

Comments of Consumers Union on
Food and Drug Administration (FDA)
Final rule on New Animal Drugs; Cephalosporin drugs; Extralabel Animal Drug Use;
Order of Prohibition
Docket Number FDA—2008—N—0326
March 6, 2012

Introduction

In July 2008, the Food and Drug Administration¹ (FDA) proposed a final rule banning *all* extralabel uses of cephalosporin antimicrobial drugs in food-producing animals. In response to comments, primarily by industry, FDA withdrew the rule in late November, 2008.² Now FDA proposes a ban on only some uses of cephalosporins in food-producing animals.

Consumers Union³ (CU) welcomes the opportunity to comment on this final rule. CU supports the ban on certain extralabel uses of cephalosporin antimicrobial drugs in certain food producing animals, and commends the FDA for taking this important needed step in protecting public health from the threat of antimicrobial resistance. Both the FDA⁴ and the World Health Organization⁵ consider cephalosporins to be critically important in human medicine. For the reasons explained below, however, we feel that this rule is only a first step, and that FDA should take further, stronger steps to significantly reduce the growing problem of the spread of antimicrobial resistance among bacteria.

Consumers Union Comments on Final Rule

CU supports the new restrictions on the extralabel use of cephalosporins, and commends the FDA for taking this important needed step in addressing the threat of antimicrobial resistance. For the reasons explained below, however, we feel that FDA should take further steps to significantly reduce the growing problem of the spread of antimicrobial resistance among bacteria. First, FDA should ban all extralabel use of cephalosporin antimicrobial drugs. Second, given the importance of cephalosporins in

¹ <http://www.gpo.gov/fdsys/pkg/FR-2008-07-03/pdf/E8-15052.pdf>

² <http://www.gpo.gov/fdsys/pkg/FR-2008-11-26/pdf/E8-28093.pdf>

³ *Consumers Union is the public policy and advocacy division of Consumer Reports. Consumers Union works for telecommunications reform, health reform, food and product safety, financial reform, and other consumer issues. Consumer Reports is the world's largest independent product-testing organization. Using its more than 50 labs, auto test center, and survey research center, the nonprofit rates thousands of products and services annually. Founded in 1936. Consumer Reports has over 8 million subscribers to its magazine, website, and other publications..*

⁴ FDA, 2003. Guidance for Industry #152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern. Available from: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf>.

⁵ WHO, 2007. Critically Important Antimicrobials for Human Medicine: Categorization for the Development of Risk Management Strategies to contain Antimicrobial Resistance due to Non-Human Antimicrobial Use Report of the Second WHO Expert Meeting Copenhagen, 29–31 May 2007. At: http://www.who.int/foodborne_disease/resistance/antimicrobials_human.pdf

human medicine, FDA should ban all uses of cephalosporins in food producing animals. Third, FDA should ban all non-therapeutic use of antimicrobial drugs.

In the meantime, we urge FDA to use the antimicrobial data from Section 105 of the 2008 Animal Drug User Fee Act (ADUFA) amendments, as well as the data from the National Antimicrobial resistance Monitoring System (NARMS), to monitor the impact of this final rule on the usage of cephalosporin and other antimicrobials.

Should FDA find that the total use of cephalosporins does not decrease, or that total use of antimicrobials increases, then we urge FDA to consider taking further enforcement action against cephalosporins in general (e.g. ban all extralabel usage, or ban all usage), or against non-therapeutic use of antimicrobials in general (e.g. ban non-therapeutic use of all antimicrobials).

Consumers Union Comment on Exemption for Extralabel use of Cephapirin

At present, there only two cephalosporins—a first generation cephalosporin, cephapirin (for treatment of mastitis in cows), and a third-generation cephalosporin, ceftiofur (used for a range of diseases in poultry, cattle, swine, sheep, and/or goats)—allowed for use in food-producing animals. Cephapirin is only approved for mastitis in lactating cows caused by susceptible strains of *Streptococcus agalactiae* and *Staphylococcus aureus*.

FDA's final rule exempts all use of cephapirin from the cephalosporin extralabel use ban. The rationale given is that since there are no cephapirin drug products approved for use in humans and, since cephapirin has a narrow spectrum of activity compared to newer cephalosporins like ceftiofur, it is less likely to cause cross-resistance to drugs in other cephalosporin classes.

We disagree with this position. Although no cephapirin drug products are used in humans, there is another first generation cephalosporin, cephalixin, that is used in human medicine. Specifically, cephalixin can be used to treat *Staphylococcus aureus* in humans. Thus, continued use of cephapirin in an off-label fashion (and for which there are no restrictions) could reduce the effectiveness of cephalixin and other first generation cephalosporins still used in human medicine. Consequently, FDA should also restrict (or ban) the extralabel use of cephapirin.

Consumers Union Comment on Exemption Allowing Certain Cephalosporins Uses

In addition to exempting all uses of cephapirin, FDA's final rule also exempts "extralabel uses to treat or control an extralabel disease indication in food-producing major species when used at a labeled dose, frequency, duration, and a route of administration approved for that species and production class." This exemption will allow ceftiofur to be used for nearly any disease in food-producing major species, but without the requirement that users submit any data to determine whether it would be beneficial to the animal and/or could contribute to the problem of antibiotic resistance.

For example, there is a long-acting form of ceftiofur, trade name Excede, which is available for use in dairy cattle, beef cattle, swine and horses.⁶ Long-acting forms of antibiotics increase the risk of antibiotic resistance, compared to shorter-acting forms.⁷ FDA's own risk assessment for use of Excede in cattle to combat bovine respiratory disease states that, in terms of microbial food safety, "the risk associated with the use of this product is high."⁸ Yet, this long-acting product could be used in extralabel fashion for other bacterial diseases in cattle or swine. These uses could exacerbate the problem of antibiotic resistance.

