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

Steven Solomon, DVM
Director, Center for Veterinary Medicine
Food and Drug Administration
HFV-1
7500 Standish Place
Rockville, MD 20855

May 4, 2020

RE: Follow-up meeting with CVM

Dear Dr. Solomon,

Thank you for meeting with the Keep Antibiotics Working Group in mid-February. Needless to say, much has happened in the intervening months. We hope you and the staff at the Center for Veterinary Medicine are doing well and are not being overwhelmed by the COVID-19 response. We are writing to reiterate some of our points from the meeting and to request another meeting between the coalition and the Center. Given the circumstances, we believe a teleconference or videoconference makes the most sense.

From our February meeting we would like to emphasize the following:

Salmonella and Quinolone Resistance:

As we noted in the meeting, we are concerned that there has not been a coordinated federal effort to address the rise in *Salmonella* resistant to quinolones even though this has long been recognized as a problem. For KAW, the challenge of quinolone resistant *Salmonella* reflects a more general problem related to a failure of federal authorities to respond in a prompt manner to growing antibiotic resistance threats. It is widely acknowledged by the U.S. government that antibiotic resistance in the food system is a problem; however, this acknowledgement has not led to more aggressive action to tackle specific threats when they arise. Part of the problem is the lack of regulatory authority to investigate outbreaks that result from pathogens originating on farms and large animal feeding operations. For this reason, we support the Expanded Food Safety Investigation Act (S.2958 and H.R. 5415) which gives the FDA authority to collect microbiological samples on farms linked to foodborne outbreaks. Still, sampling and surveillance only goes so far and at some point federal agencies with the mission to protect public health need to act when animal production companies consistently market products that lead to outbreaks. Clear examples are the hatcheries supplying birds for backyard poultry and chicken producers who have knowingly sold products contaminated with multi-drug resistant *Salmonella*. Recently, CDC reported seafood contaminated with *Salmonella* Anatum with decreased susceptibility to cephalosporins and fluoroquinolones and resistance to colistin and noted the need for better

surveillance. Yes, better surveillance is important, but at some point federal agencies need to act.

During the meeting Dr. McDermott provided some important information on quinolone resistant *Salmonella*. He noted that much of the resistance in humans is related to travel and the resistance in animals is likely the result of the introduction of a multidrug resistant organism into the U.S. poultry flock from poultry populations outside the U.S. This is helpful to know, but does not indicate a coordinated plan across federal agencies to address the rise.

Advertising/Marketing:

KAW is concerned about the negative impact of inappropriate marketing of veterinary drugs on antimicrobial stewardship. For example, in marketing materials, the drug maker Elanco inappropriately recommended "proactively" treating subclinical illness in animals with a drug approved for disease treatment. As mentioned in the meeting, this advertisement was submitted to CVM staff at the time of dissemination; however, no action was taken by the agency despite FDA having issued a warning letter for inappropriate advertising for the same product, tiamulin plus chlortetracycline, by the previous license holder. The drug maker pulled the advertising campaign only after a KAW member shared the advertisement with the media and the company received negative publicity. CVM has indicated to us that resource constraints limit the Center's ability to look closely at every advertisement. However, we ask that CVM find a way to put the submitted materials online so that groups such as Keep Antibiotics Working can review materials for inappropriate marketing content. We recognize that making available the 5,000 submissions received annually creates a challenge, but we assume there is already a system in place to digitize and share the information internally. We request that this be adapted to allow public access. Transparency efforts like this should be considered as part of FDA's efforts to modernize the agency's data strategy. As we are able, we will continue to monitor marketing materials with problematic labeling and bring them to your attention in the future, but we are limited by not having access to much of the material targeted to veterinarians and livestock producers.

Transparency around spending on antimicrobial resistance:

We continue to request that FDA increase the transparency around what is spent on antimicrobial resistance related efforts. It is difficult for the public and policy makers to evaluate what FDA is doing to address this public health threat and to make recommendations around how much spending is needed without this information.

Activities related to the Five-Year Plan to Improve Antimicrobial Stewardship in Veterinary Settings:

A. **Durations:** KAW considers requiring limited durations for medically important antibiotics as the most important of the actions included in the plan because it is the one that most directly impacts the overuse of medically important antibiotics in food animal production. We are concerned that FDA does not plan to prioritize public health in determining how durations are to be set and is instead planning to prioritize animal health

by focusing on data needed to show what duration is effective, but not requiring a determination that the identified duration is safe with respect to antimicrobial resistance. We believe that this is inconsistent with the FDA's primary role as a public health agency and creates uncertainty for drug makers attempting to balance these two potentially divergent goals.

We request 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. Our recommendation is that the default duration for medically important antibiotics be 21 days or less, consistent with FDA's own recommended approach to risk management for antimicrobial resistance as described in Guidance for Industry #152. If a sponsor seeks a duration longer than 21 days, FDA should require the sponsor to provide additional data showing that using the product for more than 21 days is both safe and that the longer duration is needed. KAW also asks that FDA add products that have indications with durations longer than 21 days to its list of affected products.

B. **Need for FDA definitions for treatment, control, and prevention:** FDA approves medically important antibiotics for use in animals to treat, control, and prevent bacterial infection, but provides no guidance on what these terms mean. This greatly hinders efforts at antimicrobial stewardship because it puts the responsibility on livestock producers to determine the conditions under which it is legal to use a drug approved for one of these types of use. The confusion between the three types of use clearly occurs with the use of the combination of tiamulin and chlortetracycline in swine. The combination is routinely used for the prevention of enteric diseases in swine as indicated by USDA National Animal Health Monitoring System surveys; however, it is only approved for enteric disease treatment except for one indication for the control of swine dysentery, a relatively rare disease. As KAW has discussed with CVM, there is also evidence from two published journal articles that ceftiofur is routinely used for disease prevention in pigs despite being approved only for control and treatment. This last case is particularly disturbing because FDA specifically prohibits the extralabel use of ceftiofur for disease prevention because of concerns about antimicrobial resistance. We once again request that the FDA define the conditions under which it is appropriate to use drugs labeled for treatment, control, and prevention. The failure to define these terms consistently across products means that labels cannot be interpreted and followed in a consistent manner.

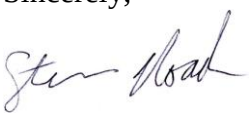
C. **Update list of medically important antibiotics:** KAW hopes that FDA promptly moves forward with updating the list of medically important antibiotics. Since its creation in 2003, the list has never been updated despite new human drug approvals and much new information on antibiotic resistance in the intervening years. We request that FDA commit to a schedule for updating the list by fall 2020.

We appreciate your continued collaboration with Keep Antibiotics Working and we look forward to providing additional input in the future. We find our meetings with CVM beneficial and

necessary for us to understand FDA's activities related to antimicrobial resistance. If possible, we would like to schedule the next meeting between KAW and CVM in May or June via teleconference. We would like to discuss the following topics:

- Expansion of NARMS to seafood and other changes to NARMS,
- FDA's work on alternatives to antimicrobials, and
- Biomass denominator work and the comprehensive report.

Sincerely,



Steven Roach