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

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

**RE: Docket No. FDA-1998-D-0038 on the Revised Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern**

**Introduction**

The undersigned members of Keep Antibiotics Working (KAW)[1] and colleague organizations appreciate this opportunity to comment on the Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern. We support the new approach for ranking drugs described in the Draft Guidance because of its broad focus on human health. This improves on the current approach which prioritizes the treatment of gastroenteritis over other infections when determining the importance of a drug.[2] Despite our general support for the proposed approach to ranking, however, we are very concerned with how it is being applied to drugs used in food animal production.

Specifically, the FDA, as part of that approach, is ignoring both information about particular mechanisms that confer resistance across classes of drugs, and also evidence of co-resistance when it would otherwise complicate the application of the ranking criteria. In applying those criteria, we believe the FDA has inappropriately and without any scientific basis separated out

[1] Keep Antibiotics Working, a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups, is dedicated to eliminating the inappropriate use of antibiotics in farm animals, a significant contributor to the rise in antibiotic resistant disease.
[2] FDA's current method for ranking drugs by medical importance is described in Appendix A of Guidance for Industry #152 CVM GFI #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern | FDA

certain drugs from within an individual drug class with the result of arbitrarily assigning the selected drug(s) a lower ranking of medical importance. Third, the FDA has not ranked bacitracin as medically important despite its clear fit within the proposed criteria for medically important drugs. Finally, the FDA has not provided sufficient information on its plans for updating the guidance when new information becomes available such as when there have been newly approved human uses of drugs within a particular class that could change the rankings of drugs within that class as to their medical importance. Our more detailed comments, organized by topic, follow:

**Cross- and Co-resistance**

We ask the FDA to clarify within the Guidance how any evidence of antibiotic resistance mechanisms that confer cross- and co-resistance within and/or across antibiotics classes may impact the application of the specified criteria to the antibiotics included in those drug classes.

The Draft Guidance ranks drugs based on the assumption "that the human health consequences associated with resistance to drugs of greater importance are more significant than the consequences associated with resistance to drugs of lesser importance" and the Draft Guidance uses this to help identify the risk from the "emergence or selection of resistant bacteria as a consequence of the proposed use of the drug in animals."[3] Cross- and co-resistance complicate the risk determination because the employment of antibiotics of lesser human importance in food-producing animals can potentially lead to the emergence and selection of bacteria resistant to antibiotics of greater importance. If risk management steps have been based on the drug of lesser importance, they likely will not be sufficient to manage the risk and thus ensure human safety. While cross- and co-resistance are mentioned in the release assessment of the Draft Guidance, considering them only at this stage will likely lead to inadequate risk management measures unless the release assessment also identifies additional hazards (i.e. resistance to drugs of greater importance than the drug being evaluated). Some of the abundant evidence that drugs

[3] Center for Veterinary Medicine. "Draft Guidance for Industry #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." U.S. Food and Drug Administration, FDA, 6 Mar. 2023, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-152-evaluating-safety-antimicrobial-new-animal-drugs-regard-their-microbiological-effects.

of lesser importance can select for resistance to drugs of higher importance through the mechanisms of cross- and co-resistance are as follows:

**Use of a *highly-important* animal phenicol antibiotic selects for resistance to the *critically-important* oxazolidinone antibiotics through cross-resistance between classes.**

Antimicrobial resistance does not always occur one drug or even one class at a time because of cross-resistance. Cross-resistance is the "ability of a microorganism to multiply or persist in the presence of other members of a particular class of antimicrobial agents or across different classes due to a shared mechanism of resistance."[4]

For example, the *cfr* gene is disseminated on plasmids and confers resistance to multiple classes of antibiotics including oxazolidinones, phenicols, lincosamides, and pleuromutilins across multiple bacterial species.[5] Moreover, the *cfr* gene is detected in numerous gram-positive and gram-negative bacteria from food-producing animals including species that are clinically relevant to both humans and animals: *Staphylococcus spp.*,[6] *Enterococcus spp.*,[7] *Streptococcus spp.*,[8] *Escherichia coli*,[9] and *Campylobacter spp.*[10]

