COMMENTS OF THE COMPETITIVE ENTERPRISE INSTITUTE REGARDING THE FDA'S DRAFT GUIDANCE ON THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS

Docket No. FDA-2010-D-0094
75 Fed. Reg. 37,450 (June 29, 2010)

The Competitive Enterprise Institute respectfully submits these comments on the agency's Draft Guidance on *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals* (Guidance #209). The Competitive Enterprise Institute (CEI) is a 501(c)(3) non-profit public interest group dedicated to promoting rational risk regulation and consumer choice. CEI has a long history of research and advocacy regarding the regulation of health and safety risks, with a particular emphasis on food and drug safety. We have frequently observed that attempts to limit exposure to certain risks unintentionally increases exposure to other, potentially more hazardous risks.

The development by human pathogens of resistance to medically important antimicrobials poses serious public health issues. However, the use of such products in animals is only one factor in the emergence of antimicrobial-resistant pathogens, and it contributes far less to the development of resistance than does misuse among human patients. Most importantly, though, the use of antimicrobial drugs in food-producing animals delivers substantial benefits for both animal and human health. Even the often criticized sub-therapeutic uses of these drugs contribute to reduced pathogen loads in animal-derived foods and have a positive impact on human safety. We therefore caution the FDA and other regulatory authorities not to forbid these uses without first assessing whether such restrictions would do more harm than good.

Background

Antimicrobial drugs have been used in humans and animals for over 60 years, and both uses have generated substantial public health benefits. Unfortunately, the development of

resistance by pathogens to this important class of drugs surely began as soon as they were introduced. Bacteria in the environment have been exposed to natural antimicrobial compounds for millions of years, and have developed mechanisms of resistance in order to ensure their survival.

Scientists isolated strains of penicillin-resistant *Staphylococcus aureus* as early as 1945, soon after that drug was introduced into widespread hospital use. By the 1950s, penicillin-resistant *S. aureus* was common in hospitals where penicillin had been heavily prescribed.[1] Over the intervening years, there has been a noticeable increase in the number of human and animal pathogens that are resistant to one or more antimicrobial drugs. And the recent identification of pathogens resistant to therapeutically important antimicrobials has become a significant public health concern. In such cases, important antimicrobial drugs may not be counted on to remain effective therapeutic agents against problematic human pathogens.

It is unrealistic to expect that the effectiveness of any given antimicrobial can be preserved indefinitely. But, when used judiciously in animals or humans, the development of resistance to antimicrobials may be delayed. Eventually, however, older classes of antimicrobials that can no longer be relied upon as effective therapeutic agents will have to be replaced with newer therapeutic options, including but not limited to new classes of antimicrobial drugs.

This does not mean, however, that society should necessarily be forced to forgo entire categories of use for the sole purpose of prolonging the effective life of any one or more antimicrobials. A refusal to permit beneficial uses in the present can have negative impacts on human and animal health just as surely as a lack of long-term efficacy can. Consequently, we ought to strive to achieve an optimal level of antimicrobial use of that balances the current benefits of antimicrobial consumption against the inevitable development of resistance. In many, if not all cases, this will include the continued use of antimicrobial drugs that are important in livestock production, including sub-therapeutic uses for growth promotion.

[1] Office of Technology Assessment, *Impact of Antibiotic-Resistant Bacteria: A Report to the U.S. Congress* (Washington, DC: U.S. Government Printing Office, 1995), p. 3.

