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

Reference: Docket No. 98D-1146, CVM 200132 – Comments on "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern"

The Draft Guidance for Industry is an important step forward. However, we believe there should be improvements and clarifications, and respectfully submit these comments. In particular, we recommend:

1. Essential human antimicrobials not yet used in animals should be considered separately from other antimicrobials. Specifically, because baseline resistance in animals for these drugs is likely to be zero, the determination of release and exposure assessments is unreliable, and should not influence ranking of the drug.
2. Ranking of human drugs should be re-evaluated, and a four-tier system considered. Drugs in the highest category – those of greatest importance to human medicine – should receive a "high" overall ranking and should automatically trigger an advisory panel review that might recommend any consideration for approval in food animals be terminated.
3. Ranking of antimicrobials should be done in a consistent manner. It is unclear why certain drugs such as penicillin and tobramycin are appropriately ranked of high importance, but tetracycline and gentamicin are of medium importance.
4. We believe the use of cross-resistance among drug classes and ease of transmissibility of resistance as factors to rank the importance of antimicrobial agents is poorly conceived. We caution these factors might inappropriately lower the consequence ranking of an antimicrobial where cross-resistance exists, that is nevertheless of high importance to human medicine. We acknowledge it is appropriate to rank antimicrobials with low cross-resistance and transmissibility as highly important to human medicine, but the converse may not be true.

Thank you for your consideration.

Respectfully submitted,

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Center for Science in the Public Interest

The Center for Science in the Public Interest (CSPI) is pleased to submit these comments to Docket No. 98D-1146, CVM 200132 - Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern. CSPI is a consumer advocacy organization whose twin missions are to conduct innovative research and advocacy programs in health and nutrition, and provide consumers with current, useful information about their health and well-being. We are deeply concerned about the growing public health crisis of antibiotic resistance. There is convincing scientific evidence that agricultural overuse of medically important antibiotics - particularly the routine, nontherapeutic use in livestock and poultry - contributes to human antibiotic resistance. We applaud the Center for Veterinary Medicine (CVM) for their recognition of the role antibiotic use in food animals plays in human antibiotic resistant infections and for their extensive work on this guidance document.

CSPI is one of the founding organizations of the coalition, Keep Antibiotics Working (KAW). Our colleagues from KAW and its member organizations will be submitting separate comments to the docket, of which we are supportive. CSPI's comments focus specifically on the document's ranking of antimicrobials in terms of their importance for human medicine. In addition, we address the use of that ranking in the document's overall risk assessment.

- CSPI's comments were prepared principally by Dr. Tamar Barlam. Dr. Barlam is the director of the Antibiotic Resistance Project at CSPI. She is a board certified infectious disease physician with over sixteen years experience at academic tertiary care centers. Prior to joining CSPI, she was an Assistant Professor of Medicine at Harvard Medical School and infectious disease attending physician at the Beth Israel Deaconess Medical Center. The Draft Guidance does not adequately address antibiotics of greatest human importance that have yet to be used in veterinary medicine. The document will fail to preserve the utility of these precious drugs unless there is further clarification provided explicitly in writing.

  To illustrate this point, we use the following scenario. If fluoroquinolones had not yet been approved for poultry treatments, and were being ranked by the Draft Guidance, the drugs would receive a "high" ranking for the consequence assessment. However, because the drug had yet to be used in animals, the exposure assessment would be zero (B2a-c). Although the CVM would perhaps not allow inclusion of an exposure assessment under these circumstances, this is not specifically noted in the Draft Guidance document. If the exposure assessment is omitted but the release assessment is then substituted, a legitimate assumption might be that due to the chromosomal nature of fluoroquinolone resistance and the lack of evidence that there is significant plasmid-mediated resistance, the risk of resistance transfer could be ranked "low." Thus, even under this alternate circumstance the risk assessment would include one factor that

indicates “low” risk. When combined with the “high” risk consequence assessment, the overall ranking would still likely be “medium.” Based on this, fluoroquinolone use might have been approved with similar parameters as the actual approval in 1995 and 1996. Specifically, the Guidance allows “medium” extent-of-use for drugs with an overall “medium” risk ranking (Guidance, page 27) – and such extent-of-use includes administration to “select groups or pens of animals,” which could apparently include the majority of birds in a poultry house as long as they were “segregated” (Guidance, page 25). Yet, as FDA is aware, fluoroquinlone-resistant *Campylobacter* infections has risen significantly in people in the last several years, prompting the CVM to propose the withdrawal of fluoroquinolones from poultry treatment, resulting in the contested drug withdrawal now taking place.