[4] Joint FAO/WHO Codex Alimentarius Commission. "Codex Alimentarius :Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance," Rome :World Health Organization : Food and Agriculture Organization of the United Nations, 2021.
[5] Long, Katherine S., et al. "The Cfr RRNA Methyltransferase Confers Resistance to Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, and Streptogramin A Antibiotics." Antimicrobial Agents and Chemotherapy, vol. 50, no. 7, July 2006, pp. 2500–05. journals.asm.org (Atypon), https://doi.org/10.1128/AAC.00131-06.
[6] Abdullahi, Idris Nasir, et al. "Comparative Review of the Nasal Carriage and Genetic Characteristics of Staphylococcus Aureus in Healthy Livestock: Insight into Zoonotic and Anthroponotic Clones." Infection, Genetics and Evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases, vol. 109, Feb. 2023, p. 105408. PubMed, https://doi.org/10.1016/j.meegid.2023.105408.
[7] Torres, Carmen, et al. "Antimicrobial Resistance in Enterococcus Spp. of Animal Origin." Antimicrobial Resistance in Bacteria from Livestock and Companion Animals, John Wiley & Sons, Ltd, 2018, pp. 185–227. Wiley Online Library, https://doi.org/10.1128/9781555819804.ch9.
[8] Huang, Jinhu, et al. "Identification and Pathogenicity of an XDR Streptococcus Suis Isolate That Harbours the Phenicol-Oxazolidinone Resistance Genes OptrA and Cfr, and the Bacitracin Resistance Locus BcrABDR." International Journal of Antimicrobial Agents, vol. 54, no. 1, July 2019, pp. 43–48. ScienceDirect, https://doi.org/10.1016/j.ijantimicag.2019.04.003.
[9] Huang, Jinhu, et al. "Identification and Pathogenicity of an XDR Streptococcus Suis Isolate That Harbours the Phenicol-Oxazolidinone Resistance Genes OptrA and Cfr, and the Bacitracin Resistance Locus BcrABDR." International Journal of Antimicrobial Agents, vol. 54, no. 1, July 2019, pp. 43–48. ScienceDirect, https://doi.org/10.1016/j.ijantimicag.2019.04.003.
[10] Tang, Yizhi, et al. "Genetic Environments and Related Transposable Elements of Novel Cfr(C) Variants in Campylobacter Coli Isolates of Swine Origin." Veterinary Microbiology, vol. 247, Aug. 2020, p. 108792. ScienceDirect, https://doi.org/10.1016/j.vetmic.2020.108792.

In addition to *cfr* genes, there are numerous other genes that confer resistance to both oxazolidinones and phenicols. One example is optrA which has been detected in U.S. cattle and swine including on a plasmid where optrA co-exists with the *cfr* gene and other resistance genes.[11] The USDA as part of NARMS also detected the *optrA* gene in oxazolidinone- and phenicol-resistant enterococci from market swine samples in 2020 and 2022. Since oxazolidinones are not used in U.S. food-producing animals, it is highly likely that the use of the phenicol florfenicol in cattle and swine is creating the selection pressure resulting in detectable linezolid resistance in U.S. food-producing animals.

Under the criteria proposed in the Draft Guidance, oxazolidinones are ranked as critically-important while other drugs for which the *cfr* gene confers resistance including florfenicol are ranked lower, as highly-important. Yet, when this gene is present among zoonotic bacteria, the use of any of these highly-important drugs will also select for resistance to the critically-important oxazolidinones. The FDA should be explicit about how the presence of *cfr* genes or other genes that create cross-class resistance are accounted for when using the drug rankings.

