(i) Parts Installation

As of the effective date of this AD, no person may install a ballscrew assembly in the drive mechanism of the HSTA on any airplane, unless it has been inspected and modified, as applicable, in accordance with paragraph (g) of this AD.

(j) Alternative Methods of Compliance (AMOCs)

The Manager, Seattle Aircraft Certification Office (ACO), FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or local Flight Standards District Office, as appropriate. If sending information directly to the manager of the ACO, send it to the attention of the person identified in the Related Information section of this AD. Information may be emailed to: *9-ANM-Seattle-ACO-AMOC-Requests@faa.gov.*

(1) Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the local flight standards district office/certificate holding district office.

(2) An AMOC that provides an acceptable level of safety may be used for any repair required by this AD if it is approved by the Boeing Commercial Airplanes Organization Designation Authorization (ODA) that has been authorized by the Manager, Seattle ACO to make those findings. For a repair method to be approved, the repair must meet the certification basis of the airplane.

(k) Related Information

(1) For more information about this AD, contact Kelly McGuckin, Aerospace Engineer, Systems and Equipment Branch, ANM–130S, FAA, Seattle Aircraft Certification Office, 1601 Lind Avenue SW., Renton, Washington 98057–3356; phone: (425) 917–6490; fax: (425) 917–6590.

(2) Boeing service information identified in this AD, contact Boeing Commercial Airplanes, Attention: Data & Services Management, P.O. Box 3707, MC 2H–65, Seattle, Washington 98124–2207; telephone (206) 544–5000, extension 1; fax (206) 766–5680; email *me.boecom@boeing.com;* Internet *https://www.myboeingfleet.com.*

(3) For Skytronics service information identified in this AD, contact Skytronics Inc., (cage 16553), P.O. Box 807, El Segundo, California 90245; phone: (310) 322–6284; fax: (310) 322–6160; Internet: *http://www.skytronicsinc.com.*

(4) For Linear Motion service information identified in this AD, contact Linear Motion LLC, 628 North Hamilton Street, Saginaw, Michigan 48602; phone: (989) 759–8300; Internet: *http://www.thomsonaerospace.com.*

(5) For Umbra Cuscinetti service information identified in this AD, contact Umbra Cuscinetti S.p.A., Technical Publications Department; Via. Piave 12, Foligno (PG) 06034, Italy; phone: +39 (0742) 348300; fax: +39 (0742) 348277; email: *tech.pubs@umbracus.com.*

(l) Material Incorporated by Reference

(1) You must use the following service information to do the actions required by this AD, unless the AD specifies otherwise. The Director of the Federal Register approved the incorporation by reference (IBR) of the following service information under 5 U.S.C. 552(a) and 1 CFR part 51:

(i) Boeing Alert Service Bulletin 737–27A1278, Revision 1, dated January 7, 2010.

(ii) Boeing Alert Service Bulletin 737–27A1277, Revision 2, dated January 8, 2010.

(2) For Boeing service information identified in this AD, contact Boeing Commercial Airplanes, Attention: Data & Services Management, P.O. Box 3707, MC 2H–65, Seattle, Washington 98124–2207; telephone (206) 544–5000, extension 1; fax (206) 766–5680; email: *me.boecom@boeing.com;* Internet: *https://www.myboeingfleet.com.*

(3) You may review copies of the service information at the FAA, Transport Airplane Directorate, 1601 Lind Avenue SW., Renton, Washington. For information on the availability of this material at the FAA, call (425) 227–1221.

(4) You may also review copies of the service information that is incorporated by reference at the National Archives and Records Administration (NARA). For information on the availability of this material at an NARA facility, call (202) 741–6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

Issued in Renton, Washington, on December 14, 2011.

Michael Kaszycki,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 2011–33351 Filed 1–5–12; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 530

[Docket No. FDA–2008–N–0326]

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, the Agency) is issuing an order prohibiting certain extralabel uses of cephalosporin antimicrobial drugs in certain food-producing animals. We are issuing this order based on evidence that certain extralabel uses of these drugs in these animals will likely cause an adverse event in humans and, therefore, present a risk to the public health.

DATES: This rule becomes effective April 5, 2012. Submit either electronic or written comments on this document by March 6, 2012.

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.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2008–N–0326 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, 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: Eric Nelson, Center for Veterinary Medicine (HFV–230), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, (240) 276–9201, *email: eric.nelson@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

A. History

In the **Federal Register** of July 3, 2008 (73 FR 38110), FDA published an order prohibiting the extralabel use of cephalosporin antimicrobial drugs in food-producing animals, with a 60-day comment period and a 90-day effective date for the final order. The order, which was to take effect as a final rule on October 1, 2008, would have resulted in a change to part 530 (21 CFR part 530) in § 530.41 to list cephalosporins as prohibited from extralabel use in food-producing animals as provided for in § 530.25(f).

In response to publication of this order, the Agency received requests for a 60-day extension of the comment period. The requests conveyed concern that the original 60-day comment period would not allow the requesters sufficient time to examine the available evidence, consider the impact of the order, and provide constructive comment.

