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March 2, 2012

SUBMITTED ELECTRONICALLY

Docket No. FDA-2008-N-0326
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-N-0326; New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition

Dear Sir or Madam:

The National Chicken Council (NCC) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) final rule entitled "New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition," published in the *Federal Register* on January 6, 2012. NCC represents vertically integrated companies that produce and process more than 95 percent of the chicken marketed in the United States. NCC's members will be directly affected by this order.

NCC and our members are committed to providing safe, wholesome, and abundant chicken products while ensuring the health and safety of our members' chicken flocks. As part of that commitment, we believe the latest science and technology should be applied to ensure healthy flocks and efficient operations, all with an eye toward providing the consumer the best, most affordable product possible. To that end, drugs like cephalosporins—when properly administered under appropriate conditions—play an important role in ensuring flock health and chick survival rates. Veterinarians need access to important antibiotics to prevent, control, and treat bacterial infections in flocks as well as to protect the general public health.

Although we recognize FDA's responsibility to ensure drugs are administered to animals in a manner not likely to harm humans, we do not believe the circumstances justify the broad prohibitions the order imposes. Moreover, we impress upon FDA the importance of providing ample opportunity to meaningfully comment on regulatory action stemming from developing policy areas and the importance of developing broad consensus on the appropriateness of such actions.

I. The Tenuous Connections Between Cephalosporin Use and Antimicrobial Resistance Do Not Justify the Broad Prohibition

Without a clearly articulated causation between cephalosporin use in food-producing animals and increased antibacterial resistance, it is inappropriate to prohibit the use of cephalosporin in

food-producing animals. Under its regulations implementing the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), FDA must have "evidence that demonstrates that the use of a drug has caused or likely will cause an adverse event" before prohibiting an extralabel use of the new animal drug. 1/ The agency has failed to meet this burden. FDA presents no evidence demonstrating cephalosporin use in food-producing animals has actually caused the adverse event of antibacterial resistance, nor does the agency establish such an event is likely to occur.

In explaining the mechanism of action for increased antibiotic resistance, the agency's primary concern appears to be inactivation of cephalosporin by β-lactamase enzymes. The agency notes an increased prevalence of CTX-M β-lactamase in Europe, which could result in decreased susceptibility to third-generation cephalosporins, but as the agency notes, this enzyme is less prevalent in the United States. Moreover, despite observing that fourth-generation cephalosporins have proven effective against bacteria producing β-lactamases in *in vitro* studies, the agency points to "some disagreement" as to their effectiveness, based on *E. coli* isolates from two patients that showed decreased susceptibility to fourth-generation cephalosporins. Conditions in other countries with different drug-use policies and isolates from two United States patients do not establish that cephalosporin use is "likely" to cause antibiotic resistance in this country. From these observations, the agency tenuously concludes that antibiotic-resistant infections "may" be treated with ineffective drugs, causing harm to humans. 2/

Similarly, in reviewing the increased prevalence of cephalosporin-resistant bacteria found through monitoring programs, the agency fails to establish that cephalosporin use in food-producing animals is the cause of the increase. Indeed, the agency's data show only a modest increase in the prevalence of bacteria resistant to certain drugs within the cephalosporin class and fail to establish the cause for this increase. Highlighting this uncertainty, in explaining why extralabel use of cephalosporin should be banned in poultry production, the agency noted merely that extralabel use, coupled with automated technology, 3/ "could" result in higher-than approved cephalosporin exposures in animals, thereby increasing human exposure to cephalosporin-resistant bacteria.

Despite FDA's protestations to the contrary, the agency appears to be applying a standard akin to the so-called precautionary principle embraced by European regulators, in which even a slight, tenuous, or not-fully-understood risk can justify significant prescriptive regulation. By contrast, under U.S. law, FDA may not prohibit the extralabel use of a new animal drug unless the agency has evidence demonstrating the use would "likely cause" an adverse event; mere possibilities or unexplained correlations do not meet this standard and thus cannot support prohibitions on extralabel uses.

To properly establish any potential causal connection between cephalosporin use in food-producing animals and antibiotic resistance in bacteria affecting humans, FDA should conduct a detailed risk assessment and scientific study on the effects of cephalosporin use and the impact a ban would have on animal and food safety and the abundance of the nation's food supply. Such

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1/ 21 C.F.R. §§ 530.3(e), 530.21(a)(2).

2/ 77 Fed. Reg. 735, 738 (Jan. 6, 2012).

3/ Although not clear, it appears from the agency's explanation that the hatcheries observed by FDA were not actually using the automated technology of concern to the agency.

an analysis is necessarily crucial for establishing the likelihood that cephalosporin use would lead to the adverse event feared by the agency and to determining the appropriateness of restricting its use.

II. Additional Considerations Overlooked

The agency appears to overlook several practical considerations associated with cephalosporin use. For example, a form of cephalosporin is approved for injection in day-old chicks to control early mortality associated with *E. coli*. 4/ The use in chickens FDA reports observing—injection into the egg rather than the day-old chick—would be an extralabel use primarily because drug manufacturers have not gone to the expense of procuring authorization for that particular use, reflecting the very situation and need for flexible application of animal drugs AMDUCA was designed to address. Moreover, cephalosporin is a critically important antibiotic in certain poultry-raising situations, such as treating acute or chronic fowl cholera in broiler chicken breeders, which, although rare, is not well controlled by older antibiotics.

These considerations underscore the importance of cephalosporin to the industry and the inappropriateness of broadly banning its use based only on supposition and correlations.

III. Meaningful Opportunity to Comment Before Final Agency Action is Essential for Well-Reasoned Regulation of Complex Policy Areas

NCC and its members impress upon FDA the importance of ensuring interested parties are provided adequate time to meaningfully comment on contemplated regulatory action before final decisions are made and regulations issued, especially in areas of emerging or complicated policy. AMDUCA's flexible approach toward drug use in animals provides veterinarians essential tools for caring for their patients. Relatively few drugs have been approved for use in animals, and for many species, no approved drugs are available to treat certain conditions. Because of the sheer variety of species they are called on to treat, veterinarians need as much flexibility in developing treatments as possible, and the agency should ensure it is fully aware of all effects of contemplated regulatory actions.

Flexible use of new animal drugs is also critically important to ensuring the health and safety of food-producing animals. Veterinarians treating food-producing animals face the same dearth of approved drug as do other veterinarians. As production technologies change and new science and best practices emerge, companies and their veterinarians require flexibility to administer antibiotics most effectively to their animals. Efficient antibiotic use ultimately benefits the consumer, who has access to a safer, more abundant, and more affordable food supply.

Because of the complexity of extralabel new animal drug use, the agency should provide advance notice of any contemplated action that would potentially remove a significant drug in wide use in animals. Doing so would ensure the agency is fully informed as to the consequences of its contemplated action as well as provide affected parties time to research and arrange alternative treatments for the animals in their care. In many instances, an agency order with a

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4/ 21 C.F.R. § 522.313c(e)(5).

60-day comment period and 90-day effective date simply provides too little time to ensure comments can have a meaningful impact on agency policy and for companies to arrange alternative treatments.

Conclusion

The agency's order inappropriately prohibits the extralabel use of cephalosporins despite no clear causal link between cephalosporin use in food-producing animals and antibiotic resistance in bacteria in humans. NCC requests FDA withdraw its order and conduct a full risk assessment and more detailed scientific study on the causal connection.

Please do not hesitate to contact us if we may be of further assistance. Thank you for your consideration.

Respectfully submitted,

Michael J. Brown
President