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IDSA
Infectious Diseases Society of America

May 19, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
RE: Docket FDA-1998-D-0038

To Whom It May Concern:

On behalf of the Infectious Diseases Society of America (IDSA), thank you for the opportunity to comment on FDA's revised Draft Guidance for Industry Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern.

IDSA represents more than 14,000 infectious diseases physicians, scientists and other public health and health care professionals. Our members care for patients with serious infections, including those caused by multidrug-resistant pathogens; lead antimicrobial stewardship and infection prevention programs; conduct research on antimicrobial resistance; and collaborate with public health departments to better prevent, detect and contain problems of antimicrobial resistance as a public health threat.

While antimicrobials are important in human health, it may not be widely understood that they are also important in the livestock industry. In fact, 44% more antibiotics of medical importance are sold for cows and pigs than for human medicine, fueling the growing threat of antimicrobial resistance that impacts humans. Therefore, IDSA greatly appreciates FDA's work to reduce inappropriate use of antimicrobial drugs in all animals. Ranking antimicrobial drugs according to their importance in human medicine in order to guide their use is an important component of these efforts. The new approach is an improvement over the current approach, which prioritizes the treatment of gastroenteritis over other infections when determining the importance of a drug.[1]

IDSA would also like to highlight that select antibiotics, including critically important classes, can be used for an extended duration without oversight. Many feed drugs are approved for continuous use, including the macrolide tylosin, which is considered by FDA to be critically important. While guidance for new drug approval is needed, it is also important to provide guidance or restrictions to curtail misuse and overuse of animal drugs.

Overall, IDSA supports the criteria and tiers proposed by FDA and is pleased to offer recommendations regarding the proposed rankings of some antimicrobials and a few additional issues for FDA to consider.

Criteria and Tiers

[1] 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.

The tiers are appropriately conservative, with drugs properly skewed toward more protective rankings. As IDSA has previously communicated to FDA, it is essential to protect all of these antimicrobial drugs, as our treatment arsenal is already diminished.

In addition, FDA may wish to consider whether the toxicity of an antimicrobial agent and the availability of better alternative therapies should be included among the criteria for ranking antimicrobials. For example, a highly toxic agent could be ranked lower when better alternatives exist, though an agent with high toxicity may still be ranked highly if few or no alternative therapies are available. FDA should also consider adding a criterion based on the potential for development of resistance to a drug or class of drugs.

Overall, the classification makes sense from the human health point of view; however, FDA should pay additional attention to the evolutionary aspects of antibiotic resistance. For example, it is very likely that **ALL** β-lactams would select for some sort of resistance regardless of the chemical structure. The "selectivity" has more to do with particular genetic mechanisms (especially those that encode β-lactamases), but in terms of non-β-lactamase mechanisms and genomic rearrangements it may not be significant. In this example, all β-lactams should be classified as critical because, eventually, they can be highly selective for resistance to other classes.

In addition, FDA should further explore the cross-resistance issues related to these drugs. Antimicrobial resistance does not always occur in one drug or even one class at a time because of cross-resistance. An obvious example is with the use of florfenicol in animal husbandry – a major driver for the selection of transferable genes (cfr, poxtA and optrA) that confer oxazolidinone resistance (the latter compounds are regarded as "critical" whereas the phenicols are not). FDA should be explicit about how the presence of genes that create cross-class resistance are accounted for when using the drug rankings.

Application of Criteria to Antimicrobial Classes and Drugs

IDSA recommends the following changes to the proposed rankings of certain antimicrobials.

First-generation cephalosporins

Cefazolin is the only first-generation cephalosporin classified as highly important in the proposed rankings. IDSA recommends that the entire group be classified as highly important, as they meet the second criterion: "Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans."

For example, cephalexin and cefadroxil are key antibiotics for treatment of cellulitis and streptococcal pharyngitis in children with penicillin allergy. They have been more frequently used recently for treatment of urinary tract infections, given the increase in fluoroquinolone and sulfa resistance rates.[2, 3] They are also commonly used now for treatment of osteomyelitis and septic arthritis because recent data have demonstrated efficacy of oral antibiotics for treatment of bone and joint infections.[4]

Sulfonamides

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[2] Stapleton A et al. *Escherichia coli* Resistance to Fluoroquinolones in Community-Acquired Uncomplicated Urinary Tract Infection in Women: A Systematic Review. Antimicrobial Agents and Chemotherapy Sep 2020. Retrieved from https://aac.asm.org/content/64/10/e00862-20.abstract.

[3] Wagenlehner FM, Naber KG. Understanding clinical variables to improve empirical antibiotic therapy for UTI. Nat Rev Urol 2019. Retrieved from https://www.nature.com/articles/s41585-019-0240-0.

[4] Ramchandar N et al. Frequency of Dosing of Cephalexin for Oral Step-Down Therapy of Pediatric Osteoarticular Infections Caused by Methicillin-Sensitive *Staphylococcus Aureus.* The Pediatric Infectious Diseases Journal. June 2020. Retrieved from https://journals.lww.com/pidj/Abstract/2020/06000/Frequency_of_Dosing_of_Cephalexin_for_Oral.13.aspx.

