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

March 19, 2024

Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: The U.S. Food and Drug Administration's regulation of animal drugs

Dear Commissioner Califf,

We the undersigned Keep Antibiotics Working and colleague organizations write to ask for your leadership on confronting the worsening antibiotic resistance crisis, and the antibiotic overuse that is among the chief reasons for its spread. Working antibiotics have been a cornerstone of the modern medical system. Ongoing overuse puts the efficacy of these precious medicines at risk. Already, at least 2.8 million drug-resistant infections occur in the United States each year. A recent Lancet study estimated nearly 1.3 million deaths worldwide in 2019 were directly caused by antibiotic-resistant bacteria, among nearly 5 million deaths "associated with" bacterial drug resistance. More and more patients are suffering infections treatable with only a single antibiotic of last resort or sometimes not treatable at all. Infections are the second leading cause of death in cancer patients and antimicrobial resistance can make these infections difficult or impossible to treat.

It is more critical than ever for the U.S. Food and Drug Administration (FDA) to confront the slow-moving resistance pandemic, often spread via animals and exacerbated by livestock husbandry practices. Among all medically important antibiotics sold in the U.S., about two-thirds are antibiotics sold for the production of food-producing animals and the amount sold for use has risen since the FDA last took a significant step to control overuse in 2017. Two recent reports highlight how the amount of antibiotic used is linked to resistance. Using federal data from the NARMS program, researchers at Johns Hopkins show that significantly less contamination with multidrug-resistant bacteria is found on meat from food animals raised under claims prohibiting antibiotic use. Similarly, European public health agencies have shown that country-level reductions in antibiotic use in food animal production is associated with lower levels of drug resistance among bacteria causing human disease.

FDA has long recognized the integral connection between antibiotic use in animal agriculture and antibiotic resistance. Nevertheless, the agency has been ineffective and exceedingly slow to act to address the overuse described above. In fact, two recent FDA proposed guidance documents show the agency is moving backward concerning this growing public health threat. In recent revisions to the 2003 Guidance For Industry #152 (GFI#152) and in draft Guidance for Industry #273 (draft GFI#273) the FDA is undermining the safety standards applied to new animal drugs by allowing animal health concerns to be the determining factor in human safety decisions about drugs used in food-producing animals. This is most clearly illustrated in a proposed change to GFI#152 but is also apparent in draft GFI#273.

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), drugs used in food-producing animals must be shown to be safe with respect to human health including safe with respect to antibiotic resistance. For a proposed use of a drug to be considered safe, there must be "a reasonable certainty of no harm". Since 2003, GFI#152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern", has described the FDA's process for determining the safety of a proposed use of an antibacterial new animal drug with respect to antimicrobial resistance. The safety assessment results in an estimation of the risk to human health from the proposed use with high, medium, and low risk as potential outcomes. On its face, a safety assessment finding of high or medium risk of negative human health impact certainly would appear inconsistent with the FD&C Act safety standard of "a reasonable certainty of no harm". Instead of denying approval for proposed uses that that have been found to have high- or medium-risk; however, the existing GFI#152 allows these drugs to be approved under five **specific use restrictions.** GFI#152 (page 24) states that "FDA believes that antimicrobial drugs ranked as **high** risk may be approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions".

One specific use restriction in the original GFI#152 is a so-called duration limit, e.g. a limit on how long a drug can be used. Under the original guidance, high- or medium-risk drugs should be restricted to low extent of use (Table 8, page 25) defined as no more than 21 days in groups of animals (Table 7, page 23). In the currently proposed draft, however, the following language has been added to the section of the guidance which defines what is considered high extent of use (Table 7, page 20):

> * *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.*

In other words, the draft GFI#152 would replace the 21-day limit that was explicitly intended to protect human health with a duration based on animal health. This substitution is completely unacceptable for the FDA as a public health agency, and flies against the Congressional intent behind the FD&C Act to provide a reasonable certainty of no harm when it comes to animal drugs. It is inappropriate for animal health needs, such as proposed in the quoted text above, to be included in a human safety review of new animal drugs. FDA regulations do not allow balancing the human safety of veterinary drugs against animal health benefits.

Of the five specific use restrictions contained in the original GFI#152 – restrictions designed to make the animal use of high-risk drugs safer – two others have already been eliminated. One of the five was eliminated almost immediately when the FDA asserted during Veterinary Medicine Advisory Council Meetings in 2004 and 2006 that it has no authority during animal drug approval to require the restrictions on extra-label uses of these drugs that were recommended within GFI#152. As a result, the FDA has never applied this particular restriction based on a finding of high-risk during an assessment under GFI#152. Another of the specific use restrictions contained in GFI#152, review by an advisory committee, is no longer an option because the Veterinary Advisory Committee was disbanded in 2013.

Draft GFI#273 "Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals" moves the FDA further into the territory of weighing the benefits to animal health in making decisions related to drug safety. Draft GFI#273 has the human safety goal "to mitigate

the development of antimicrobial resistance" (Page1) but requires all decisions about durations – the focus of the guidance – to be based solely upon animal health benefits i.e. a duration that covers any situation that "might sometimes be encountered in the United States" (Page 16). In draft GFI#273, data related to human safety (i.e. data on antibiotic resistance) is wholly excluded from decision-making around durations even though the stated goal is safety with respect to antibiotic resistance.

The FDA appears to recognize the inconsistency between the recommended durations in the original GFI#152 and the unrestricted durations in GFI#273 but resolves them not in a way to protect human health but instead removes the inconsistency by removing the public health protection from GFI#152 by adding the italicized language above.

These are just the latest examples of the FDA not using its existing authorities to address the antibiotic resistance crisis. In addition, the FDA has failed to use its existing authority to collect information on antibiotic use from feed mills, and the agency also has yet to create any metrics to measure the progress of its efforts to combat antibiotic-resistant bacteria including targets to reduce antibiotic overuse and improve antibiotic stewardship in animal agriculture.

We therefore call on the FDA to:

1) Maintain the existing maximum duration of no more than 21 days in Guidance #152 as a needed public health protection by removing the italicized language above;
2) Reestablish the Veterinary Medicine Advisory Committee and require review of new drug approvals when appropriate;
3) Modify GFI#273 to be consistent with the original GFI#152;
4) Use the agency's existing authority to begin collecting medicated feed distribution data from feed mills as a source of data on antibiotic use; and
5) Set goals for the reduction of antibiotic use in food-producing animals.

We would welcome the opportunity to meet with you to discuss the growing threat of antibiotic resistance and its connection to agriculture.

Food Animal Concerns Trust
Antibiotic Resistance Action Center, the George Washington University
Center for Biological Diversity
Center for Food Safety
Earthjustice
Environmental Working Group
Friends of the Earth
PIRG