

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

RE: Docket No. FDA-2020-N-1736 on the Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs

Introduction

The undersigned members of Keep Antibiotics Working (KAW)¹ and colleague organizations appreciate this opportunity to comment on the [FDA's potential approach for ranking antimicrobial drugs according to their importance in human medicine](#). We support the new approach for ranking drugs described in the concept paper because of its broad focus on human health. This is an improvement over the current approach which prioritizes the treatment of gastroenteritis over other infections when determining the importance of a drug.²

An increasing number of resistant human infections are linked to animal sources,³ and sales of antibiotics in the United States for use in swine and cattle have risen by more than 11 percent

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](#)

³ Silbergeld, Ellen, Awa Aidara-Kane, and Jennifer Dailey. "Agriculture and Food Production as Drivers of the Global Emergence and Dissemination of Antimicrobial Resistance." AMR Control: Overcoming Global Antimicrobial Resistance, July 27, 2017. <http://resistancecontrol.info/2017/agriculture-and-food-production-as-drivers-of-the-global-emergence-and-dissemination-of-antimicrobial-resistance/>; Lawal, Opeyemi U., Maria J. Fraqueza, Ons Bouchami, Peder Worning, Mette D. Bartels, Maria L. Gonçalves, Paulo Paixão, et al. "Early Release - Foodborne Origin and Local and Global Spread of Staphylococcus Saprophyticus Causing Human Urinary Tract Infections - Volume 27, Number 3—March 2021 - Emerging Infectious Diseases Journal - CDC." Accessed February 19, 2021. <https://doi.org/10.3201/eid2703.200852>.

from 2017 to 2019.⁴ It is more critical than ever for the FDA to update this list in the context of reducing antibiotic overuse and reducing the threat of antibiotic resistance.

Despite our general support for the proposed ranking method, we have serious concerns with how it has been applied to drugs used in food animal production. Specifically, the FDA has not ranked bacitracin as medically important despite its clear fit within the proposed criteria. We also strongly support the suggestions made by the Infectious Disease Society of America (IDSA) in determining the importance of drug classes, as described below.

Our more detailed comments, organized by topic, follow:

Criteria

We strongly support the criteria as they appropriately focus on protecting the efficacy of those antibiotics that are most important for human health. However, we do ask that the FDA clarify how antibiotic resistance impacts the application of the criteria. Specifically, we are concerned how the FDA will address mechanisms of resistance that reduce the effectiveness of drugs in more than one class and how the FDA will address co-resistance, where widely disseminated mobile elements contain genes conferring resistance to multiple drug classes.

In a recently published study, researchers found the MCR-1 (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.⁵ As evidenced by the paper, animal use of bacitracin may increase selection pressure for bacteria carrying the MCR-1 gene, thereby increasing the 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-

⁴ Center for Veterinary Medicine. “FDA Releases Annual Summary Report on Antimicrobials Sold or Distributed in 2019 for Use in Food-Producing Animals.” FDA, December 15, 2020. <https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing>.

⁵ Xu, Fuzhou, Ximin Zeng, Atsushi Hinenoya, and Jun Lin. “MCR-1 Confers Cross-Resistance to Bacitracin, a Widely Used In-Feed Antibiotic.” *MSphere* 3, no. 5 (September 5, 2018). <https://doi.org/10.1128/mSphere.00411-18>.

colistin usage risk factor for the transmissible colistin resistance.” In the concept paper the FDA correctly ranks polymyxin class drugs such as colistin as “critically important” but errs in its ranking of polypeptides as “not important”.

Another example of cross-resistance between classes is the widespread distribution of the cfr gene in *Staphylococcus spp.* and *Escherichia coli* which concurrently confers resistance to multiple classes of antibiotics including oxazolidinones, phenicols, lincosamides, and pleuromutilins.⁶ Under the proposed criteria, oxazolidinones are ranked as critically important while other drugs for which cfr genes confer resistance 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.

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.^{7,8}

As stated by the FDA in the concept paper, management and mitigation measures (such as certain antimicrobial use limitations) should be appropriately applied to those situations where potential human health risks are greatest. We urge the FDA to clarify how it will take into consideration resistance and co-resistance in ranking drugs and applying the rankings to risk management decisions.