**Use of the *highly-important* tetracycline class antibiotics selects for resistance to the *critically-important* fluoroquinolones and cephalosporin antibiotics.**

In addition to resistance mechanisms that confer resistance across classes there is also co-resistance where multiple resistance genes are present on a single transferable resistance element such as a plasmid, making the management of antibiotic resistance more difficult.[12,13] Co-resistance has been shown to have a significant impact on human health as illustrated by the global spread of MDR *Salmonella Infantis*. The spread of this *Salmonella* clone resistant to the critically-important cephalosporins and fluoroquinolones was likely promoted by use of tetracyclines, since the *tet*(A) gene conferring resistance to tetracyclines was on the plasmid

[11] Tyson, Gregory H., et al. "Novel Linezolid Resistance Plasmids in Enterococcus from Food Animals in the USA." Journal of Antimicrobial Chemotherapy, vol. 73, no. 12, Dec. 2018, pp. 3254–58. Silverchair, https://doi.org/10.1093/jac/dky369.
[12] Kanwar, Neena, et al. "Impact of Treatment Strategies on Cephalosporin and Tetracycline Resistance Gene Quantities in the Bovine Fecal Metagenome." Scientific Reports, vol. 4, May 2014, p. 5100. NASA ADS, https://doi.org/10.1038/srep05100.
[13] Cantón, Rafael, and Patricia Ruiz-Garbajosa. "Co-Resistance: An Opportunity for the Bacteria and Resistance Genes." Current Opinion in Pharmacology, vol. 11, no. 5, Oct. 2011, pp. 477–85. ScienceDirect, https://doi.org/10.1016/j.coph.2011.07.007.

containing the resistance genes in the Infantis clone.[14] The use of chlortetracycline in cattle has also been shown to lead to selection for cephalosporin resistance among bacteria isolated from cattle.[15]

**Use of the *not medically important* polypeptide bacitracin and selection for resistance to *critically-important* polymyxin and glycopeptide antibiotics.**

Until 2011, the FDA included polymyxin B and bacitracin in the same polypeptide antimicrobial class when reporting antibiotic sales for use in food animals. Then and now this was the appropriate response because bacitracin, polymyxin B, and colistin are structurally related, creating the risk that use of one of these antibiotics can produce cross-resistance to the others.[16] New evidence shows this to be the case. In a recently published study, researchers specifically found the *mcr* (mobilized colistin resistance) gene confers cross-resistance not only to the polymyxin drug class but also to the polypeptide antibiotic bacitracin, a widely used antibiotic in animal production.[17] As evidenced by the paper, animal use of bacitracin may increase selection pressure for bacteria carrying the *mcr* gene, thereby increasing the animal reservoir of resistance not only to polypeptides but also to polymyxins. As the authors of the study reiterated, when demonstrating this link between polymyxins and polypeptides, "Imprudent and extensive usage of bacitracin in food animals may serve as a non-colistin usage risk factor for the transmissible colistin resistance." Further research continues to show there is cross-resistance between bacitracin and polymyxin B.[18] Researchers in Brazil have detected *mcr* genes in poultry flocks

[14] Tyson, Gregory H., et al. "A Multidrug-Resistant Salmonella Infantis Clone Is Spreading and Recombining in the United States." Microbial Drug Resistance, vol. 27, no. 6, June 2021, pp. 792–99. DOI.org (Crossref), https://doi.org/10.1089/mdr.2020.0389.
[15] Kanwar, Neena, et al. "Effects of Ceftiofur and Chlortetracycline Treatment Strategies on Antimicrobial Susceptibility and on Tet(A), Tet(B), and Bla CMY-2 Resistance Genes among E. Coli Isolated from the Feces of Feedlot Cattle." PLoS ONE, vol. 8, no. 11, Nov. 2013, p. e80575. PubMed Central, https://doi.org/10.1371/journal.pone.0080575.
[16] Marshall, Bonnie M., and Stuart B. Levy. "Food Animals and Antimicrobials: Impacts on Human Health." Clinical Microbiology Reviews, vol. 24, no. 4, Oct. 2011, pp. 718–33. journals.asm.org (Atypon), https://doi.org/10.1128/CMR.00002-11.
[17] Xu, Fuzhou, et al. "MCR-1 Confers Cross-Resistance to Bacitracin, a Widely Used In-Feed Antibiotic." MSphere, vol. 3, no. 5, Sept. 2018, pp. e00411-18. journals.asm.org, https://doi.org/10.1128/mSphere.00411-18.
[18] Gallardo, Alejandro, et al. "Involvement of Hpap2 and DgkA Genes in Colistin Resistance Mediated by Mcr Determinants." Antibiotics, vol. 9, no. 9, 9, Sept. 2020, p. 531. www.mdpi.com, https://doi.org/10.3390/antibiotics9090531.

