



FOOD ANIMAL CONCERNS TRUST

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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

The Food Animal Concerns Trust (FACT) supports the Food and Drug Administration's new proposed criteria for [ranking antimicrobial drugs according to their importance in human medicine](#). FACT has signed on to another comment in this docket submitted by the Keep Antibiotics Working coalition which more comprehensively addresses our main points with respect to the proposed ranking method. The following comments are being submitted on behalf of the Food Animal Concerns Trust in order to provide additional information about our concerns related to the Food and Drug Administration's decision to exclude drugs used as topicals from the rankings. FACT opposes the decision to exclude topicals as it undermines public health and weakens efforts to promote antimicrobial stewardship in veterinary settings.

During the Food and Drug Administration (FDA) public meeting on November 16, 2020 FDA staff stated "topical-only uses such as bacitracin have not been included in the rankings given they act locally, they did not meet the criteria considered in the ranking process as outlined in the guidance in the concept paper."¹ However, there is no mention of topical drugs or drugs that act locally within the concept paper. We recommend FDA keep the criteria included in the concept paper and apply them to topical drugs.

Excluding topicals from being evaluated by the proposed ranking criteria will mean that drugs like mupirocin, which is used to treat resistant infections that pass between humans and animals, will not be considered medically important. Mupirocin, a topical antibiotic ointment prescribed to both humans and animals for treatment of skin infections², is one of a select number of antimicrobials used for decolonization and treatment of methicillin-resistant *Staphylococcus*

¹ "Public Meeting Transcript 1.5.21" Regulations.Gov. Accessed February 19, 2021.
<https://www.regulations.gov/document/FDA-2020-N-1736-0018>.

² Park, Ji-Hyung, Jung-Hun Kang, Jae-Eun Hyun, and Cheol-Yong Hwang. "Low Prevalence of Mupirocin Resistance in *Staphylococcus Pseudintermedius* Isolates from Canine Pyoderma in Korea." *Veterinary Dermatology* 29, no. 2 (2018): 95-e37. <https://doi.org/10.1111/vde.12518>.

aureus (MRSA) infections.³ Resistance to mupirocin has been recognized in human *S. aureus*, human coagulase-negative staphylococci (CoNS), and now in methicillin-resistant staphylococci isolated from diseased dogs and cats.⁴ In the aforementioned study, which collected these resistant isolates from companion animals i.e. dogs and cats, the isolates showed high-level mupirocin resistance (HLMR). Because of the limited available treatments for MRSA infections in animals, alternative therapies such as mupirocin are often utilized.⁵ In fact the practice of mupirocin use in companion animals is likely to increase in the coming years.⁶ Researchers Kizerwetter-Swida et al. claimed, “The emergence of mupirocin resistance among MRSA and other staphylococci in humans suggests that it may be potentially transferred to staphylococci of animal origin. The close contacts of owners with their dogs and cats favour the spread of resistant bacteria, including mupirocin-resistant ones. The transmission of mupirocin resistance genes from human *S. aureus* isolates to canine *S. pseudintermedius* is highly probable, although it may occur in both directions.”⁷ The example of mupirocin, as evidenced by this study and others cited therein, illustrates the need to include topicals when considering antimicrobial resistance threats related to antimicrobial use in animals.

Other topical antimicrobials play a role in treating infections in humans. In a study published by Heal et al, researchers found that topical antibiotics applied to healing surgical wounds probably reduce the risk of surgical site infections.⁸ The polypeptide topical antimicrobial bacitracin is used to prevent sternal wound infections after cardiac surgery⁹, manage pediatric burns¹⁰, and

³McConeghy, Kevin W., Dennis J. Mikolich, and Kerry L. LaPlante. “Agents for the Decolonization of Methicillin-Resistant *Staphylococcus Aureus*.” *Pharmacotherapy* 29, no. 3 (March 2009): 263–80. <https://doi.org/10.1592/phco.29.3.263>.

⁴Kizerwetter-Świda, Magdalena, Dorota Chrobak-Chmiel, and Magdalena Rzewuska. “High-Level Mupirocin Resistance in Methicillin-Resistant Staphylococci Isolated from Dogs and Cats.” *BMC Veterinary Research* 15, no. 1 (July 10, 2019): 238. <https://doi.org/10.1186/s12917-019-1973-y>.

⁵ McCarthy AJ, Harrison EM, Stanczak-Mrozek K, Leggett B, Waller A, Holmes MA, Lloyd DH, Lindsay JA, Loeffler A. “Genomic insights into the rapid emergence and evolution of MDR in *Staphylococcus pseudintermedius*.” *J Antimicrob Chemother.* 2015;70:997–1007.; Frank LA, Loeffler A. “Methicillin-resistant *Staphylococcus pseudintermedius*: clinical challenge and treatment options.” *Vet Dermatol.* 2012;23:283–91.