Several layers of protection have been put in place to ensure that antibiotics used to keep animals healthy do so without harm to public health. But it is also important to remember that food animals are not the only source for the development of antimicrobial resistant pathogens. As little as 10 percent of the problem of antimicrobial drug-resistant pathogens in humans can be attributed to livestock.[2] The contribution of antimicrobial drug use in companion animals to the development of resistant pathogens has been poorly characterized, as most estimates are simply derived from studies that attempt to quantify resistance development in livestock.[3] But antimicrobial drug use by human patients in hospitals and in physicians' office practice is generally considered to be the biggest contributing factor in the development of resistant pathogens. As much as 50 percent of antibiotic use in human patients may be considered inappropriate because the drugs are prescribed for non-bacterial ailments that antimicrobials cannot cure, such as cold and flu viruses and allergies.[4]

These inappropriate human uses undoubtedly increase selection pressure for the emergence and spread of antibiotic-resistant bacteria. But, even when they are prescribed to treat bacterial infections, human use of antimicrobial drugs can contribute to pathogen resistance in a variety of ways, such as inappropriate dosing, improper pairing of the prescribed drug to the patient's ailment, and the failure of patients to finish an antibiotic prescription.[5] Indeed, even when the same antimicrobial resistant pathogen is identified in both animals and humans, it may be just as likely that the bacteria spread from humans to the animals as vice versa.[6] The public health community has only recently begun to take this issue seriously, though, and animal uses continue to bear the brunt of efforts to control the development of resistant pathogens. Such policies may be counterproductive, however.

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[2] Kenneth H. Mathews, Jr., "Antimicrobial Drug Use and Veterinary Costs in U.S. Livestock Production," USDA *Agriculture Information Bulletin* No. 766 (May 2001).
[3] *See* Institute of Food Technologists, *Antimicrobial Resistance: Implications for the Food System* (Chicago: IFT Foundation, July 2006).
[4] Office of Technology Assessment, *Impact of Antibiotic-Resistant Bacteria*, p. 4.
[5] Nancy E. Halpern, "Antibiotics in Food Animals: The Convergence of Animal and Public Health, Science, Policy, Politics and the Law," *Drake Journal of Agricultural Law*, vol. 14 (2009) pp. 401-436.
[6] E. van Duijkeren et al., "Transmission of a Panton-Valentine Leucocidin-Positive, Methicillin-Resistant *Staphylococcus Aureus* Strain Between Humans and a Dog, *Journal of Clinical Microbiology*, vol. 43 (2005) pp. 6209-6211; American Veterinary Medical Association, "Education is Key to Combating Rise in MRSA," JAVMA News (Jan. 15, 2009), http://www.avma.org/onlnews/javma/jan09/090115g.asp.

In the United States today, as in other industrialized nations, the introduction of antimicrobial drugs for use in humans and/or animals is strictly regulated. And the regulation of antimicrobial use in animals is particularly stringent. Before they may be approved by the Food and Drug Administration for use in animals, manufacturers must demonstrate the antimicrobial is safe for the animals in question and that meat, milk, and eggs from treated animals are safe for human consumption.[7] Under the terms of the agency's *Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* (Guidance #152), manufacturers must also evaluate the likelihood that resistant pathogens will arise from use of the drug, the likelihood that human consumers will be exposed to those resistant pathogens, and the likely human health consequences of such exposure. These analytical steps, and the usage restrictions that arise from them, all serve to minimize the potential for harm to human health.

Generally, even when antimicrobial-resistant bacteria are present in livestock, the likelihood of human exposure remains quite remote, in part because risk management strategies to minimize and contain resistant pathogens have been implemented throughout the food chain. FDA and U.S. Department of Agriculture rules requiring food production facilities to implement Hazard Analysis/Critical Control Point (HACCP) plans set standards for the hygienic harvest, slaughter, and processing of food animals and animal products. Of course, this does not prevent animal-borne human pathogens from reaching the food supply. But, even when human consumers are exposed to antimicrobial-resistant bacteria, the effect of the drug-resistance is typically inconsequential. General intestinal enteritis caused by *Salmonella*, for example, is rarely treated with antibiotics,[8] leaving little opportunity for a therapeutic failure. And, in other cases where antibiotic treatment is indicated, bacteria that are resistant to one or more antimicrobials remain sensitive to other alternative drugs and may be treated successfully. While not zero, the risk of a treatment failure in human patients arising from the development of antibiotic-resistant pathogens in food animals is quite low.[9]

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[7] 21 CFR 514.1(b)(8).

