administration (i.e. individual animals, select groups, or entire flocks) and duration of use (short, medium and long).[5] In the example provided by the guidance, drugs with long duration of use (i.e.> 21 days) have a "high" extent of use when administered to groups or flocks of animals. The guidance identifies avoidance of such high extent of use as a reasonable strategy for managing the risk of drugs that are "high" or "medium" in terms of risks of contributing to antimicrobial resistance (e.g. medically important antimicrobials that have a medium or high probability of creating resistant bacteria in widely-consumed food animals). While this approach does not exclude other risk management strategies, the agency notes that other risk management approaches taken by the sponsor should be supported by adequate evidence to ensure safety risks can be effectively managed under those conditions.

Strengthen data collection on both antimicrobial use and resistance:

The five-year plan includes goals related to data collection (Goal #3). Despite FDA's recognition for almost two decades of the need to collect data on how antibiotics are used on farms, there has been very limited progress on filling this data gap.[6] 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.[7] USDA, under the National Animal Health Monitoring System (NAHMS), collects data through periodic voluntary surveys of livestock producers. But neither of these provide a clear picture of the amount of antibiotics used nor the reason for their use.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-152-evaluating-safety-antimicrobial-new-animal-drugs-regard-their-microbiological-effects
[6] https://www.cdc.gov/drugresistance/pdf/aractionplan-archived.pdf
[7] https://www.fda.gov/industry/animal-drug-user-fee-act-adufa/adufa-reports

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; however, they are infrequent, rely on voluntary participation, and do not collect data on the amount of antibiotics administered or detailed data on reason for use.[8] 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 establish a program to sample feed distribution records kept as required by the Veterinary Feed Directive regulations [9] as another source of data that would include information on both the amount of antibiotics administered in feed and reason for use.

Update FDA's list of medically important antimicrobials:

We support the goal (1.3.1) in the five-year action plan to update the FDA's list of medically important antimicrobials. 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. For example, Bacitracin, which is currently not considered to be medically important by FDA, has been shown to select for resistance to the last resort drug colistin.[10] The drug tiamulin, considered medically important by the World Health Organization, has not been added to FDA's list, though use in pigs has been shown to select for resistance to medically important drugs in other classes including linezolid.[11] [12]

We encourage 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.

[8] https://www.gao.gov/assets/690/683130.pdf
[9] 21 CFR 558.6 (c) (3)
[10] https://msphere.asm.org/content/3/5/e00411-18
[11] https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1
[12] https://academic.oup.com/jac/article/69/8/2022/873861

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 on a calendar basis with the third generation cephalosporin ceftiofur as a "control" for respiratory disease.[13] In the absence of guidance, these producers are using a drug approved for control in a manner consistent with disease prevention -- i.e., routinely administered multiple times on a calendar basis independent of the presence of disease in the animals -- not control. FDA explicitly prohibits the use of ceftiofur for disease prevention as part of extra-label restrictions published in 2012.[14] 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 marketing materials, the drug maker Elanco recommends "proactively" treating subclinical illness for a drug approved for disease treatment.[15] In the absence of guidance, the drug maker effectively blurs the distinction between treatment and prevention. FDA must provide guidance on what is meant by the use of the terms "treatment," "control," and "prevention" on antibiotic 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, increasing the risk of adverse effects such as antibiotic resistance.[16]

[13] See Fig. 1 in https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0208430
[14] https://www.govinfo.gov/content/pkg/FR-2012-01-06/html/2012-35.htm
[15] https://www.nytimes.com/2019/06/07/health/drug-companies-antibiotics-resistance.html
[16] https://academic.oup.com/tas/article/3/1/185/5235607

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 accomplished.

Formed in 2001, Keep Antibiotics Working is a coalition of 18 advocacy organizations working together to ensure that untreatable superbugs resulting from the overuse of antibiotics on industrial farms do not reverse the medical advances of the past century. We appreciate your consideration.

Sincerely,

Antibiotic Resistance Action Center (ARAC) at the Milken Institute School of Public Health, George Washington University
Association for Professionals in Infection Control and Epidemiology
Center for Biological Diversity
Center for Food Safety
Consumer Federation of America
Consumer Reports
Food & Water Action
Food Animal Concerns Trust
Humane Society Legislative Fund
Humane Society of the United States
Humane Society Veterinary Medical Association
Johns Hopkins Center for a Livable Future
Natural Resources Defense Council
Socially Responsible Agricultural Project
Society of Infectious Diseases Pharmacists
U.S. PIRG