March 6, 2012

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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

The Center for Science in the Public Interest (“CSPI”)\(^1\) appreciates the opportunity to comment on the Food and Drug Administration’s (“FDA”) Final Rule regarding extralabel uses of cephalosporin antimicrobial drugs in certain food-producing animals. CSPI supports the ban, and encourages the agency to increase its efforts to limit the use of important antibiotics in animal production.

Cephalosporin antibiotics are critically important for human medicine. In 2007, the World Health Organization prioritized cephalosporins—along with quinolones and macrolides—as the classes of drugs for which comprehensive risk management strategies are needed most urgently.\(^2\) This prioritization indicates the gravity of the risk posed by antibiotic resistance to cephalosporins: “These drugs [are] one of sole or few therapies of serious disease in humans and used to treat diseases caused by organisms that may be transmitted or acquire resistance genes from non-human sources. In addition, these drugs are used widely and the absolute numbers of people affected by the diseases for which they are the sole therapies are relatively common. These drugs also are used to treat diseases due to organisms where there is the greatest degree of confidence of a non-human source of bacteria or genes.”\(^3\) Cephalosporins in particular serve a crucial role for the treatment of disease in children, and are among the major drug treatments for a large number of childhood infections and foodborne infections, including those related to *Salmonella*.

Antibiotic resistance is an issue of serious concern for consumers. Because fewer antibiotics are being developed, it is critical that those antibiotics most important to human medicine retain their effectiveness. Inappropriate use of antibiotics in animal agriculture allows pathogens to develop resistance over time, thereby weakening the effectiveness of antibiotics later used to prevent disease.

\(^1\) The Center for Science in the Public Interest is a nonprofit health advocacy and education organization focused on food safety, nutrition, and alcohol issues. CSPI is supported principally by the 850,000 subscribers to its *Nutrition Action HealthLetter* and by foundation grants. We accept no government or industry funding.


\(^3\) Id. at 27.
treat human disease. CSPI has been tracking foodborne illness outbreaks in which the implicated pathogens showed resistance to antibiotics. Prior to 2001, there were no outbreaks with pathogens that displayed resistance to drugs in the cephalosporin class. Since 2001, seven Salmonella outbreaks were caused by pathogens with resistance to cephalosporins, resulting in 231 illnesses, 71 hospitalizations, and one death. This data indicates that antibiotic-resistant outbreaks linked to cephalosporins appear to be increasing, and supports FDA’s action to limit their extralabel use.

The rule on prudent use of cephalosporin drugs in cattle, swine, chickens, and turkeys—while narrowly crafted—is a step forward in the process of arresting antibiotic overuse and the attendant concerns of antibiotic resistance. CSPI agrees that FDA has identified many common routes of overuse of cephalosporins in its ban, and has targeted these extralabel uses fairly and efficiently. These include:

- Using cephalosporin drugs at unapproved dose levels, frequencies, durations, or routes of administration;
- Using cephalosporin drugs in cattle, swine, chickens, or turkeys that are not approved for use in that species (e.g. cephalosporins intended for humans or companion animals); and
- Using cephalosporin drugs for disease prevention.

However, CSPI has identified some additional areas of concern for the agency to consider as well. First, there are still a number of extralabel uses of cephalosporins—and a large number of approved uses—allowed and in frequent use by food producers. Until those uses are curtailed, there will likely not be a dramatic decrease in the rates of cephalosporin-related resistance outbreaks. Similarly, the rule’s narrow drafting ensures that, for now, the large number of other antimicrobials used in food animal production will likely continue to contribute to antibiotic resistance. CSPI, in collaboration with other consumer and medical groups, has called on FDA to limit the use of critically important antibiotics in animal agriculture. A 1999 petition filed by CSPI, the Union of Concerned Scientists, Environmental Defense Fund, Food Animal Concerns Trust, and Public Citizen’s Health Research Group specifically asked the agency to withdraw approval for sub-therapeutic uses of medically important antibiotics in animal feed. Although that petition was recently denied, CSPI hopes that the agency views this cephalosporin rule as a beginning step, and still intends to use its authority to implement stricter standards for the judicious use of antibiotics in animal agriculture.