[8] National Research Council, *The Use of Drugs in Food Animals: Benefits and Risks* (Washington, D.C.: National Academy Press, 1999).

[9] See, for example, S.A. Anderson, R.W. Yeaton Woo, and L.M. Crawford, "Risk assessment of the impact on human health of resistant *Campylobacter jejuni* from fluoroquinolone use in beef cattle," *Food Control*, vol. 12 (2001) pp. 13–25; Randall S. Singer, et al., "Modeling the Relationship Between Food Animal Health and Human Foodborne Illness," *Preventive Veterinary Medicine*, vol. 79 (2007) pp. 186-203; Louis A. Cox, Jr. and Douglas A.

Still, particular concern has been expressed regarding the development of multiple-resistant pathogens arising from sub-therapeutic doses of medically important antimicrobial drugs—the class intended to be protected by Guidance #209. The development of antimicrobial-resistant pathogens, particularly multiple resistant strains, warrants constant monitoring. Although extraordinarily rare, multiple-resistant strains of potentially lethal human pathogens do pose a genuine human health risk. However, we must not lose sight of the fact that use of antibiotics in livestock for treatment, disease prevention, and growth promotion purposes, produces real human health benefits. Unfortunately, when reviewing a new animal antimicrobial drug, or considering the withdrawal of one already on the market, the FDA does not consider the potential health benefits to humans that arise from healthier livestock those products generate.[10] This is a significant flaw in the agency's risk management practices, and one that should be expected to frustrate the FDA's goal of improving overall human health.

The Importance of Risk/Risk Balancing

The FDA surely recognizes that the use of antimicrobial drugs in livestock, even at sub-therapeutic doses, is important for ensuring animal health and that it delivers economic benefits to the meat, milk, and egg production industry. However, any appropriate analysis of the propriety of continued antimicrobial drug use in livestock must also account for the tremendous benefits that human consumers derive from these applications. Consumers benefit from the availability of a broad array of food choices at increasingly affordable prices. But humans also derive health benefits from the presence of safer and healthier livestock animals.

The use of antimicrobials in livestock production for growth promotion purposes enhances the efficiency of nutrient uptake, as the animals devote less energy to fending off intestinal bacteria and parasites and more to building lean muscle. The ability to generate more muscle mass per unit of feed results in reduced feed consumption and reduced fecal output, as well as a shorter time to reach market weight. And an ability to suppress potential pathogens throughout a herd or flock improves overall animal welfare and reduces the variation in the

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Popken, "Quantifying potential human health impacts of animal antibiotic use: enrofloxacin and macrolides in chickens," *Risk Analysis*, vol. 26 (Feb. 2006) pp. 135-46; H. Scott Hurd, et al., "Swine Health Impact on Carcass Contamination and Human Foodborne Risk," *Public Health Reports*, vol. 123 (May-June 2008) pp. 343–351.

[10] See Nancy E. Halpern, "Antibiotics in Food Animals."

slaughter size of the animals. That, in turn, simplifies carcass processing and improves the quality of meat that reaches the market.[11]

In short, using growth-promoting doses of antimicrobial drugs reduces the cost of producing meat, milk, and eggs, and it in turn makes possible increasingly lower food prices for consumers. Less variability in carcass size contributes to food safety by making slaughter more uniform and predictable, reducing the likelihood that the gastrointestinal tract will be disturbed. And, because it permits farmers to produce more food with fewer animals and less feed, it also has significant environmental benefits—including, but not limited to, a need for less land in raising livestock and animal feed crops, and less waste from the animals.[12]

