

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 530

[Docket No. FDA-2008-N-0326]

DDM

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Certifier A. Corbin

**New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use;
Order of Prohibition**

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order prohibiting the extralabel use of cephalosporin antimicrobial drugs in food-producing animals. We are issuing this order based on evidence that extralabel use of these drugs in food-producing animals will likely cause an adverse event in humans and, as such, presents a risk to the public health.

DATES: This rule becomes effective [*insert date 90 days after date of publication in the Federal Register*]. Submit written or electronic comments on this document by [*insert date 60 days after date of publication in the Federal Register*].

ADDRESSES: You may submit comments, identified by [Docket No. FDA-2008-N-0326], by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]:

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

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number(s), found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Neal Bataller, Center for Veterinary Medicine (HFV–230), Food and Drug Administration, 7519 Standish Pl., Rockville, MD, 20855, 240–276–9200, e-mail: neal.bataller@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

A. AMDUCA

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Public Law 103–396) was signed into law on October 22, 1994. It amended the Federal Food, Drug, and Cosmetic Act (the act) to permit licensed veterinarians to prescribe extralabel uses of approved animal and human drugs in animals. In the **Federal Register** of November 7, 1996 (61 FR 57732), we published the implementing regulations (codified at part 530 (21 CFR part 530)) for AMDUCA. The sections regarding prohibition of extralabel use of drugs in animals are §§ 530.21, 530.25, and 530.30. These sections describe the basis for issuing an order prohibiting an extralabel drug use in animals and the procedure to be followed in issuing an order of prohibition.

We may issue a prohibition order if we find that extralabel use of a drug in animals presents a risk to the public health. Under § 530.3(e), this means that we have evidence demonstrating that the use of the drug has caused, or likely will cause an adverse event.

Section 530.25 provides for a public comment period of not less than 60 days. It also provides that the order of prohibition become effective 90 days after the date of publication, unless we revoke or modify the order, or extend the period of public comment. The list of drugs prohibited from extralabel use is found in § 530.41.

B. Cephalosporins

Cephalosporins are members of the β -lactam class of antimicrobials. These antimicrobials work by targeting synthesis of the bacterial cell wall, resulting in increased permeability and eventual hydrolysis of the cell. Members of the

cephalosporin class have a β -lactam ring fused to a sulfur-containing ring-expanded system (Ref. 1).

Certain cephalosporins are currently approved for use in a number of animal species. These approved uses include the treatment of respiratory disease in cattle, swine, sheep, and goats, as well as acute bovine interdigital necrobacillosis, acute metritis, and clinical and sub-clinical mastitis in cattle. They are also approved for the control of bovine respiratory disease, and the control of early mortality associated with *Escherichia coli* infections in day-old chicks and poults. Furthermore, approved animal uses of cephalosporins include the treatment of skin and soft tissue infections in dogs and cats, genitourinary tract infections (cystitis) in dogs, and respiratory tract infections in horses.

Cephalosporins are also some of the most widely used antimicrobial agents in human medicine. Older agents are widely used as therapy for skin and soft tissue infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, as well as treatment of upper respiratory tract infections, intra-abdominal infections, pelvic inflammatory disease, and diabetic foot infections. Newer cephalosporins, with or without aminoglycosides, have been considered drugs of choice for serious infections caused by *Klebsiella*, *Enterobacter*, *Proteus*, *Providencia*, *Serratia*, and *Haemophilus* spp. These cephalosporins are also used to treat systemic salmonellosis, although not specifically approved for this purpose. Fourth generation cephalosporins are indicated for treatment of urinary tract infections, febrile neutropenia, intra-abdominal infections, pneumonia, and skin and skin structure infections (Ref. 2).

FDA is concerned that the extralabel use of cephalosporins in food-producing animals is likely to lead to the emergence of cephalosporin-resistant strains of foodborne bacterial pathogens. If these drug-resistant bacterial strains infect humans, it is likely that cephalosporins will no longer be effective for treating disease in those people. Therefore, FDA is issuing an order prohibiting the extralabel use of cephalosporins because, as discussed in section II of this document, the agency has determined that such extralabel use will likely cause an adverse event and as such presents a risk to the public health.

II. Basis for Prohibiting the Extralabel Use of Cephalosporins

A. Cephalosporin-Resistant Zoonotic Foodborne Bacteria

A recent review of β -lactam resistance in bacteria of animal origin states that an emerging issue of concern is the increase in reports of broad-spectrum β -lactamases (CMY-2 and CTX-M) (Ref. 3). Acquired resistance to β -lactams in animal isolates has been observed in surveillance programs such as the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP), and the U.S. National Antimicrobial Resistance Monitoring System (NARMS).