If certain determinants that confer resistance to multiple classes of antibiotics are present in bacterial populations in animals, for example, then those antibiotics should be treated as if they were in the same category as the drug of the highest importance. The presence of cfr genes

⁶ Long, Katherine S., Jacob Poehlsgaard, Corinna Kehrenberg, Stefan Schwarz, and Birte Vester. “The Cfr RRNA Methyltransferase Confers Resistance to Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, and Streptogramin A Antibiotics.” *Antimicrobial Agents and Chemotherapy* 50, no. 7 (July 2006): 2500–2505. <https://doi.org/10.1128/AAC.00131-06>.

⁷ Kanwar, Neena, H. Morgan Scott, Bo Norby, Guy H. Loneragan, Javier Vinasco, Jennifer L. Cottell, Gabhan Chalmers, Muckatira M. Chengappa, Jianfa Bai, and Patrick Boerlin. “Impact of Treatment Strategies on Cephalosporin and Tetracycline Resistance Gene Quantities in the Bovine Fecal Metagenome.” *Scientific Reports* 4, no. 1 (May 29, 2014): 5100. <https://doi.org/10.1038/srep05100>.

⁸ “Co-Resistance: An Opportunity for the Bacteria and Resistance Genes - ScienceDirect.” Accessed March 1, 2021. <https://www.sciencedirect.com/science/article/abs/pii/S1471489211001299>.

would indicate that the use of highly important lincosamides can select for resistance to the critically important linezolid. Similarly, the use of non-medically important bacitracin can select for resistance to critically important polymyxins. In each case these resistance determinants should be taken into consideration when guiding risk management strategies and raise the relative importance of lower ranked drugs.

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. Our greatest concern is the FDA ranking bacitracin as “not medically important” despite its use in human medicine. The antibiotic should be considered medically important under proposed criterion number 3. In the concept paper, 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”. Despite its use in human medicine and fulfillment of criterion 3, the FDA ranks the antimicrobial bacitracin as non-medically important. Bacitracin is used topically on the skin,⁹ in the eyes,¹⁰ and for postoperative prophylaxis,¹¹ as well as orally for treatment of human clostridium difficile infections.¹²

During a presentation at the FDA’s public meeting on November 16, 2020, IDSA made additional suggested changes to the application of the rankings and voiced the need for greater expert review. We recommend that the FDA integrate expert review to ensure consistent

⁹ 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>.

¹⁰ “Drugs for Some Common Eye Disorders.” *JAMA* 323, no. 5 (February 4, 2020): 470–71. <https://doi.org/10.1001/jama.2019.20663>.

¹¹ Heal, Clare F., Jennifer L. Banks, Phoebe D. Lepper, Evangelos Kontopantelis, and Mieke L. van Driel. “Topical Antibiotics for Preventing Surgical Site Infection in Wounds Healing by Primary Intention.” *The Cochrane Database of Systematic Reviews* 11 (November 7, 2016): CD011426. <https://doi.org/10.1002/14651858.CD011426.pub2>.

¹² Beinortas, Tumas, Nicholas E. Burr, Mark H. Wilcox, and Venkataraman Subramanian. “Comparative Efficacy of Treatments for Clostridium Difficile Infection: A Systematic Review and Network Meta-Analysis.” *The Lancet Infectious Diseases* 18, no. 9 (September 1, 2018): 1035–44. [https://doi.org/10.1016/S1473-3099\(18\)30285-8](https://doi.org/10.1016/S1473-3099(18)30285-8).

application of criteria and provide further justification for drugs ranked not medically important (NMI).

During the 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.”¹³ However, the concept paper makes no mention of “topical” antibiotics or criteria that impact 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 skin¹⁴ and ophthalmological topical antibiotics in people.¹⁵

Given the frequency and severity of skin and soft tissue infections, excluding topicals from consideration in drug rankings is unsound and unwise.¹⁶

The FDA should rank bacitracin as medically important based on its use in human medicine and on the potential for its use to select for resistance to the critically important polymyxin class of antibiotics.