IDSA also recommends that sulfonamides be ranked as critically important. As FDA considers the importance of a drug in treating infections across the lifespan and in treating infections in immunocompromised patients, we assert that sulfadiazine (a sulfonamide) is the drug of choice in some patients, including infants with congenital toxoplasmosis, children with toxoplasma chorioretinitis and recurrence of toxoplasmosis.[5]

We also urge FDA to consider the potential for the development of resistance to a drug or class of drugs as a further basis for classifying sulfonamides as critically important. Trimethoprim/sulfamethoxazole (TMP/SMX) exposure has been found in some studies as a potential risk factor for CTX-M extended-spectrum β-lactamases (ESBL) *E. coli,* and the genes causing resistance to TMP/SMX in the CTX-M *E. coli* are primarily sulfonamide resistance genes. CTX-M Enterobacteriaceae can colonize both humans and animals, and animals are a potential source of human acquisition.

Bacitracin

The draft guidance ranks bacitracin as "not medically important" despite its use in human medicine. Bacitracin is used topically on the skin and in the eyes. The antibiotic should be considered medically important under proposed criterion 3 in the draft guidance: "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 draft guidance ranks the antimicrobial bacitracin as non-medically important. During the February 2021 public meeting, FDA staff 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."[6] However, the draft guidance makes no mention of "topical" antibiotics or criteria that impact drugs that "act locally." As it is one of the most commonly used antibiotics in food animal production, FDA should reconsider the treatment of bacitracin in the guidance and rank bacitracin as medically important based on use in human medicine, evidence that its use selects for resistance to critically important antibiotics and can promote increased virulence in pathogens and the potential for its use to select for resistance to innate immunity in humans and animals.

Additional Category and Class

IDSA recommends that antifungals, specifically azoles, be added to the FDA ranking of antimicrobial drugs according to their therapeutic use in human medicine. CDC ranks drug-resistant *Candida auris* as an urgent threat that can cause severe infections and spread easily among patients in hospitals and nursing homes. *C. auris* is often multidrug resistant, with some strains resistant to all three available classes of antifungals. *C. auris* began spreading in the United States in 2015. CDC reported clinical cases of *C. auris* in the U.S. rose from 476 in 2019 to 1,471 in 2021. Screening cases tripled from 2020 to 2021, for a total of 4,041.[7]

Triazole resistance is another increasing problem in invasive aspergillosis (IA). Small case series show mortality rates of 50%–100% in patients infected with a triazole-resistant *Aspergillus fumigatus*, though a direct comparison with triazole-susceptible IA is lacking. A multicenter retrospective cohort study found that

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[5] Zhang Y et al. Current treatment of ocular toxoplasmosis in immunocompetent patients: a network meta-analysis Acta Tropica. September 2018. Retrieved from https://www.sciencedirect.com/science/article/abs/pii/S0001706X17315267.

[6] "Public Meeting Transcript 1.5.21" Regulations.Gov. Retrieved from https://www.regulations.gov/document/FDA-2020-N-1736-0018.

[7] "Increasing Threat of Spread of Antimicrobial-Resistant Fungus in Healthcare Facilities." Centers for Disease Control and Prevention. 2021. Retrieved from https://www.cdc.gov/media/releases/2023/p0320-cauris.html#:~:text=CDC%20has%20continued%20to%20see,2019%20to%201%2C471%20in%202021.

voriconazole resistance was associated with excess overall mortality of 21% at day 42 and 25% at day 90 in patients with IA.[8]

Updating the Rankings of Medically Important Antimicrobials

IDSA recommends that the FDA process for updating these rankings engage external experts and key stakeholders, including medical societies, through formal comment opportunities. To keep pace with the development of resistance, IDSA recommends that FDA review relevant data every two years to determine the need for an update. Every five years, FDA should undertake a more formal update process. A five-year interval should be sufficient to account for new antimicrobial drug development, based upon the current pipeline.

In addition to these routine reviews and updates, FDA should establish a process through which external experts, including medical societies, may formally call for a review at any time based upon a timely need, including new human drug approvals that may be relevant for the rankings.

Once again, IDSA thanks FDA for its leadership on this important effort. For further information, please contact Amanda Jezek, IDSA senior vice president for public policy & government relations, at ajezek@idsociety.org.

Sincerely,

Carlos del Rio, MD, FIDSA
President

[8] Lestrade PP, Bentvelsen RG, Schauwvlieghe AFAD, Schalekamp S, van der Velden WJFM, Kuiper EJ, van Paassen J, van der Hoven B, van der Lee HA, Melchers WJG, de Haan AF, van der Hoeven HL, Rijnders BJA, van der Beek MT, Verweij PE. Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2019 Apr 24;68(9):1463-1471. Retrieved from https://pubmed.ncbi.nlm.nih.gov/30307492.