

**Draft
Guidance for Industry**

**Evaluation of the Human Health Impact of the Microbial
Effects of Antimicrobial New Animal Drugs Intended for
Use in Food-Producing Animals**

This draft guidance document is being distributed for comment purposes only.

This draft guidance document announces that FDA now believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs.

This guidance represents the agency's current thinking on this matter. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

The comment period for this draft guidance will begin on the day the Notice of Availability of the guidance publishes in the Federal Register. The Federal Register notice will state the length of the comment period. Comments and suggestions regarding the document should be submitted to the Docket Number that will be provided in the Federal Register notice.

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Food and Drug Administration
Center for Veterinary Medicine (CVM)
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Introduction

This draft guidance document announces that FDA now believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs¹ intended for use in food-producing animals.² To assess this impact, the following two separate, but related aspects, should be evaluated: 1) the quantity of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug (resistance); and 2) changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load). In the past, the agency evaluated the human health impact of the microbial effects of only certain uses of antimicrobial new animal drugs in animal feeds (1). Based on the scientific evidence referenced below, the agency now believes that sponsors of all antimicrobial new animal drugs intended for use in food-producing animals should provide information relating to resistance and pathogen load to allow the agency to determine that such products are safe under the Federal Food, Drug, and Cosmetic Act.³

Resistance

The use of antimicrobial drugs in animals selects for resistant bacteria (2-7). These resistant bacteria, if transferred to people via food or the environment, can have an adverse effect on human health. This effect can be direct, if the resistant bacteria are themselves human pathogens, or indirect, if the resistant bacteria are not human pathogens but transfer their resistance genes to human pathogens. Antimicrobial resistance sometimes develops in enteric bacteria that contaminate food and cause human illness (2,5-7). When food borne infections are caused by a resistant pathogen, medical treatment may be compromised (6,7). For example, the use of fluoroquinolones to treat various respiratory diseases in poultry has led to the development of fluoroquinolone-resistant *Campylobacter* in the intestinal tract of birds treated in The Netherlands (3). In poultry, *Campylobacter* from the intestinal tract can contaminate the carcass at slaughter and during processing. Improperly cooked poultry is a vehicle for *Campylobacter* infections in humans. Therefore, humans could become infected with fluoroquinolone-resistant *Campylobacter* by consuming poultry previously treated with a fluoroquinolone. Because a fluoroquinolone, Ciprofloxacin, may be used as an empiric treatment for diarrheal disease in humans (7), the emergence of fluoroquinolone-resistant *Campylobacter* in poultry could compromise the public health by reducing the effectiveness of a treatment.

Antimicrobial resistance sometimes develops in enteric bacteria that contaminate food but

¹ The term "antimicrobial" is used in this document to refer to new animal drug products that have bacteriostatic or bactericidal activity.

² For guidance on how to assess the safety of an antimicrobial new animal drug residue in edible tissue, see Guidance 52 "Microbiological Testing of Antimicrobial Drug Residues in Food."

³ Since the 1970's FDA has evaluated the effects of an antimicrobial drug product on enteric bacteria of food-producing animals in determining whether certain feed uses of an antimicrobial new animal drug are safe under section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b).

do not typically cause human illness (2,8). When humans ingest resistant enteric bacteria of food animal origin, the resistance genes can be transferred to bacteria indigenous to the intestinal tract of humans. Bacteria indigenous to the human intestinal tract frequently cause human disease. If these indigenous human bacteria become resistant to drugs used in human therapy, human health may be compromised due to limited therapeutic options (2,8).

Pathogen Load

Bacteria present in the intestinal tract of the animal at slaughter including *Salmonella*, *Campylobacter*, and *Escherichia coli* can contaminate food and cause human illness (9). In the U.S., an estimated 1% of the beef carcasses, 8.7% of the swine carcasses and 20% of the poultry carcasses are contaminated with *Salmonella*. Also, 4% of the beef carcasses, 31.5% of the swine carcasses and 88% of the broiler chickens are contaminated with *Campylobacter* (10). Generally, antimicrobial drug therapy cures clinical infections by reducing the level of specific pathogens. However, this therapy may also disturb the normal intestinal microbial ecosystem in the animal causing an increase in the bacteria that cause human infections or duration of the carrier state of such bacteria (pathogen load), thereby increasing the potential for contamination of food and consequent human illness (2,4).

Conclusion

The consumption of animal products contaminated with bacteria may compromise human health. Changes in animal enteric bacteria, including increased pathogen load and antimicrobial resistance, may occur as a result of any antimicrobial use (not just feed use) in food-producing animals. Therefore, FDA believes that drug sponsors of all antimicrobial new animal drug products intended for use in food-producing animals should evaluate the human health impact of microbial effects of such drugs. Pre-approval study(s) may be needed. FDA recognizes that there is no standardized protocol established for determining the human health impact of the microbial effect(s) of an antimicrobial product, and that one standard protocol is likely to be inappropriate for all intended uses. FDA believes, however, that the principles are available to assess resistance, pathogen load, and the interaction of these microbial effects. Before conducting a study, drug sponsors are encouraged to consult with the agency on study design.

Citations

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. U.S. Food and Drug Administration, "Human Health Safety Criteria," Center for

Veterinary Medicine, Guideline 18.

2. U.S. Food and Drug Administration, "Penicillin Use in Animal Feeds," 42 FR 43769-43793, August 30, 1977.

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4. Aserkoff, B., and J. V. Bennett, "Effect of Antibiotic Therapy in Acute Salmonellosis on the Fecal Excretion of *Salmonella*," *New England Journal of Medicine*, 281, 636-640, 1969.

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6. D'Aoust, J-Y., *Salmonella Species*, In: Food Microbiology Fundamentals and Frontiers, edited by Doyle, M. P., L. R. Beuchat, and T. J. Montville. ASM Press, Washington, DC, pp. 129-158. 1997.

7. Nachamkin, I., *Campylobacter jejuni*, In: Food Microbiology Fundamentals and Frontiers. edited by Doyle, M. P., L. R. Beuchat, and T. J. Montville. ASM Press, Washington, DC, pp. 159-170. 1997.

8. Bates, J., J. Z. Jordens, and D. T. Griffiths, "Farm Animals as a Putative Reservoir for Vancomycin-resistant Enterococcal Infection in Man," *Journal of Antimicrobial Chemotherapy*, 34, 507-514, 1994.

9. Department of Agriculture, Food Safety Inspection Service, "Pathogen Reduction; Hazard Analysis and Critical Control Point (HACCP) Systems; Final Rule," 61 FR 38805, July 25, 1996.

10. Department of Agriculture, "Nationwide Beef Microbiological Baseline: Steers and Heifers," October 1992-September 1993; "Nationwide Broiler Chicken Microbiological Baseline," July 1994-June 1995; and "Nationwide Pork Microbiological Baseline: Market Hogs," April 1995-March 1996: Food Safety Inspection Service, Data Collection Programs, Microbiology Division.

11. U.S. Food and Drug Administration, "Microbiological Testing of Antimicrobial Drug Residues in Food," Center for Veterinary Medicine, Guideline 52.