

## PolicyPennings by Daryll E. Ray &amp; Harwood D. Schaffer

## FDA's reasoning behind restricting use of cephalosporins for food-producing animals

The possible role of the veterinary use of antibiotics in the development of antibiotic-resistant strains of pathogens that have the potential to cause serious human illness has generated considerable attention in recent years. Concern has been focused on the low-level prophylactic use of these drugs in animal feed to prevent—as opposed to treat—disease. Also, this low-level use of antibiotics typically results in higher rates of weight gain per unit of feed, resulting in lower production costs for meat animal producers.

Such use of antibiotics has been banned in the European Union and the US Food and Drug Administration (FDA) initiated and then withdrew regulations to ban extralabel use of one antibiotic, cephalosporin, in the waning months of the George W. Bush administration. On January 6, 2012, the FDA reissued those regulations with some modifications—<http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf>. All quoted material in this column comes from this order.

Decisions regarding the use of antibiotics are governed by the Animal Medicinal Drug Use Clarification Act of 1994 and the implementing regulations that were published in the Federal Register on November 7, 1996. Under these regulations the FDA must establish that it “has evidence demonstrating that the use of the drug has caused, or likely will cause, an adverse event.” In reissuing the order, the FDA argues that it “has determined that such extralabel use likely will cause an adverse event and, therefore, presents a risk to the public health.”

In making its case, the FDA describes the “importance of cephalosporins in veterinary and human medicine.” While the FDA discussion of these uses are necessarily technical in nature, cephalosporin is used in the treatment of a wide range of human microbial diseases ranging from pneumonia, to pelvic inflammatory disease, to gastrointestinal tract infections. The FDA points out that “newer cephalosporins are the antibiotics of choice in the treatment of serious *Salmonella* and *Shigella* infections, particularly in children where fluoroquinolones may be avoided due to potential for toxicity.”

The approved use of ceftiofur, a form of cephalosporin, in food-producing animal species include: “(1) The treatment of respiratory disease in cattle, swine, sheep, and goats; (2) the treatment of acute bovine interdigital necrobacillosis (foot rot) and acute bovine metritis; (3) the control of bovine respiratory disease; and (4) the control of early mortality associated with *E. coli* infections in day-old chicks and poults. In

addition, ceftiofur is approved as an intramammary infusion for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae*, and *E. coli*.”

Having described the importance of cephalosporin in the treatment of both human and animal disease, the FDA engages in a discussion of the mechanism involved in the development of cephalosporin resistance that undoubtedly can be understood by pathologists and microbiologists, but goes well over the heads of two agricultural economists. The FDA then provides data that indicate an increase in pathogenic resistance to ceftiofur over time.

While ceftiofur is not used in the treatment of human disease in the US, a closely related antibiotic in the cephalosporin family, ceftriaxone, “is a critically important antimicrobial approved for use in humans.... The prevalence and spread of [an enzyme that confers resistance] is reflected in the surveillance data on ceftriaxone and ceftiofur susceptibility and supports the finding that cephalosporin use in food-producing animals is likely contributing to an increase in cephalosporin-resistant human pathogens.”

The FDA identified extralabel uses of cephalosporin that are of greatest concern.

USDA, Food Safety and Inspection Service (FSIS), data shows a particular problem with culled dairy cows, although problems are also associated with beef cattle and veal calves. Factors involved in the presence of drug residue in cattle “include, but were not limited to, the following: (1) Poor or nonexistent animal treatment records for adequately monitoring treated animals; (2) inadequate animal identification systems for monitoring treated animals; (3) animal owners’ lack of knowledge regarding withdrawal times associated with the animal drug product; (4) the animal drug product was administered by a route not included in the approved labeling; (5) the animal drug product was administered at a dose higher than stated in the approved labeling; and (6) the animal drug product was administered to a type of animal (e.g., veal calves) not listed in the approved labeling.... More than half of the violations involved ceftiofur residue levels more than 10 times the established tolerance level.”

Two strains of *Salmonella* found in dairy cattle “are often multi-drug resistant and appear to be associated with more severe human disease than other [*Salmonella* subtypes]. These infections can lead to treatment failures, greater hospitalization or death rates, and higher costs than infections with susceptible

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strains. Consumption of dairy products, as well as dairy farm contact, represents important risk factors for human *Salmonella* Newport...infection.”

The concern with poultry focuses on “ceftiofur... being administered via egg injection, rather than by the approved method of administering the drug to day-old chicks. The [FDA] is concerned that this extralabel use, particularly when employed in conjunction with automated technology, could result in levels of cephalosporin exposure in food-producing animals that are significantly higher than exposure levels from the approved uses.”

“Other extralabel uses that increase drug exposure... include higher doses and longer durations of administration than approved and extralabel routes of administration that facilitate mass dosing of large numbers of animals, such as through drinking water. A similar concern is the use of a cephalosporin drugs to prevent an extralabel disease or condition, particularly when such use involves entire flocks or herds of animals. FDA believes that exposing large numbers of animals to cephalosporin drugs when such use has been neither evaluated nor approved by FDA presents a risk to the public health.”

The FDA is concerned by “the extralabel use of ceftiofur in a compounded new animal drug product known as Biobullets. According to the manufacturer’s website, Biobullets deliver a solid pellet of ceftiofur sodium...encased in a biodegradable bullet propelled by an air rifle into the muscle of cattle. Such use clearly represents an extralabel use because ceftiofur sodium is only approved for injection in liquid form by hypodermic needle. Since the rate and extent of dissolution and distribution of ceftiofur sodium in solid form delivered as an implant has not been established, the microbiological and toxicological profile of this extralabel use is unknown; thus, the safety of human

food derived from animals treated in this manner is also unknown.”

The last extralabel use the FDA discusses is the administration “of cephalosporin drugs that are only approved for use in humans. The use of these human drug products in food-producing animals presents a risk to public health because, like Biobullets, the microbiological and toxicological profile of this extralabel use is unknown; thus, the safety of human food derived from animals treated with these drugs is also unknown. Also, since none of these drugs are approved for use in food-producing animals, there are no approved labels to guide the use of these drugs regarding, for example, dosing regimen or withdrawal period. FDA has evidence of the extralabel use of human cephalosporins (cephalexin) by veterinarians for the treatment of cattle. This evidence was obtained during inspections of farms and veterinary hospitals by FDA investigators. Furthermore, one of the comments on the [previous] order of prohibition reported that cephalosporin drugs that are either being researched or approved for human use are being administered to food-producing animals, including via drinking water.”

Having established that its action in issuing the regulations are in compliance with existing regulations, the FDA then responds to comments made to the regulations issued under the Bush administration. These responses as well as the FDA’s conclusions will be the subject of the next column.

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