⁶ Valentine BK, Dew W, Yu A, Weese JS. “*In vitro* evaluation of topical biocide and antimicrobial susceptibility of *Staphylococcus pseudintermedius* from dogs.” *Vet Dermatol.* 2012. <https://doi.org/10.1111/j.1365-3164.2012.01095.x>.

⁷ Kizerwetter-Świda, Magdalena, Dorota Chrobak-Chmiel, and Magdalena Rzewuska. “High-Level Mupirocin Resistance in Methicillin-Resistant Staphylococci Isolated from Dogs and Cats.” *BMC Veterinary Research* 15, no. 1 (July 10, 2019): 238. <https://doi.org/10.1186/s12917-019-1973-y>.

⁸ 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>.

⁹ Chan, Joshua L., Andrada C. Diaconescu, and Keith A. Horvath. “Routine Use of Topical Bacitracin to Prevent Sternal Wound Infections After Cardiac Surgery.” *The Annals of Thoracic Surgery* 104, no. 5 (November 1, 2017): 1496–1500. <https://doi.org/10.1016/j.athoracsur.2017.04.017>.

¹⁰ Arbuthnot, Mary K., and Alejandro V. Garcia. “Early Resuscitation and Management of Severe Pediatric Burns.” *Seminars in Pediatric Surgery, Surgical Critical Care*, 28, no. 1 (February 1, 2019): 73–78. <https://doi.org/10.1053/j.sempedsurg.2019.01.013>.

adult burn wounds.¹¹ Bacitracin is approved as a prescription ophthalmic ointment and is used for common eye disorders¹². Retapamulin, a pleuromutilin antibiotic, is approved for topical treatment of impetigo (NDA 022055) and is being considered as an alternative to mupirocin for MRSA decolonization.¹³ Bacitracin and the pleuromutilin tiamulin are some of the most commonly used antibiotics in food animals. It is likely that their current rankings as non-medically important likely contribute to their high level of use considering both can be used without a veterinarians order and bacitracin can be used for growth promotion.

The connection between the widespread use of these drugs, selection for resistance in food animals and the potential impacts on the treatment of human skin infections has not been well documented or studied. However, skin infections on the lower half of the body are often caused by bacteria found in the human gastrointestinal tract.¹⁴ Given the well-documented ability of bacteria from food animals to colonize and cause infections in the human gastrointestinal tract, a pathway exists for antibiotic use in food animals to select for resistant bacteria that may cause resistant skin infections in humans.

FDA should also consider further studying the potential for antifungal treatments in companion animals to contribute to resistant fungal infections in humans.¹⁵

There is the potential for antibiotic resistance developed in food animals to impact the treatment of human infections with topical antibiotics. Thus, topical antimicrobials should not be excluded from the ranking of drugs by medical importance.

Sincerely,

Food Animal Concerns Trust

¹¹ Manzoor, Sobia, Farid Ahmad Khan, Sohail Muhammad, Rehan Qayyum, Imran Muhammad, Umer Nazir, and Muhammad Mustehsan Bashir. "Comparative Study of Conventional and Topical Heparin Treatment in Second Degree Burn Patients for Burn Analgesia and Wound Healing." *Burns* 45, no. 2 (March 1, 2019): 379–86. <https://doi.org/10.1016/j.burns.2018.05.010>.

¹² "Drugs for Some Common Eye Disorders." *JAMA* 323, no. 5 (February 4, 2020): 470–71. <https://doi.org/10.1001/jama.2019.20663>.

¹³ Patel, Ami B., Jennifer Lighter, Yi Fulmer, Richard Copin, Adam J. Ratner, and Bo Shopsin. "Retapamulin Activity Against Pediatric Strains of Mupirocin-Resistant Methicillin-Resistant Staphylococcus Aureus." *The Pediatric Infectious Disease Journal Online First* (March 2, 2021). <https://doi.org/10.1097/INF.0000000000003123>.

¹⁴ Ki, Vincent, and Coleman Rotstein. "Bacterial Skin and Soft Tissue Infections in Adults: A Review of Their Epidemiology, Pathogenesis, Diagnosis, Treatment and Site of Care." *The Canadian Journal of Infectious Diseases & Medical Microbiology* 19, no. 2 (March 2008): 173–84.

¹⁵ Seyedmousavi, Seyedmojtaba, Sandra de M G Bosco, Sybren de Hoog, Frank Ebel, Daniel Elad, Renata R Gomes, Ilse D Jacobsen, et al. "Fungal Infections in Animals: A Patchwork of Different Situations." *Medical Mycology* 56, no. Suppl 1 (April 2018): S165–87. <https://doi.org/10.1093/mmy/myx104>.