where polymyxins were not used but where bacitracin was used providing further evidence that use of bacitracin can select for resistance to polymyxins.[19]

There is also evidence that bacitracin use in food-producing animals through co-selection can select for resistance to the critically-important glycopeptide antibiotics. When investigating the effects of bacitracin use in broiler chickens as a growth promoter, researchers found bacitracin and vancomycin resistance were often correlated.[20] They state, "It was traditionally argued that the AGPs commonly used as feed additives in food animal production (i.e., bacitracin, virginiamycin, tylosin, and avoparcin) are not a public health concern since they are generally not administered in humans. However, indirect evidence suggests that the use of AGPs can facilitate resistance to clinically relevant antibiotics through co-selection and cross-resistance." Other researchers found that bacitracin use through co-selection was responsible for the maintenance of a clinically relevant glycopeptide-resistant lineage of *Enterococcus faecalis*.[21] Farm use of bacitracin also has been linked to selection of resistance to other medically important drugs, via the spread of the bacitracin resistance locus, *bcrABDR,* on plasmids. The presence of plasmids containing the *bcrABDR* locus has been associated with resistance to antimicrobials other than bacitracin, especially erythromycin, streptomycin, kanamycin, florfenicol and tetracycline.[22]

**Growing evidence that use of ionophores can select for resistance to medically important antibiotics.**

Under the FDA's current classification, ionophores are classified as "not medically important" antimicrobials. Increasingly, this classification is not supported by the science. There's a body of existing and ever-growing evidence that ionophore use in food-producing animals can result in

[19] Lentz, Silvia AM, et al. "Letter to the Editor: Escherichia Coli Harbouring Mcr-1 Gene Isolated from Poultry Not Exposed to Polymyxins in Brazil." Eurosurveillance, vol. 21, no. 26, June 2016, p. 30267. www.eurosurveillance.org, https://doi.org/10.2807/1560-7917.ES.2016.21.26.30267.
[20] Gupta, Chhedi Lal, et al. "Longitudinal Study on the Effects of Growth-Promoting and Therapeutic Antibiotics on the Dynamics of Chicken Cloacal and Litter Microbiomes and Resistomes." Microbiome, vol. 9, no. 1, Aug. 2021, p. 178. Springer Link, https://doi.org/10.1186/s40168-021-01136-4.
[21] Rushton-Green, Rowena, et al. "Agricultural Origins of a Highly Persistent Lineage of Vancomycin-Resistant Enterococcus Faecalis in New Zealand." Applied and Environmental Microbiology, vol. 85, no. 13, June 2019, pp. e00137-19. journals.asm.org (Atypon), https://doi.org/10.1128/AEM.00137-19.
[22] Chen, Mu-Ya, et al. "Multilevel Selection of BcrABDR-Mediated Bacitracin Resistance in Enterococcus Faecalis from Chicken Farms." Scientific Reports, vol. 6, no. 1, 1, Oct. 2016, p. 34895. www.nature.com, https://doi.org/10.1038/srep34895.

resistance to medically important antimicrobials. The Norwegian poultry industry stopped using the ionophore narasin because evidence showed that narasin use led to resistance to the critically-important glycopeptides in *Enterococcus*. After narasin's use was stopped, glycopeptide-resistant *Enterococcus* were no longer detected in Norwegian poultry;[23] glycopeptides are considered medically important, including the first generation glycopeptide, vancomycin. Subsequently, researchers have uncovered additional evidence that "narasin and certain other polyether ionophores can contribute to the persistence of VRE (vancomycin-resistant Enterococci) in poultry populations."[24] New research from the Netherlands shows that resistance to ionophores—particularly salinomycin and narasin—in *Enterococcus faecalis* and *E. faecium* is caused by the narAB operon, invariably found on a plasmid also containing resistance to other medically-important antibiotics (MIAs) such as tetracycline and erythromycin.[25] The study further noted, "the results show plasmid co-localization of narAB with multiple other genetic resistance determinants, in particular with genes conferring TET [highly-important tetracycline] and ERY [critically-important macrolide] resistance. This implies that selective pressure caused by application of ionophores will promote the persistence of TET and ERY resistance in the enterococcal population."