We offer the following possible solutions for consideration. First, it would be relatively easy to identify those drugs of the very highest importance to human health. These would include the fluoroquinolones, third and fourth generation cephalosporins, carbapenems, and monobactams, to name a few. The CVM could create a fourth category for these truly essential antibiotics that set them above the others in the high-risk group of the consequence assessment table (e.g. in Appendix A). They could, and should, be considered separately from other drugs. These drugs should automatically receive a high overall ranking removing the concerns about the use of the release and exposure assessments. In addition, these drugs should immediately trigger an advisory panel review. In some instances,

certain drugs might be deemed inappropriate for any use in food animals and not go through any further review process.

- A four-tier drug ranking might also help address our next concern. The ranking of the antibiotics does not seem to have been done in a consistent manner. Thus, penicillin received a "high" ranking, but the tetracyclines were rated "medium." Amikacin was ranked as "high" consequence, but gentamicin was only ranked of "medium" consequence.

  We disagree with the "medium" ranking of tetracycline and gentamicin. Both have important roles in human medicine. Doxycycline is a frequent treatment for patients with atypical pneumonia and other complicated infections. It is commonly used to treat tickborne illnesses such as Lyme Disease, ehrlichiosis, and is the drug of choice for unusual infections such as Rocky Mountain spotted fever. It is also commonly used for sinus and skin infections, and in adolescents for acne. It is also worth noting that doxycycline was one of the drugs-of-choice during the recent anthrax outbreak. Minocycline is still an important option for several infections and treatments including meningococcal prophylaxis.

  Although the tetracyclines are not used to treat foodborne infections, they have another connection to zoonotic illness that should be taken into account. As noted, it is fairly common for a person to be treated with a tetracycline antibiotic for a variety of reasons. Some treatments, for example for acne, are prolonged.

When a person takes tetracycline (or any other antibiotic), his or her commensal bacteria – those that normally inhabit the gut without causing disease – are disrupted by the antibiotic. As a result, he or she is more-than-usually vulnerable to infection by disease-causing bacteria carried into the digestive tract on food. If those bacteria are already tetracycline-resistant, as they may well be given the widespread use of tetracycline in agriculture, the individual faces an increased risk of developing a tetracycline-resistant disease – which is particularly worrisome given that several other resistance genes are typically linked to tetracycline resistance. This is more completely summarized in the report sponsored by the Alliance for the Prudent Use of Antibiotics and published recently.[1] For these reasons, the tetracyclines should be classed as being of high importance in human medicine.

With regard to the gentamicin ranking, the Draft Guidance document suggests that gentamicin is less important than tobramycin or amikacin. This is, in fact, not true. Many hospitals still use gentamicin as their workhorse aminoglycoside and are able to keep amikacin or tobramycin in reserve for particularly difficult cases. Not only is this antibiotic used to treat critically ill patients with gram-negative infections, it is the aminoglycoside best studied as a synergistic agent in staphylococcal and enterococcal infections. To rank this drug "medium" is not well founded on its actual importance in clinical practice.

[1] Barza M, Gorbach SL, eds. The need to improve antimicrobial use in agriculture: ecological and human health consequences. Clin Infect Dis 2002;34 (Suppl 3)

- Finally, we would also like to express concern and misgivings about the use of cross-resistance and ease of transmissibility of resistance in Appendix A, factors 7 through 10, to rank antibiotics. If a drug, such as a fluoroquinolone, does not cause much cross-resistance and does not transmit resistance, it is indeed of very high importance in human medicine. However, the converse is not true – that is, we do not concur that antibiotics with easily transmitted resistance are of less importance to human medicine. To use tetracycline again as an example, despite the frequent presence of plasmid-mediated resistance for some bacteria, it is still widely used for a myriad of infections to other pathogens. In addition, the very fact that resistance is often to multiple drugs and is easily transmissible increases its public health risk and the risk of contracting antibiotic-resistant zoonoses. This factor may minimize the importance of certain drugs, and should be readdressed.

The goal of the Guidance document is to maintain effective veterinary treatments while at the same time preserving the utility of medically important antibiotics. The three factors – release, exposure, and consequence assessments – are all appropriate. However, ultimately it is human health that must come first, as the words of the Food Drug and Cosmetic Act make clear. To that end, in general consideration should be given to allotting the medical consequence category more weight than the other two categories when the ultimate decisions are made about drug approvals and indications for use.

This document is important progress and once again, we applaud the Center for Veterinary Medicine and the Food and Drug Administration for their progress on this important topic.