Further, in addition to long-acting formulations of ceftiofur which could be used in an extralabel fashion, this exemption also allows cephalosporin "use to treat or control an extralabel disease." However, there is no definition of what "control [of] an extralabel disease" means. In addition, this policy bans extralabel use of cephalosporins "for disease prevention purposes" in food-producing major species, yet there is no definition of "disease prevention purposes." We urge FDA to define both "prevention" and "control," to ensure that there is not an overlap in the meaning of the two terms. Without a clear definition, "control" could be construed to mean treating an entire herd or entire flock for a disease that might occur in a single animal or for a disease that is found in nearby flocks or herds, but not in the flock or herd being treated – a use that would defeat the public health protections offered by this final rule.

Consumers Union Comment on Exemption for All Extralabel Uses of Cephalosporins in Food-Producing Minor Species

The final rule allows extralabel use of cephalosporins in food-producing minor species (e.g. goats, sheep, aquaculture, deer, duck, goose, rabbit, bison, elk, etc.), on the basis that these minor species represent very little use of cephalosporins as compared to the use in cattle, poultry and swine. This exemption is also premised on the idea that significantly lower usage of cephalosporins results in much less selection for antimicrobial resistance, and because there is a lack of approved antimicrobials for these minor species. While we do not object to this exemption on its face, FDA should monitor the use of cephalosporins in these minor species in order to ensure that there are no negative public health impacts to antibiotic resistance as a result of this exemption.

⁶ <http://www.excede.com/Excede.aspx?country=US&Species=OO&drug=XT&sec=000>

⁷ Sun, Y, Scruggs DW, Peng Y, Johnson JR and AJ Shukla. 2004. Issues and challenges in developing long-acting veterinary antibiotic formulations. *Advanced Drug Delivery Reviews*, 56(10): 1481-1496. At: <http://www.sciencedirect.com/science/article/pii/S0169409X04000754>

⁸ FDA, 2006. Freedom of information summary, supplemental new animal drug application Nada 141-209, EXCEDE Sterile Suspension (ceftiofur crystalline free acid). At: <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm117768.pdf>

FDA Should Monitor Antimicrobial Usage Data and Data on Antimicrobial Resistance to Determine Impact of Final Rule

FDA indicates that the agency “may further restrict extralabel use of cephalosporin antimicrobial drugs in animal in the future if it has evidence that demonstrates that such use has caused or will likely cause an adverse event.” We therefore urge FDA to closely monitor sales and *use* of cephalosporins to determine the impact of the final rule.

Specifically, we urge FDA to use the antimicrobial data from Section 105 of ADUFA, as well as NARMS data, to answer of the following questions:

- Does the total amount of cephalosporins used decline after implementation of this final rule?
- Does the total amount of other antimicrobials that may be used in place of cephalosporins—such as tetracycline, gentamicin, or beta-lactams—change in any way? If so, how? For example, an FDA investigation found that gentamicin and ceftiofur were both used in extralabel fashion in turkey and broiler hatcheries.⁹ If ceftiofur is no longer used in extralabel fashion in hatcheries (e.g. injected into eggs), could use of gentamicin increase?

If total use of cephalosporins does not decrease, or if total use of antimicrobials increases, then FDA should consider taking further enforcement action against cephalosporins in general (e.g. ban all extralabel usage, or ban all usage), or against non-therapeutic use of antimicrobials in general (e.g. ban non-therapeutic use of all antimicrobials).

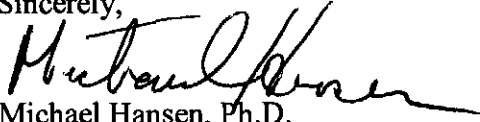
We also urge FDA to use the NARMS data to monitor the impact of this final rule on the resistance of bacterial isolates from food animals, retail meat, and sickened individuals. Given the importance of ceftiofur resistance in *Salmonella* isolates in cattle and poultry (which have increased over time and peaked in 2010 NARMS data) and the fact that ceftiofur use in dairy herds is associated with increased prevalence of ceftriaxone¹⁰ resistance in *E. coli*, FDA should particularly focus on these bacteria/antimicrobial combinations. If ceftiofur resistance in *Salmonella* isolates from cattle and poultry does not decline, or if ceftriaxone resistance in *E. coli* isolates from dairy cattle does not decline, FDA should consider taking further enforcement action against cephalosporins in general (e.g. ban all extralabel usage, or ban all usage), or against non-therapeutic use of antimicrobials in general (e.g. ban non-therapeutic use of all antimicrobials).

⁹ FDA, 2002. Summary of Data from Hatchery Inspections Conducted September –October 2001, April 15, 2002.

¹⁰ Ceftriaxone is an important cephalosporin used in human medicine.

Finally, we strongly urge FDA to publish a plan to monitor the impact of this final rule and to describe the concrete steps that will be taken in case the rule fails to address the risk to public health, e.g. if cephalosporin use does not decline and/or resistance to ceftiofur does not decline in *Salmonella*, and/or ceftriaxone resistance in *E. coli* isolates from dairy cattle do not decline. Those extra steps should include further restrictions on cephalosporins (ban all extralabel use, consider banning all use) or on antimicrobials (e.g. ban non-therapeutic use).

Sincerely,

A handwritten signature in black ink, appearing to read "Michael Hansen". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Michael Hansen, Ph.D.
Senior Scientist