**FDA revisions to Guidance 152 must reflect science, and be clear how increased human health risks will be considered, and managed and mitigated appropriately, given the occurrence of co-resistance, and cross-class selection for resistance.**

Science has established that co-resistance and cross-class selection for resistance occur and impact human health. In the Draft Guidance, the FDA states that management and mitigation measures (such as certain antimicrobial use limitations) should be appropriately applied to those situations where potential human health risks are greatest. Because the current version of Guidance 152 fails to reflect the existence of co-resistance and cross-class selection for

[23] Simm, Roger, et al. "Significant Reduction of Vancomycin Resistant E. Faecium in the Norwegian Broiler Population Coincided with Measures Taken by the Broiler Industry to Reduce Antimicrobial Resistant Bacteria." PLOS ONE, vol. 14, no. 12, Dec. 2019, p. e0226101. PLoS Journals, https://doi.org/10.1371/journal.pone.0226101.
[24] Naemi, Ali-Oddin, et al. "NarAB Is an ABC-Type Transporter That Confers Resistance to the Polyether Ionophores Narasin, Salinomycin, and Maduramicin, but Not Monensin." Frontiers in Microbiology, vol. 11, Feb. 2020, p. 104. PubMed Central, https://doi.org/10.3389/fmicb.2020.00104.
[25] Pikkemaat, M. et al. Ionophore Resistance and Potential Risk of Ionophore Driven Co-Selection of Clinically Relevant Antimicrobial Resistance in Poultry. Wageningen Food Safety Research, 2022. DOI.org (Crossref), https://doi.org/10.18174/565488.

resistance, the FDA's assessment of where human health risks are greatest is flawed and incomplete. The FDA must clarify in the draft Guidance how its updated rankings of the medical importance of antimicrobial drugs and classes, and any risk management decisions based upon those rankings, will incorporate the possibility of and any existing evidence for co-resistance and cross-class resistance.

**Application of Criteria to Drugs or Drug Classes**

While we support the ranking criteria, we have serious concerns with how they have been applied to certain antibiotics.

**Bacitracin should be ranked as medically important.**

Our greatest concern is that the Draft Guidance ranks bacitracin as "not medically important" despite its use in human medicine. Bacitracin is used topically on the skin, in the eyes, and for postoperative prophylaxis, as well as orally for treatment of human *Clostridium difficile* infections. The antibiotic should be considered medically important under proposed criterion number 3 in the Draft Guidance. Criterion 3 covers: "Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available." The Draft Guidance ranks drugs meeting criterion 3 as "medically important". Despite its use in human medicine and fulfillment of criterion 3, the Draft Guidance ranks the antimicrobial bacitracin as non-medically important.

During the February 2021 public meeting, FDA staff, in response to queries regarding bacitracin, stated that "while there may not be a large scale use of bacitracin in animals, we know it is used in antimicrobial and animal feed, as it relates to the current proposal in terms of the ranking of bacitracin in this process, unlike oral antimicrobials, topical-only use such as bacitracin have not been included in the rankings given they act locally, did not meet the criteria considering in the ranking process as outlined in the guidance in the concept paper." [26] However, the Draft Guidance like the concept paper makes no mention of "topical" antibiotics or criteria that impact

[26] "Public Meeting Transcript 1.5.21" Regulations.Gov. Accessed February 19, 2021. https://www.regulations.gov/document/FDA-2020-N-1736-0018.

drugs which "act locally". The FDA must be completely transparent about the methodology used to determine criteria and then apply them consistently. In addition, bacitracin is one of the most commonly used antibiotics in food animal production and the FDA downplaying its use in animal agriculture is troubling.