The 2005 European Antimicrobial Resistance Surveillance System (EARSS) report indicated that most European countries reported less than 5 percent resistance to third generation cephalosporins in foodborne pathogens including *Enterococcus faecalis*, *E. faecium*, and *E. coli*. However, the report noted that resistance was rising in 23 of 28 countries, with significant trends identified for 15 countries. The EARSS report states that third generation cephalosporin resistance appears to be increasing rapidly, even in countries with formerly very low levels of resistance (Ref. 4).

Ceftiofur is a third generation cephalosporin approved for certain uses in animals. Since 1997, the NARMS program has monitored ceftiofur resistance in *Salmonella* isolated from food-producing animals at slaughter. In 1997, no isolates from cattle or swine were resistant to ceftiofur, while ceftiofur resistance among isolates from chickens and turkeys was 0.5 percent and 3.7 percent, respectively. By 2006, the prevalence of ceftiofur resistance among *Salmonella* slaughter isolates increased to 18.8 percent for cattle, 2.0 percent for swine, 12.8 percent for chickens, and 5.3 percent for turkeys (Ref. 5).

Food-producing animals have been shown to be a source of resistant *Salmonella* infections in humans (Ref. 6). Data collected as part of NARMS have shown an increase in multi-drug resistance among *Salmonella* isolates from humans, including resistance to third generation cephalosporins. The prevalence of ceftiofur resistance among non-Typhi *Salmonella* isolates from humans rose from 0.2 percent in 1996 to 3.4 percent in 2004. A similar trend was observed over this same period (i.e., 1996 to 2004) for decreased susceptibility to ceftriaxone, a third generation cephalosporin approved for use in humans (Ref. 7).

Although ceftiofur is not used in human medicine, the observed trend of increasing resistance to this drug in human isolates highlights concerns about the movement of foodborne bacterial pathogens between animals and humans. In particular, as discussed in more detail in this document, resistance to certain cephalosporins is of public health concern in light of the evidence of cross-resistance among drugs in the cephalosporin class. Expanded-spectrum cephalosporins (e.g., ceftriaxone and cefotaxime) are the antimicrobial agents of choice for invasive *Salmonella* infections of pediatric patients (Ref. 8). FDA believes that the surveillance data cited supports the finding that certain

cephalosporin use in animals is likely contributing to an increase in cephalosporin-resistant human pathogens.

B. Scope of Order of Prohibition

The cephalosporins are one of the most diverse classes of antimicrobials, and have been subject to several different classification schemes, including those using chemical structure, microbial activity, pharmacokinetics, or marketing date to divide the various molecular entities into distinct groups. While there is considerable overlap among proposed schemes, individual cephalosporin drugs do not always fall into the same groups in all classifications. For example, a commonly used scheme that classifies cephalosporins into “generations” provides some general idea of the first marketing date for the various cephalosporins. However, classification by generation does not necessarily group together cephalosporins with similar microbiological or pharmacokinetic characteristics. Therefore, because classification into “generations” is not based on specific properties of individual cephalosporins, there can be disagreement on which drugs belong in which generation.

FDA considered the possibility of limiting the order of prohibition to certain individual cephalosporin drugs or to certain generations of cephalosporins. However, given the potential for confusion regarding the classification of individual cephalosporin drugs into various generations, FDA concluded that it would be problematic to define the scope of the prohibition based on cephalosporin “generation.” Furthermore, as discussed in more detail in this document, data regarding mechanisms by which bacteria become resistant to cephalosporins have demonstrated cross-resistance among various

individual cephalosporin drugs and among various generations of cephalosporin drugs.

In general, there are three mechanisms by which bacteria become resistant to antimicrobial agents: (1) Alteration of the antimicrobial target, (2) efflux of the antimicrobial or changes in permeability of the bacterial cell, and (3) inactivation of the antimicrobial agent itself. Gram negative bacterial resistance to cephalosporins occurs mainly through inactivation of the cephalosporin by β -lactamases. These enzymes can be both innate and acquired (Ref. 9).

