

**Testimony
Before the Food & Drug Administration's
Veterinary Medicine Advisory Committee
On an Application for Cefquinome**

**Susan Prolman, Esq.
The Union of Concerned Scientists
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Thank you for this opportunity to provide comments on behalf of the Union of Concerned Scientists (UCS) to the Food and Drug Administration's (FDA) Veterinary Medicine Advisory Committee (VMAC) on "Cefquinome formulations for parenteral injection for the treatment of bovine respiratory disease, Risk estimation under FDA/CVM Guidance #152, March 31, 2006" (Risk Estimation). This document, prepared by the Center for Veterinary Medicine (CVM), summarizes the risk estimate conducted by Intervet, the sponsor of an application to have cefquinome, a fourth-generation cephalosporin, approved for use in cattle.

UCS is the leading science-based nonprofit working for a healthy environment and a safer world. UCS combines independent scientific research and citizen action to develop innovative, practical solutions and secure responsible changes in government policy, corporate practices, and consumer choices. Among our other objectives, we seek to ensure that food is produced in a safe and sustainable manner.

This is a precedent-setting application. As evidenced by the interest of the medical community in this application, fourth-generation cephalosporins are drugs of vital importance to human medicine. If approved, cefquinome would be the first fourth-generation cephalosporin approved for use in animal agriculture in the United States. Widespread use of this important drug in animals could undercut the efficacy of the fourth-generation cephalosporins and related drugs and lead to more severe and more expensive diseases in U.S. hospitals and clinics. In an era of rampant loss of drug efficacy due to resistance, CVM and the FDA should think hard before taking such a step. For this reason, UCS applauds CVM for convening VMAC to consider the important issues raised by these formulations.

UCS also commends the agency for continuing to approach these approvals in the context of CVM's Guidance for Industry #152 (Guidance 152). We strongly support the agency for using this scientific framework to assess potential for harm from resistance resulting from the veterinary use of antibiotics, although we see opportunities to update and improve Guidance 152 as explained below.

It is important that reviews under Guidance 152 be conducted in a transparent manner with meaningful participation from the medical and public health communities. We

appreciate this opportunity to comment and we trust that today's public comments as well as the views expressed by the committee will be reflected in the FDA's final determination.

Overall it is our view that fourth-generation cephalosporins should not be approved for the treatment of bovine respiratory disease in cattle. We fully support the approval of veterinary antibiotics to treat sick animals. However, we are cautious regarding drugs that will be used prophylactically to treat large numbers of animals, as we expect will be the case with these formulations. We believe that a proper analysis of the use under Guidance 152 as discussed below in the response to the FDA's questions supports our position.

We recommend that VMAC reject the sponsor's analysis and ask CVM for further analysis in line with the comments below.

Question 1.

Do the findings presented in the sponsor's (qualitative risk) assessment demonstrate that cefquinome is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans?

Answer: No.

The basic question before the committee is whether the cefquinome formulations at issue in this approval are safe with respect to their potential for transferring antimicrobial-resistant organisms to humans. The answer to that question depends on the proper analysis of the resistance under Guidance 152.

The Risk Estimation failed to adequately assess the following two critical pieces of information.

First, the European experience:

Data from Europe where fourth-generation cephalosporins are used in animal agriculture show that resistance to fourth-generation cephalosporins is on the increase, while resistance in the United States, where the drugs are not used, is uncommon. The European experience is a red flag for the United States and must be included in the risk assessment.

Second, the cross-resistance of third and fourth-generation cephalosporins:

The use of fourth-generation cephalosporins could select for traits (extended spectrum betalactamases) that will not only confer resistance to the fourth-generation drugs, but also cross-select for the third-generation cephalosporins. This fact affects the consequence assessment of fourth-generation cephalosporins because the third-generation cephalosporins are considered "critically important" by the FDA.

The FDA's standard for safety is reasonable certainty of no harm. Unless both of these lines of evidence are satisfactorily addressed in the assessment, the sponsors cannot meet the burden of demonstrating that resistance is reasonably certain not to develop.