As discussed by IDSA at the public meeting, all cephalosporins should be characterized as critically important, not just third and fourth generation cephalosporins as proposed by the FDA.

¹³ “Public Meeting Transcript 1.5.21” Regulations.Gov. Accessed February 19, 2021.

<https://www.regulations.gov/document/FDA-2020-N-1736-0018>.

¹⁴ 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>.

¹⁵ 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>.

¹⁶ 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>.

In North America and throughout the world, *Escherichia coli* resistance to ciprofloxacin in women with community-acquired UTIs has increased significantly over the last 10 years.¹⁷ In a recent publication in *Nature*, researchers reported a strong long-term correlation between antibiotic resistance to six antibiotics, including the first generation cephalosporin cephalexin, and antibiotic consumption for UTIs.^{18,19} Cephalexin is also the recommended antibiotic for the treatment of invasive methicillin-sensitive *Staphylococcus aureus* osteoarticular infections in children.²⁰

Similarly, as pointed out by IDSA, all sulfonamides, not only sulfonamides in combination with the diaminopyrimidines like trimethoprim, should also be considered “critically important” given they are the sole or one of limited therapies for toxoplasmosis treatment in immunocompromised hosts.²¹ The concept paper ranks sulfonamides as “important” while ranking the sulfonamide diaminopyrimidines combination as “critically important”.

Caution should be exercised 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.

¹⁷ Stapleton, Ann E., Florian M. E. Wagenlehner, Aruni Mulgirigama, and Monique Twynholm. “*Escherichia Coli* Resistance to Fluoroquinolones in Community-Acquired Uncomplicated Urinary Tract Infection in Women: A Systematic Review.” *Antimicrobial Agents and Chemotherapy* 64, no. 10 (September 21, 2020). <https://doi.org/10.1128/AAC.00862-20>.

¹⁸ Yelin, I. et al. “Personal clinical history predicts antibiotic resistance of urinary tract infections.” *Nat. Med.* 25, 1143–1152 (2019).

¹⁹ Wagenlehner, Florian M., and Kurt G. Naber. “Understanding Clinical Variables to Improve Empirical Antibiotic Therapy for UTI.” *Nature Reviews Urology* 16, no. 12 (December 2019): 695–96. <https://doi.org/10.1038/s41585-019-0240-0>.

²⁰ Ramchandrar, 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>.

²¹ 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>.

Finally, in Table 3 the FDA incorrectly states that no polymyxin class drugs are approved for use in food or companion animals, yet topicals with polymyxins are approved for both (e.g. NADA 008-763 and NADA 049-762).

Tier System

Under the proposed system drugs are already ranked into four levels of importance (i.e. not important, important, highly important, and critically important) as well as being categorized as medically important and not medically important. The FDA has not clearly explained how the additional lumping of categories into three tiers would aid in efforts to manage antimicrobial resistance. The Tier system figure directly contradicts the FDA's proposed criteria for ranking by indicating that some drugs approved for use in human medicine, and thus medically important under the FDA's proposed criteria, would be in Group 1 of drugs considered not medically important. We recommend that the FDA not include the Tier system as it moves forward and that the FDA, consistent with its own proposed criteria, rank all drugs in classes approved for use in humans as medically important.

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. As stated in the concept paper, it is appropriate to periodically reassess the list of medical importance rankings to align with contemporary science and current human clinical practices.

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. The FDA should establish timelines for implementation, adequately address cross-resistance and co-resistance in the ranking system, apply the criteria correctly, including classifying bacitracin as medically important, and eliminate or clarify the tier system. These changes will ensure effective implementation of the criteria and reduce the public health threat of antibiotic resistance in the food production sector.

Sincerely,

Antibiotic Resistance Action Center, George Washington University
Association for Professionals in Infection Control and Epidemiology
Center for Food Safety
Consumer Reports
Food Animal Concerns Trust
Green Century Capital Management – Andrea Ranger
Interfaith Center on Corporate Responsibility
Natural Resources Defense Council
U.S. PIRG