CSPI also notes that the agency may find it difficult to effectively enforce the rule as drafted, particularly the ban on extralabel use for disease prevention, because of a lack of funding for oversight of veterinary prescription practices.

To address these concerns, CSPI urges FDA to develop and publish a plan for monitoring the impact of the rule and describe next steps in the case that the rule fails to address the identified risk to public health. Specifically, CSPI recommends that FDA set goals for the reduction in cephalosporin use, and for the reduction of cephalosporin resistance in isolates from food animals, retail meat, and consumers. As part of the monitoring plan, FDA should monitor cephalosporin use

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in dairy cattle and in poultry as these are identified as “extralabel uses of greatest concern” in the final rule. Specifically, dairies should be monitored both by surveys of antibiotic use and through residue monitoring. Given the relatively small number of domestic hatcheries FDA should investigate antimicrobial use in these directly as it did in 2001.

Overall cephalosporin use can be monitored through the drug distribution data reporting required under the 2008 Animal Drug User Fees Act (ADUFA) reauthorization. The chart below is data reported by sponsors of antimicrobial drugs under ADUFA, and illustrates changes in cephalosporin use and in other antimicrobials. That data clearly illustrates that while cephalosporin use appears to be decreasing, other important classes of antimicrobials are either remaining steady or increasing in use.

<table>
<thead>
<tr>
<th>Table 1. Antimicrobial Drugs Approved for Domestic Use in Food-Producing Animals* 2009-2010.</th>
<th>2009 Annual Totals (KG)</th>
<th>2010 Annual Totals (KG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>339,678</td>
<td>200,794</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>41,328</td>
<td>24,588</td>
</tr>
<tr>
<td>Ionophores</td>
<td>3,740,627</td>
<td>3,821,138</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>115,837</td>
<td>154,653</td>
</tr>
<tr>
<td>Macrolides</td>
<td>861,985</td>
<td>553,229</td>
</tr>
<tr>
<td>Penicillins</td>
<td>610,514</td>
<td>870,948</td>
</tr>
<tr>
<td>Sulfas</td>
<td>517,873</td>
<td>506,218</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>4,611,892</td>
<td>5,592,123</td>
</tr>
<tr>
<td>Not Independently Reported (NIR)**</td>
<td>2,227,366</td>
<td>1,517,447</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13,067,100</strong></td>
<td><strong>13,241,138</strong></td>
</tr>
</tbody>
</table>

* For all classes except aminoglycosides and ionophores, includes antimicrobial drug products which are approved and labeled for use in both food- and nonfood-producing animals, such as dogs and horses.

**NIR is used for antimicrobial classes with fewer than three sponsors actively marketing products. Includes Aminocoumarins, Amphenicols, Diaminopyrimidines, Fluoroquinolones, Glycolipids, Pleuromutilins, Polypeptides, Quinoxalines, Streptogramins

 Having identified an unacceptable public health risk from the spread of cephalosporin resistant foodborne pathogens that occurs due to the use of antibiotics in food animals, FDA must commit to monitoring the impact of the rule and to taking additional steps as needed to protect public health. Those steps could include a complete extralabel ban on cephalosporin use, and the withdrawal of some or all cephalosporin approvals for use in food producing animals.

To ensure that the rule is as effective as possible, CSPI urges the agency to make clear in its final rule the difference between “control” and “prevention” of disease. As currently drafted, the
proposed rule fails to adequately clarify between the two. It is critical that FDA clearly define these terms, as their definition goes to the heart of the extralabel use restrictions intended to stem the tide of injudicious use of cephalosporins.

FDA’s action on cephalosporins is a welcome and important advance against drug resistance, and CSPI applauds the agency for its action. At the same time, we note that the agency has a responsibility to act more broadly on this issue. Consumers rely on many of the same antibiotics that are imprudently applied in animal agriculture, and FDA must act on the public’s behalf to preserve the effectiveness of these drugs. We urge FDA to continue taking steps forward on this critical public health issue.

Sincerely,

Sarah Klein
Staff Attorney
Food Safety Department