There is evidence of resistance reducing the effectiveness of both skin[27] and ophthalmological topical antibiotics in people.[28] Given the frequency and severity of skin and soft tissue infections, excluding topicals from consideration in drug rankings is unsound and unwise.[29] There is currently a very deadly outbreak of extensively drug-resistant *Pseudomonas aeruginosa* linked to three deaths and eight cases of vision loss clearly illustrating the potential severity of these types of infections.[30] There have also been documented instances of the transfer of skin infections resistant to topical antibiotics between people and animals.[31]

In addition, while not FDA approved for this purpose, oral bacitracin has been reported as an effective antibiotic treatment for patients infected with vancomycin-resistant enterococci (VRE). After successfully treating a recurring VRE infection, these researchers "suggest that clinicians consider oral bacitracin as a VRE GI suppression strategy in patients with VRE intestinal domination, in other VRE-colonized patients considered at high risk for VRE bacteremia, or in patients with persistent VRE bacteremia potentially from the GI tract."[32]

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[27] Williamson, Deborah A., Glen P. Carter, and Benjamin P. Howden. "Current and Emerging Topical Antibacterials and Antiseptics: Agents, Action, and Resistance Patterns." *Clinical Microbiology Reviews* 30, no. 3 (July 1, 2017): 827–60. https://doi.org/10.1128/CMR.00112-16.

[28] Grzybowski, Andrzej, Piotr Brona, and Stephen Jae Kim. "Microbial Flora and Resistance in Ophthalmology: A Review." *Graefe's Archive for Clinical and Experimental Ophthalmology* 255, no. 5 (2017): 851–62. https://doi.org/10.1007/s00417-017-3608-y.

[29] Kaye, Keith S, Lindsay A Petty, Andrew F Shorr, and Marya D Zilberberg. "Current Epidemiology, Etiology, and Burden of Acute Skin Infections in the United States." *Clinical Infectious Diseases* 68, no. Supplement_3 (April 8, 2019): S193–99. https://doi.org/10.1093/cid/ciz002.

[30] CDC. Outbreak of Extensively Drug-Resistant Pseudomonas Aeruginosa Associated with Artificial Tears | HAI | CDC. 17 Apr. 2023, https://www.cdc.gov/hai/outbreaks/crpa-artificial-tears.html.

[31] Manian, Farrin A. "Asymptomatic Nasal Carriage of Mupirocin-Resistant, Methicillin-Resistant Staphylococcus Aureus (MRSA) in a Pet Dog Associated with MRSA Infection in Household Contacts." Clinical Infectious Diseases, vol. 36, no. 2, Jan. 2003, pp. e26–28. Silverchair, https://doi.org/10.1086/344772.

[32] Tran, Truc T., et al. "Oral Bacitracin: A Consideration for Suppression of Intestinal Vancomycin-Resistant Enterococci (VRE) and for VRE Bacteremia From an Apparent Gastrointestinal Tract Source." Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, vol. 60, no. 11, June 2015, pp. 1726–28. PubMed Central, https://doi.org/10.1093/cid/civ130.

As we describe above, there is abundant evidence that the use of bacitracin can select for resistance to other medically important drugs including critically-important drugs. Further, resistance to bacitracin in the important swine and human pathogen *Streptococcus suis* has been linked to increased virulence, increased fitness, and to resistance to other drugs. This study found that "*S. suis* colonization and virulence requires bacitracin tolerance."[33] A recent report also found that the use of polypeptide antibiotics like bacitracin may lead to the "evolution of resistance to the innate immune system of humans and animals."[34]

The FDA should rank bacitracin as medically important based on its use in human medicine, evidence that its use selects for resistance to medically important including critically-important antibiotics, evidence that its use can promote increased virulence in pathogens, and the potential for its use to select for resistance to innate immunity in humans and animals. Given the clear evidence of risk, allowing the continued indiscriminate use of bacitracin for growth promotion as is currently allowed under the "not medically important" ranking puts animal and human health at an unacceptable risk.

