Dr. Scott Gottlieb
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
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Dear Dr. Gottlieb,

We write as 155 physicians, pharmacists, nurses, microbiologists and other concerned health professionals to encourage the U.S. Food and Drug Administration (FDA) to take action to eliminate over-the-counter (OTC) use of polymyxins in human and veterinary medicine.

As you know, physicians rely on polymyxin antibiotics (colistin and polymyxin B) to treat patients when no other drug will work.[1] The spread of polymyxin resistance along with carbapenem resistance indicates that we are already entering into the post-antibiotic era.[2] The U.S. Center for Disease Control and Prevention (CDC) has described resistance to polymyxins as one of the two resistance mechanisms of greatest concern.[3] The World Health Organization in 2017 included polymyxins among a handful of "reserve group antibiotics" - those that should only be used in specific settings where other antibiotics would not work.[4]

Despite their incredible importance in fighting otherwise untreatable infections, polymyxin antibiotics are available in most drug stores and groceries in topical form with no prescription. Because of kidney toxicity, systematic use of polymyxins in humans has been rare and has only been revived recently because the spread of resistance has left doctors with no other options.[5] While systematic use was precluded because of toxicity, when applied topically or orally there is limited absorption so nephrotoxicity is avoided.[6] Today, hundreds of topical products containing polymyxin B are sold without medical supervision or even demonstration of medical need.

As these products are over-the-counter, the only restriction concerning their sale is that they have to comply with over-the-counter regulations under an FDA final monograph regarding indications, labeling, administration, and formulation.[7] This regulation, written in 1987, allows polymyxin B to be legally marketed as part of double or triple combination

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[1] Kaye KS, et al. Agents of Last Resort: Polymyxin Resistance. Infect Dis Clin North Am. 2016 June.
[2] Bulman ZP, et al. Polymyxin Combinations Combat *Escherichia coli* harboring *mcr-1* and *bla* NDM-5: Preparation for a Postantibiotic Era. MBio. 2017 July.
[3] Chen L, et al. Notes from the Field: Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016. CDC MMWR. 2017 Jan.
[4] WHO. The Selection and Use of Essential Medicines. 2017.
[5] Li J, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infectious Disease. 2008 Sept.
[6] Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systemic review of the evidence from old and recent studies. Crit Care. 2006 Feb.
[7] https://www.accessdata.fda.gov/scripts/cder/training/OTC/topic3/topic3/da_01_03_0100.htm

topical therapies in combination with bacitracin, neomycin sulfate, oxytetracycline, or some combination of these drugs.[8] These topical products can be sold despite limited evidence of efficacy and safety. When the FDA authorized these over-the-counter uses, FDA did not require evidence from head-to-head controlled trials comparing the effectiveness of topical first aid combination therapies with and without the addition of polymyxin B.[9] FDA at that time also did not know how important this class of drugs would become for treating multi-drug resistant infections and did not require studies showing the impact of use on resistance.[10]

Polymyxin class drugs are also available as over-the-counter eye ointment for use in cattle and sheep in the U.S.[11] In addition to the topical ointments, injectable polymyxins are approved but not marketed for use in poultry.[12] Outside the U.S., livestock producers frequently administer polymyxins to food producing animals in feed or water[13]. Public health officials did not recognize that polymyxin use in food-producing animals created a public health risk until 2011 when researchers in China discovered transferable polymyxin resistance in Escherichia coli from a pig.[14] Since that first detection, food-producing animal use of polymyxins has been linked to the global spread of this resistance.[15] Like for the human topical uses, the potential for selecting transferable resistance and the current importance of these drugs for combatting otherwise untreatable infections was unknown when they were approved for use in food producing animals.[16]

In conclusion, despite their toxicity polymyxins have become some of the most important drugs for treating seriously ill patients due to the spread of multi-drug resistant gram-negative infections. The rise in importance of this class of drugs was not predicted when they were approved for over-the-counter uses in humans and animals. We call on the FDA to re-examine these uses based on the new evidence of the vital importance of these drugs for human health and to prohibit their over-the-counter use in people and to prohibit their use in food-producing animals altogether.

Thank you for your consideration.

Sincerely,

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[8] Topical Antimicrobial Drug Products for Over-the-counter Human Use; Final Monograph for OTC First Aid Antibiotic Drug Products, 52 Fed. Reg. 238 (December 11, 1987).
[9] Ibid.
[10] Li J, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infectious Disease. 2008 Sept.
[11] 21 C.F.R. §524.1662b
[12] 21 C.F.R. §522.468; 21 C.F.R. §522.2340
[13] Davies M, Walsh T. A colistin crisis in India. Lancet Infectious Disease. 2018 January.
[14] Liu YY, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infectious Disease. 2016 February
[15] Elnahriry SS, et al. Emergence of Plasmid-Mediated Colistin Resistance Gene mcr-1 in a Clinical Escherichia coli Isolate from Egypt. Antimicrobial Agents and Chemotherapy. 2016 April.
[16] Li J, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infectious Disease. 2008 Sept.

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