Question 2.

Are there other issues to consider relative to this class of antimicrobial agents (4th generation cephalosporins)?

Other species for which it should/should not be approved?

Routes of administration that are/are not acceptable?

Indications that are/are not appropriate?

Other relevant issues?

Answer: Yes.

Other issues relative to this class of antimicrobial agents:

Guidance 152 sets forth a framework for the qualitative assessment of the harm of resistance that assess three elements—release, exposure, and consequence. The result of the assessment leads to estimations of risk and recommendations for the management of the risks.

UCS believes that the FDA should update the categorization of drugs used in its consequence assessment to reflect the current state of knowledge. Especially in the field of antibiotic resistance, CVM should have a mechanism for reassessing the importance of antibiotics to human medicine over time.

Guidance 152 currently lists fourth-generation cephalosporins as “highly important drugs,” one level below “critically important drugs.” The categorization is based on years-old information that new developments suggest are outdated. For example, the World Health Organization’s (WHO) 2005 analysis, “Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-Human Use,” rates fourth-generation cephalosporins as “critically important.”

In addition to the WHO analysis, new information has arisen indicating that fourth-generation cephalosporins are used to treat a wider class of diseases than were taken into account in the Guidance 152 classification. In particular, the public health community now views urinary tract infections as food-borne illnesses. *See* Ramchandani, M., Manges, A.R., DebRoy, C., Smith, S.P., Johnson, J.R., and Riley, L.W., *Possible animal origin of human-associated, multidrug-resistant, uropathogenic Escherichia coli*, CLINICAL INFECTIOUS DISEASES, Vol. 40, 251–257 (2005). Indeed, the sponsor acknowledges that a fourth-generation cephalosporin, Cefepime (Maxipime®), is used, inter alia, to treat urinary tract infections in humans. *See* Risk Estimation at 12. The fact that scientists have linked urinary tract infections in humans to cattle-based food-borne *E. coli* calls into question the claim made in the sponsor’s Risk Estimation (at12) that Cefepime “is not indicated for the treatment of food-borne pathogens.” All *E. coli* infections, including urinary tract infections, septicemia, and meningitis, are potentially food-borne. Moreover, the sponsor acknowledges that this drug is used to treat intra-abdominal infections. *See id.* The broader spectrum of diseases treated by fourth-generation cephalosporins argues for their greater importance in medicine and supports the argument that they should be categorized as “critically important.”

UCS asks VMAC to recommend that the FDA update Guidance 152 in light of these new developments and to defer consideration of this application of cefquinome formulations until that reconsideration is complete. In our view, the evidence strongly supports considering fourth cephalosporins as “critically important drugs.”

On the exposure component of the assessment, UCS questions the sponsor’s contention that its formulations of cefquinome are intended to be used in individual animals only. We believe VMAC and CVM should consider this proposed use, which can be expected to involve routine injection of possibly millions of cattle, to be a herd-wide use, not an individual use. In any case, VMAC should not proceed with this application until it has from the sponsor reliable information on the number of cattle each year that will receive an injection of each of these formulations.

If VMAC proceeds with this application, it should ask CVM to take concrete steps to ensure that the drug will be used *only for therapy, not for prevention* of respiratory diseases in cattle. The respiratory diseases at issue are endemic due to the conditions in which the cattle are transported, housed, and fed. The drug could be used for prophylactic, compensatory purposes in millions of animals. UCS recommends that if the FDA chooses to approve this drug, the approval should be limited to the treatment of animals diagnosed with the disease and others at imminent risk of contracting the disease. In no case should approval extend to routine use to prevent disease.

Other species for which it should/should not be approved:

If the application is approved, it should be restricted to narrowly delineated treatment of bovine respiratory disease only in beef cattle. VMAC should recommend that these drugs never be used in dairy cattle, poultry, swine, aquatic species, or any other species of “food” animal.

Without control of extralabel use, these necessary restrictions will be easily evaded. Therefore, VMAC should recommend that if the drugs are approved, there should be strong prohibitions on extra-label use.