**The Draft Guidance inappropriately divides antimicrobial classes into subclasses with different rankings.**

The FDA should use greater caution when considering ranking subclasses of a drug differently than its overall class. In the majority of cases, subclasses of specific drugs should not be ranked by varying degrees of importance. While this approach may be applicable for certain drug classes such as penicillins, this approach would not be appropriate for other classes of drugs, such as macrolides or the following:

<u>Cephalosporins</u>

All cephalosporins should be treated as critically-important, not just third and fourth generation cephalosporins as proposed in the Draft Guidance. The FDA without providing justification has

[33] Ma, Jiale, et al. "Bacitracin Resistance and Enhanced Virulence of Streptococcus Suis via a Novel Efflux Pump." BMC Veterinary Research, vol. 15, no. 1, Oct. 2019, p. 377. BioMed Central, https://doi.org/10.1186/s12917-019-2115-2.

[34] Jangir, Pramod K., et al. "The Evolution of Colistin Resistance Increases Bacterial Resistance to Host Antimicrobial Peptides and Virulence." ELife, edited by Vaughn S Cooper et al., vol. 12, Apr. 2023, p. e84395. eLife, https://doi.org/10.7554/eLife.84395.

arbitrarily divided the cephalosporins classes going so far as to separate out a single first-generation cephalosporin cefazolin from the other first-generation cephalosporins. Unless the FDA has evidence that there are not shared mechanisms of resistance between cefazolin and the other first-generation cephalosporins then all should be ranked the same. In addition, another first-generation cephalosporin Cephalexin is the recommended antibiotic for the treatment of invasive methicillin-sensitive *Staphylococcus aureus* osteoarticular infections in children.[35] Urinary tract infections are some of the most common infections requiring antibiotic treatment and first-generation cephalosporins have been found to have similar "clinical cure, hospital stay, and reinfection" as other antimicrobials.[36] Because of a narrower spectrum, first-generation cephalosporins are less likely to be "associated with selection of and subsequent colonization and/or infection with *Clostridium difficile* or antibiotic-resistant organisms" as other treatment options.[37]

Sulfonamides

All sulfonamides, not only sulfonamides in combination with the diaminopyrimidines like trimethoprim, should also be considered "critically-important" given they meet criteria one since they are the sole or one of limited therapies for toxoplasmosis treatment in immunocompromised hosts.[38] The Draft Guidance ranks sulfonamides as "important" while ranking the sulfonamide diaminopyrimidines combination as "critically-important".

Tetracyclines

[35] Ramchandar, Nanda, John Arnold, Chris Cannavino, and John S. Bradley. "Frequency of Dosing of Cephalexin for Oral Step-Down Therapy of Pediatric Osteoarticular Infections Caused by Methicillin-Sensitive Staphylococcus Aureus." *The Pediatric Infectious Disease Journal* 39, no. 6 (June 2020): 523–25. https://doi.org/10.1097/INF.0000000000002661.

[36] Díaz-Brochero, Cándida, et al. "First-Generation Cephalosporins for the Treatment of Complicated Upper Urinary Tract Infection in Adults: A Systematic Literature Review." International Journal of Infectious Diseases, vol. 116, Mar. 2022, pp. 403–10. ScienceDirect, https://doi.org/10.1016/j.ijid.2021.12.363.

[37] Athena L. V. Hobbs, Katherine M. Shea, Mitchell J. Daley, R. Gordon Huth, Theresa C. Jaso, Jack Bissett, Vagish Hemmige, Are first-generation cephalosporins obsolete? A retrospective, non-inferiority, cohort study comparing empirical therapy with cefazolin versus ceftriaxone for acute pyelonephritis in hospitalized patients, Journal of Antimicrobial Chemotherapy, Volume 71, Issue 6, June 2016, Pages 1665–1671, https://doi.org/10.1093/jac/dkw035

[38] Zhang, Yanxia, Xiao Lin, and Fangli Lu. "Current Treatment of Ocular Toxoplasmosis in Immunocompetent Patients: A Network Meta-Analysis." *Acta Tropica* 185 (September 1, 2018): 52–62. https://doi.org/10.1016/j.actatropica.2018.04.026.