Among bacteria of human health concern, the two most important classes of β -lactamase enzymes are the AmpC cephalosporinases and the extended-spectrum β -lactamases (ESBL). AmpC enzymes are found on the chromosome of most *Enterobacteriaceae*, and are also currently found on promiscuous plasmids in *Salmonella* and *E. coli*. These enzymes provide resistance to first, second, and third generation cephalosporins. “Fourth generation” cephalosporins are active in vitro against AmpC producing bacteria, but there is some disagreement as to the clinical significance of that activity. The AmpC enzymes are currently the predominant β -lactamases associated with *Salmonella* collected from animals and humans in the United States displaying resistance to ceftiofur and decreased susceptibility to ceftriaxone (Ref. 3).

ESBLs present in bacteria of human health concern include members of the TEM, SHV, and CTX-M families. These enzymes are plasmid mediated and have the potential to provide resistance to all cephalosporins. Different ESBLs hydrolyze different cephalosporins at different efficiencies and rates, thus leading to varying patterns of in vitro susceptibility. However, although a particular ESBL may not raise the minimum inhibitory concentration (MIC) for a given cephalosporin to a level above the breakpoint for resistance, these

strains commonly prove to be resistant in vivo (Ref. 9). Therefore, there are specific guidelines for screening bacterial isolates for the presence of ESBLs when MIC's fall in the susceptible range. Any bacterial isolate which produces either an AmpC enzyme or an ESBL is reported to clinicians as resistant to all cephalosporins even though susceptibility testing may show in vitro susceptibility to some of the cephalosporins (Ref. 10). Thus, regardless of in vitro susceptibility results, the effect of resistance mediated by an AmpC enzyme or ESBL is that the organism is treated as if it is cross-resistant to all cephalosporins.

In a review of the CTX-M family of ESBLs, Livermore et al. (Ref. 11) noted that until the late 1990s, European surveys found the TEM and SHV families of ESBLs almost exclusively. CTX-M enzymes were recorded rarely, although large outbreaks of *Salmonella Typhimurium* with CTX-M-4 and CTX-M-5 were reported in Latvia, Russia, and Belarus in the mid 1990s. However, CTX-M enzymes are now the predominant ESBLs in many European countries, and *E. coli* has joined *Klebsiella pneumoniae* as a major host. CTX-M enzymes are supplanting TEM and SHV in East Asia as well as in Europe. Only in North America do TEM and SHV still predominate, although CTX-M enzymes have been occasionally detected. Once mobilized, CTX-M enzymes can be hosted by many different genetic elements, but are most often found on large multi-drug resistance plasmids. Therefore, FDA is concerned that if CTM-X becomes prevalent in the United States, as has occurred in other countries, cephalosporin resistance may escalate.

Given that β -lactamases have been identified in zoonotic bacteria of human health concern, and given that β -lactamases can impart cross-resistance among

cephalosporins (Ref. 12), FDA concluded that measures to prohibit extralabel use should be directed at the entire cephalosporin class of drugs.

C. Extralabel Use of Cephalosporins in Animals

As summarized previously, certain cephalosporins are currently approved for use in a number of animal species for a variety of indications. However, under the provisions of AMDUCA, cephalosporins that are approved for use in animals or humans may be used in an extralabel manner in animals provided certain conditions are met. Although few data are available regarding the extent to which such extralabel use currently occurs in the various food-producing animal species, evidence exists that extralabel use is occurring. FDA conducted inspections at U.S. poultry hatcheries in 2001 and examined records relating to the hatcheries' antimicrobial use during the 30-day period prior to inspection. FDA found that six of the eight hatcheries inspected that used ceftiofur during that period were doing so in an extralabel manner (Ref. 13). For example, ceftiofur was being administered at unapproved dosing levels or by unapproved methods of administration. In particular, ceftiofur was being administered by egg injection, rather than by the approved method of administering the drug to day-old chicks.

As is recognized for the use of antimicrobial drugs in general, the use of cephalosporins provides selection pressure that favors expansion of resistant variants. FDA believes the extralabel use of cephalosporins likely will contribute to the emergence of resistance and compromise human therapy. Given the importance of the cephalosporin class of drugs for treating disease in humans, FDA believes that preserving the effectiveness of such drugs is critical. Therefore, FDA believes it is necessary to take action to limit the extent

to which extralabel use of cephalosporin in animals may be contributing to the emergence of resistant variants.

FDA is particularly concerned about the extralabel use of cephalosporins in food-producing animals given that such animals are known reservoirs of foodborne bacterial pathogens such as *Salmonella*. Based on information regarding cephalosporin resistance as discussed previously, FDA believes it is likely that the extralabel use of cephalosporins in food-producing animals is contributing to the emergence of cephalosporin-resistant zoonotic foodborne bacteria. Therefore, FDA has determined that such extralabel use likely will cause an adverse event and, as such, presents a risk to the public health.

III. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA only through FDMS at <http://www.regulations.gov>.

IV. Order of Prohibition

Therefore, I hereby issue the following order under §§ 530.21 and 530.25. We find that extralabel use of the cephalosporin class of antimicrobial drugs in food-producing animals likely will cause an adverse event, which

constitutes a finding that extralabel use of these drugs presents a risk to the public health. Therefore, we are prohibiting the extralabel use of the cephalosporin class of antimicrobial drugs in food-producing animals.

V. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Livermore, D. M. and L. D. Williams, "β-Lactams: Mode of Action and Mechanisms of Resistance," pp. 502–578, Victor Lorian (ed.), *Antibiotics in Laboratory Medicine*, Williams & Wilkins, Baltimore, 1991.
2. U.S. Food and Drug Administration, Maxipime (cefepime hydrochloride) for injection, NDA 50–679/S–021, http://www.fda.gov/medwatch/SAFETY/2003/03MAR_PI/Maxipime_PI.pdf (accessed March 13, 2007).
3. Li, X. Z., M. Mehrotra, S. Ghimire, and L. Adewoye, "β-Lactam Resistance and β-Lactamases in Bacteria of Animal Origin," *Veterinary Microbiology*, 121:197–214, 2007.
4. European Antimicrobial Resistance Surveillance System, EARSS Annual Report 2005, pp. 1–147, Bilthoven, The Netherlands, 2006.
5. U.S. Department of Health and Human Services, National Antimicrobial Resistance Monitoring System/Enteric Bacteria (NARMS/EB) Salmonella Annual Veterinary Isolates Data, U.S. Department of Agriculture, <http://www.ars.usda.gov/Main/docs.htm?docid=6750&page=4>, 2006.
6. Holmberg, S. D., J. G. Wells, and M. L. Cohen, "Animal-to-Man Transmission of Antimicrobial-Resistant *Salmonella*: Investigations of U.S. Outbreaks, 1971–1983," *Science*, 225:833–835, 1984.

7. CDC, "National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report," 2004, Atlanta, GA, U.S. Department of Health and Human Services, CDC, 2007.

8. Giles, W.P. , A. K. Benson, M. E. Olson, R. W. Hutkins, J. M. Whichard, P. L. Winokur, and P. D. Fey, "DNA Sequence Analysis of Regions Surrounding bla_{CMY-2} From Multiple *Salmonella* Plasmid Backbones," *Antimicrobial Agents and Chemotherapy*, 48:2845–2852, 2004.

9. Livermore, D. M., "Beta-Lactamases in Laboratory and Clinical Resistance," *Clinical Microbiology Review*, 8:557–584, 1995.

10. Clinical and Laboratory Standards Institute, Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth Informational Supplement, M100-S16, Wayne, PA, USA: CLSI, 2006.

11. Livermore, D. M., R. Canton, M. Gniadkowski, P. Nordmann, G. M. Rossolini, G. Arlet, J. Ayala, T. M. Coque, I. Kern-Zdanowicz, F. Luzzaro, L. Poirel, and N. Woodford, "CTX-M: Changing the Face of ESBLs in Europe," *Journal of Antimicrobial Chemotherapy*, 59:165–174, 2007.

12. Jacoby, G. A. and L. S. Munoz-Price, "The New B-Lactamases," *New England Journal of Medicine*, 352:380–391, 2005.

13. U.S. Food and Drug Administration, Center for Veterinary Medicine, unpublished report, Summary of Data From Hatchery Inspections Conducted September-October 2001, April 15, 2002.

List of Subjects in 21 CFR Part 530

Administrative practice and procedure, Advertising, Animal drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to

the Director of the Center for Veterinary Medicine, 21 CFR part 530 is amended as follows:

PART 530—EXTRALABEL DRUG USE IN ANIMALS

■ 1. The authority citation for 21 CFR part 530 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b, 371, 379e.

■ 2. In § 530.41, add paragraph (a)(13) to read as follows:

§ 530.41 Drugs prohibited for extralabel use in animals.

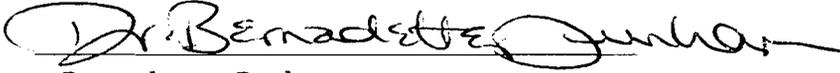
(a) * * *

(13) Cephalosporins.

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Dated: 6/24/08

June 24, 2008.



Bernadette Dunham,
Director,
Center for Veterinary Medicine.

[FR Doc. 08-????? Filed ??-??-08; 8:45 am]

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