Routes of administration that are/are not acceptable:

VMAC should recommend that CVM ensure that fourth-generation cephalosporins are never used orally and that the drug only be delivered by injection.

Other relevant issues:

UCS believes that approval of these formulations are not needed for two reasons: 1) other drugs can address bovine respiratory disease associated with shipping; and 2) shipping fever in cattle is widespread because of poor management practices that should be addressed before resorting to drugs. To protect the public health, the federal government should look not only at alternative drugs, but also at options for disease prevention, including improving the conditions in which the animals are raised and transported in order to lower the rates of respiratory diseases. It is incumbent upon the federal government to thoughtfully examine why rates of bovine respiratory disease are so high

and what preventative measures can be taken to reduce the rates of disease and the huge reliance on pharmaceuticals to prevent deaths at concentrated feeding facilities.

Question 3.

Are the risk management recommendations appropriate, or should they be modified?

Answer: No.

As indicated above, UCS opposes the approval of these drugs.

If however, CVM does approve the drug, the risk management recommendations in the Risk Estimation are inadequate and should be modified.

The sponsor contends that that “no extra-label use limitations or other measures are appropriate for cefquinome, because fourth-generation cephalosporins are not critically important and the extent of use projected in low.” As discussed above, UCS believes that fourth-generation cephalosporins are critically important drugs and that the cefquinome formulations would likely be administered to millions of feedlot cattle in the United States. Such widespread use should be the uppermost limit of the exposure of food animals and the bacteria they host to these critical drugs. All extra-label uses should be prohibited. In addition, the formulations should be administered by prescription (as the sponsor suggests). The drugs should be administered only to individual animals and not to whole truck-loads, herds, pens, or other groups of animals.

Moreover, if the application is approved, it will be essential to monitor microbial populations for the evolution of resistance. This will require increased surveillance through the National Antimicrobial Resistance Monitoring System (NARMS) program. At present, NARMS does not test for resistance to fourth-generation cephalosporins in the human population and as a result of budget cuts does not have resources available to take on monitoring resistance to fourth-generation cephalosporins. If the FDA moves forward with this application, UCS urges the VMAC to recommend that significantly increased NARMS funding be a prerequisite to FDA approval for use of these cefquinome formulations or any fourth-generation cephalosporin use in animal agriculture. Unless the funding can be found to monitor for resistance, the application should be denied.

Interpreting the results of monitoring requires contemporaneous information on drug use. Requirements for detailed, timely drug use reporting should accompany FDA approval for use of these cefquinome formulations or any fourth-generation cephalosporins used in animal agriculture. Without reliable, meaningful data on the quantity of use, the purpose for the use, and the type, number, and location of animals treated, it will be exceedingly difficult to interpret fluctuations in rates of resistance. UCS recommends that all such information be made available to the public at the same time as it is shared with the FDA.

CVM Should Extend Guidance 152 Reviews to Antibiotics Currently on the Market.

UCS would like to take this opportunity to make a general point about the regulation of antibiotics used in animal agriculture. While UCS understands and agrees that applications for *new* approvals of antibiotics in animal agriculture raise important issues of antibiotic resistance, such applications represent small quantities of use compared to already approved uses. Currently millions of pounds of antibiotic drugs in classes used in human medicine are being used in animal agriculture, most often for growth promotion and routine disease prevention. The risk associated with this massive, ongoing use constitutes a public health crisis that should be addressed immediately. We urge the FDA to set a timetable for reviewing the antibiotics used in animal agriculture for other than therapeutic reasons.

Finally, we reiterate our plea for comprehensive, government-collected antimicrobial use data on which to base public health decisions, including risk estimates like those discussed here today. Such estimates would be more accurate and reliable if based upon solid use data. With such data it would be possible to detect and respond to the emergence of resistant strains. At this juncture, UCS renews its call for the federal government to establish a meaningful system to collect, compile and as appropriate make available to the public data on the use of antimicrobial drugs in the United States.

Thank you for your thoughtful consideration of UCS's comments.