Tetracyclines are by far the most commonly used medically important antibiotic in U.S. food animals. The Draft Guidance separates this class into the critically-important doxycycline, omadacycline, eravacycline, and tigecycline with the rest of the drugs in the class ranked as highly-important. There is emerging evidence that the use of the highly-important tetracyclines may be compromising the effectiveness of the critically-important tetracyclines by selecting for plasmid-mediated *tet(x)* genes that confer resistance to all of the drugs in the class.[39] Despite not being used in food animals the presence of *tet(x)* genes is higher in food animals than in human clinical settings suggesting that the heavy use of the highly-important drugs in food animals is selecting for resistance to the critically-important drugs as well.[40] Given the shared mechanism of resistance, we recommend ranking all tetracyclines as critically-important and applying risk management steps as appropriate to the increased level of risk.

**Table A2 should indicate that polymyxin b is approved for use in food producing animals.**

The table lists colistin as an example of polymyxins approved for use in food animals, but notes it has never been marketed. It fails to note that polymyxin b is approved and marketed for use in sheep and cattle wrongly suggesting that no polymyxin-class drugs are marketed for use in food animals.

**Frequency of Updates**

The frequency of updates to the list of medically important antimicrobials is drastically insufficient. Until this year, the current list had not been updated since its first publishing in 2003. The list should be updated at least every 3 years, or sooner per the emergence of significant new data. If a new drug class is approved for human use and has relevance to animal health or has current animal approval then the list should be updated within a year. The first pleuromutilin was approved for human use in 2007; however, 13 years later the importance of the class to human medicine has not been determined. This cannot be the norm.

[39] Sun, Jian, et al. "Plasmid-Encoded Tet(X) Genes That Confer High-Level Tigecycline Resistance in Escherichia Coli." Nature Microbiology, vol. 4, no. 9, 9, Sept. 2019, pp. 1457–64. www.nature.com, https://doi.org/10.1038/s41564-019-0496-4.

[40] Pan, Yu, et al. "Preliminary View of the Global Distribution and Spread of the Tet(X) Family of Tigecycline Resistance Genes." Journal of Antimicrobial Chemotherapy, vol. 75, no. 10, Oct. 2020, pp. 2797–803. Silverchair, https://doi.org/10.1093/jac/dkaa284.

In order to ensure that new evidence is not overlooked, the FDA should include information on significant new findings that may impact the ranking of certain antimicrobial drugs in its annual drug sales report. The FDA should also create an open docket where research groups, institutions, and other collaborating organizations can contribute and make suggestions to the list as they monitor novel research and scientific findings in this field. The FDA should publish a clear plan outlining events that will trigger additional review and should integrate AMR risk into NEPA required review of new drugs or novel drug classes.

While discussing timelines, we call on the FDA to move forward swiftly with updating and applying the method for ranking drugs. This should be finished within a year.

**Conclusion**

KAW supports the proposed criteria for ranking drugs according to their importance to human medicine, however these criteria must be applied consistently and correctly. Currently, that is not the case with the FDA incorrectly classifying bacitracin as not medically important, and also inappropriately giving antibiotics belonging to the same drug class different rankings of medical importance, despite the possibility of cross-resistance; in fact, cross-resistance and co-resistance can and must be addressed better within the ranking system more generally. Finally, the final Guidance should incorporate timelines for its implementation. These changes will ensure effective implementation of the criteria and if then applied to risk management decisions may reduce the public health threat from antibiotic resistance related to antibiotic use in food production.

Sincerely,

Antibiotic Resistance Action Center, George Washington University
Center for Biological Diversity
Center for Food Safety
Consumer Reports
Food Animal Concerns Trust
Humane Society Legislative Fund
Humane Society Veterinary Medical Association
Natural Resources Defense Council
The Humane Society of the United States