The human benefits are not solely economic, however. The use of antimicrobials in livestock production has proven effective in controlling and reducing the spread of a number of zoonotic diseases, and it is associated with a generalized reduction in health problems in the animals in which they are used.[13] Naturally, this has important benefits for both the treated animals as well as for the humans who handle the live animals and animal carcasses, and for human consumers.[14] Human health concerns surrounding the use of antimicrobial drugs in livestock often focus on the potential for resistant pathogens to impact human health. The FDA itself has acknowledged that its "overriding concern is the decreased or lost effectiveness of antimicrobial drugs in humans as a consequence of human exposure to resistant bacteria through ingestion of animal derived food products."[15] However, it is wholly inappropriate for regulators, or the public health community more broadly, to discount or ignore the human health benefits of disease reduction in livestock populations.

The use of antimicrobial drugs in livestock results in healthier animals with fewer zoonotic infections, which in turn reduces the likelihood that these diseases will spread to humans from animals or animal-derived food products. Recent research indicates that carcasses

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[11] See, generally, Thomas R. Shryock and Stephen W. Page, "Growth Promotion Uses of Antimicrobial Agents," in Steeve Giguère et al., eds., *Antimicrobial Therapy in Veterinary Medicine* 4th ed. (Ames, Ia.: Blackwell Publishing, 2006) pp. 389-415.
[12] Ibid.
[13] National Research Council, *The Use of Drugs in Food Animals*.
[14] Randall S. Singer, et al., "Modeling the Relationship Between Food Animal Health and Human Foodborne Illness," *Preventive Veterinary Medicine*, vol. 79 (2007) pp. 186-203.
[15] FDA, *Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* (October 23, 2003).

from slaughtered animals not treated with antimicrobials are more likely to be contaminated with human pathogenic microorganisms than those from treated animals.[16] Preventing the occurrence of disease in individual animals, and stopping the spread of such diseases throughout herds and flocks once they appear are important for keeping these diseases from affecting human populations. Farmers and slaughterhouse workers who handle animals are better protected, and the meat, milk, and eggs from those animals are made safer and more healthful for consumers. Thus, animal applications of antimicrobial drugs can have important and direct human health benefits even as inevitable pathogenic resistance is developing.

On the other hand, it remains unclear whether further restrictions on antimicrobial use in livestock would even deliver the benefit of reduced resistance. Several other countries have enacted total or partial bans on antimicrobials use for growth promotion purposes, but with little or no benefit. The experience of Denmark is particularly instructive. Denmark began to restrict the use of some antimicrobial drugs in various livestock applications as early as 1995. And, beginning in January 2000, Denmark restricted the use of antimicrobials in all livestock to therapeutic use, by prescription only.[17]

Although it has achieved the intended effect of eliminating use of antimicrobials for growth promotion, the ban has done little or nothing to advance that country's goal of reducing the occurrence of antimicrobial resistant pathogens or improving human health. The use of antimicrobial drugs for growth promotion fell gradually from 1995 to 1999, as did the total use for all purposes. And, between 1996 and 2005, the total use of antimicrobial drugs in livestock declined by approximately 30 percent. However, use of antimicrobials for therapeutic purposes rose 135 percent during that time period.[18] This trend is consistent with the view that use of antimicrobials for growth promotion plays an important role in preventing the occurrence of animal disease and helps to mitigate its spread throughout animal herds and flocks.

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[16] See, for example, Louis A. Cox, Jr. and Douglas A. Popken, "Quantifying potential human health impacts of animal antibiotic use"; H. Scott Hurd, et al., "Swine Health Impact on Carcass Contamination and Human Foodborne Risk."

[17] J.J. Dibner and J.D. Richards, "Antibiotic Growth Promoters in Agriculture: History and Mode of Action," *Poultry Science*, vol. 84 (2005) pp. 634–643.

[18] Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, *DANMAP 2005—Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark* (Søborg, Denmark: Danish Institute for Food and Veterinary Research, July 2006).

