Guidance for Industry

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

(This document replaces the draft guidance document entitled "Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animals Drugs Intended for Use in Food-Producing Animals," dated November 1998 and April 1999 and the guidance document entitled "Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals," dated December 1999)

This guidance document addresses how, pursuant to section 512 of the Federal Food, Drug, and Cosmetic Act, FDA intends to consider the potential 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. A Notice of Availability for this document as draft was published on November 18, 1998 (63 FR 64094).

This guidance document 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.

Comments regarding this guidance document will be accepted at any time. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1061, 5630 Fishers Lane, Rockville, MD 20852. Comments should be identified with the Docket Number 98D-0969.

For questions regarding this guidance document, contact Sharon Thompson, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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Introduction

This guidance document addresses how, pursuant to section 512 of the Federal Food, Drug, and Cosmetic Act (the act), FDA intends to consider the potential human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs[1] intended for use in food-producing animals.[2] To assess this impact, it may be necessary to evaluate the following two separate, but related aspects: 1) the rate and extent of development 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 intends to consider the potential human health impact of the microbial effects of all antimicrobial new animal drugs intended for use in food-producing animals in determining that such products are safe under section 512 of the 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 instead 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 and improperly handling uncooked poultry are vehicles for *Campylobacter* infections in humans. Therefore, humans could become infected with fluoroquinolone-resistant *Campylobacter* by consuming poultry previously

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[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).

treated with a fluoroquinolone. Because a fluoroquinolone, such as ciprofloxacin, is usually used as an empiric treatment for severe diarrheal disease in humans, 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 foods but does 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 animals' enteric bacteria, including increased pathogen load and the development of antimicrobial resistance, may occur as a result of antimicrobial use in food-producing animals. Therefore, the FDA believes that drug sponsors of all antimicrobial new animal drug products intended for use in food-producing animals should consider the potential human health impact of microbial effects of such drugs. Pre-approval study(s) may be needed. The Agency believes that such study(s) should be conducted when necessary to answer questions regarding the human health impact of the microbial effects of an antimicrobial product. New studies for estimating resistance may not necessarily be needed for all products. Sponsors may be able to use information from other required studies or published literature to demonstrate that the exposure of the treated animal's enteric bacteria to the antimicrobial would be very limited and would not lead to the development of resistance. Sponsors of antimicrobials not used in human medicine may not need to submit resistance data unless cross-resistance to a human therapeutic drug is an issue.

The 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 a single standard protocol is unlikely to be appropriate for all intended uses. The 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. The agency intends to provide additional guidance in the future on the appropriate design of such studies and, as necessary, to revise existing guidance related to the evaluation of the human safety of antimicrobial products intended for use in food-producing animals.[4]

[4]Guidance documents in current use that provide guidance pertinent to the evaluation of the human health safety of antimicrobial new animal drugs intended for use in food-producing animals may not be in full conformity with Guidance for Industry #78. The FDA expects to eventually revise or rescind these guidance documents. However, because they contain other information still relevant to assessing the human health safety of antimicrobial new animal drugs, it would be inappropriate to simply rescind them at this time. Sponsors are encouraged to visit the Homepage, contact the CVM to obtain a paper copy of the latest guidance, or most importantly, consult with staff to learn the latest developments.

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 9:00 a.m. and 4:00 p.m., Monday through Friday.

1. U.S. Food and Drug Administration, "Human Health Safety Criteria," Center for Veterinary Medicine, Guideline 18.[5]

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

3. Endtz, H., G. Ruiijs, et. al., "Quinolone resistance in *Campylobacter* Isolated from Man and Poultry Following the Introduction of Fluoroquinolones in Veterinary Medicine," *Journal of Antimicrobial Chemotherapy*, 27, 199-208, 1991.

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.

5. Seyfarth, A.M., H. C. Wegener, and N. Frimodt-Moller, "Antimicrobial Resistance in *Salmonella enterica* subsp. *enterica* serovar *typhimurium* from Humans and Production Animals," *J. Antimicrobial Chemotherapy*, 40, 67-75, 1997.

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

[5]See footnote 4.

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.[6]

[6]See footnote 4.