Perhaps more importantly, while resistance to some antimicrobials decreased among some pathogens in various livestock animal species between 1997 and 2005, resistance among other pathogens to other antimicrobials in other animals rose. That is, the ban on antimicrobials as growth promoters produced no consistent results. Furthermore, there is little evidence that the occurrence of antimicrobial resistant pathogens in humans declined at all. The occurrence of ciprofloxacin-resistant *E. coli*, *Campylobacter jejuni*, and *Salmonella* Typhimurium in humans rose substantially, as did virginiamycin-resistant, vancomycin-resistant, and tetracycline-resistant *Enterococcus faecium*. And, while ampicillin-resistant *S.* Typhimurium declined in poultry, it rose in swine and in humans.[19]

Denmark's experience is not unique. Similar effects were observed following a comparable ban in the United Kingdom instituted in 1970.[20] And, following the European Union-wide restriction on sub-therapeutic use of antibiotics for livestock growth promotion, this effect was seen across the region. Vancomycin-, quinupristin-, and teicoplanin-resistant enterococci were not commonly found in humans prior to the ban, but their incidence increased dramatically following the ban.[21] "The expected decrease in the incidence of resistant human pathogens did not occur. Instead, prevalence of many resistant human pathogens increased, in some cases up to 49 percent of the pre-ban incidence."[22] And, while no consistent effect has been measured, the increase in use of antimicrobial drugs to treat active infections in livestock is often seen in drug classes that are more important to human medicine.[23]

Thus, European restrictions on antimicrobial use for growth promotion exerted negative economic impacts on the livestock industry, and had no consistent, measurable safety benefits for human consumers. Introducing such restrictions in the United States would likely be similarly detrimental to animal health and livestock producers, while delivering little or no clear human benefits. Instead, the FDA would be wise to permit continued prudent use of

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[19] Ibid.
[20] Louis A. Cox, Jr. and Paolo F. Ricci, "Causal Regulation vs. Political Will: Why Human Zoonotic Infections Increase Despite Precautionary Bans on Animal Antibiotics," *Environmental International*, vol. 34 (2008) pp. 459-475.
[21] Ian Phillips, "Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health," *International Journal of Antimicrobial Agents*, vol. 30 (2007) pp. 101-107.
[22] Nancy E. Halpern, "Antibiotics in Food Animals," p. 417.
[23] Alan G. Mathew, Robin Cissell, and S. Liamthong, "Antibiotic Resistance in Bacteria Associated with Food Animals: A United States Perspective of Livestock Production," *Foodborne Pathogens and Disease*, vol. 4 (2007) pp. 115-133.

antimicrobial drugs in livestock growth promotion and to prevent and control the spread of diseases throughout animal herds and flocks, while taking other steps to prevent the spread of resistant pathogens to humans and to equip the medical community with newer therapeutic options, including new classes of antimicrobial drugs.

Conclusion

Although the FDA and the broader public health community may be tempted to phase out or otherwise restrict the use of important antimicrobial drugs for livestock growth promotion, the experience of European countries in instituting similar restrictions should serve as a clear caution. The effect of antimicrobial resistance on human health is a complex problem that cannot be solved by superficially appealing solutions. Before finalizing this Guidance #209, FDA should undertake a more comprehensive analysis of the potential negative human health effects of the proposed limits on medically important antimicrobial drugs.

In addition, we urge FDA to explore ways to accelerate the development and introduction of new antimicrobial drug classes, and other alternatives for maintaining human and animal health. Among the most important things FDA can do on its own is to streamline the research, development, and approval process for new drugs and drug classes. No matter how judiciously antimicrobial drugs are used, and no matter what restrictions on their use are imposed by the FDA or other regulatory authorities, pathogens will inevitably develop resistance to antimicrobial drugs. Having new therapeutic options will be essential in the coming decades, and a less burdensome regulatory review process for therapeutic innovations would go a long way toward enhancing our ability to deal with pathogenic threats in the coming years.

Respectfully submitted,

Gregory P. Conko
Senior Fellow and
Director of Food and Drug Policy

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