FDA considered the requests and, in the **Federal Register** of August 18, 2008 (73 FR 48127), extended the comment period for the order for 60 days, until November 1, 2008. Accordingly, FDA also delayed the effective date of the final rule 60 days, until November 30, 2008.

The Agency received many substantive comments on the July 3, 2008, order of prohibition. Therefore, to allow more time to fully consider the comments, FDA decided to revoke the order so that it would not take effect November 30, 2008. Accordingly, in the **Federal Register** of November 26, 2008 (73 FR 71923), FDA withdrew the final rule and indicated that if, after considering the comments and other relevant information the Agency decided to issue another order of prohibition addressing this matter, FDA would follow the procedures in § 530.25 that provide for a public comment period prior to implementing the new order.

B. Comments on the July 3, 2008, Order of Prohibition

The Agency received comments from approximately 170 organizations and individuals on the July 3, 2008, order of prohibition. Comments were received from a trade organization representing new animal drug manufacturers, several trade organizations representing food animal producers, several professional associations representing veterinarians, a consumer protection organization, several new animal drug manufacturers, and many individuals including food animal veterinarians, farmers, and ranchers. Only two of the commenters supported the July 3, 2008, order of prohibition as written. All others felt that the prohibition should be revised in some manner before enactment or that it was unnecessary and should not be enacted in any form. These comments can be summarized into two general categories:

(1) The scope of the order was too broad in that it unnecessarily prohibited certain extralabel uses that do not significantly contribute to the problem of cephalosporin resistance. Many of these commenters were concerned about the unintended negative consequences on animal health that would result from such action; and

(2) FDA failed to meet the legal standard for issuing a prohibition order. Some of these comments alleged that FDA appeared to have applied the ''precautionary principle'' rather than basing its decision on sound scientific evidence.

Although FDA does not agree with comments alleging that the Agency did not meet the legal standard for issuing an order of prohibition, the Agency does agree with comments that the scope of the original order of prohibition could have been more targeted. After considering the comments and information submitted in response to the July 2008 order of prohibition, FDA has re-examined the basis for the original order. Based on this re-examination, FDA has determined that there is sufficient basis for prohibiting certain extralabel uses of cephalosporin drugs in food-producing major animal species. Specifically, as explained in detail later in this document, FDA is prohibiting the extralabel use of cephalosporin antimicrobial drugs (not including cephapirin) in cattle, swine, chickens, and turkeys: (1) For disease prevention purposes; (2) at unapproved doses, frequencies, durations, or routes of administration; and (3) if the drug is not approved for that species and production class.

Thus, with the exception of extralabel uses of cephapirin, the final effect of this order will be to prohibit many extralabel uses of cephalosporin drugs in food-producing major animal species (cattle, swine, chickens, and turkeys) including:

(1) Use for disease prevention purposes;

(2) Use at unapproved dose levels, frequencies, durations, or routes of administration (*e.g.,* Biobullets in cattle and injection or dipping of poultry eggs); and

(3) Use of products not approved in the major food species (*e.g.,* use of human or companion animal cephalosporin drugs).

The extralabel uses that are not prohibited by this order include:

(1) Use of approved cephapirin products in food-producing animals;

(2) Use to treat or control an extralabel disease indication as long as such use adheres to a labeled dosage regimen (*i.e.,* dose, route, frequency, and duration of administration) approved for that species and production class; and

(3) Use in food-producing minor species.

The Agency is prohibiting these extralabel uses in food-producing major species because we believe such uses in these animals will likely cause an adverse event in humans and, therefore, present a risk to the public health. FDA may further restrict extralabel use of cephalosporin antimicrobial drugs in animals in the future if it has evidence that demonstrates that such use has caused or likely will cause an adverse event.

II. Basis for Prohibiting the Extralabel Use of Cephalosporins With Certain Exceptions

A. AMDUCA and Cephalosporins

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Public Law 103–396) was signed into law October 22, 1994. It amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to permit licensed veterinarians to prescribe extralabel uses of approved human and animal drugs in animals. In the **Federal Register** of November 7, 1996 (61 FR 57732), FDA published the implementing regulations (codified at part 530) for AMDUCA that include, among other things, a definition for the term ''extralabel use'' as well as provisions for prohibiting extralabel uses.

Section 530.3 states that *extralabel use* means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to:

(1) Use in species not listed in the labeling;

(2) Use for indications (disease or other conditions) not listed in the labeling;

(3) Use at dose levels, frequencies, or routes of administration other than those stated in the labeling; and

(4) Deviation from the labeled withdrawal time based on these different uses.

The sections in FDA's implementing regulations governing the prohibition of extralabel use of drugs in animals include §§ 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 such an order. FDA may issue a prohibition order if it finds that extralabel use of a drug in animals presents a risk to the public health. Under § 530.3(e), this means that FDA has evidence demonstrating that the use of the drug has caused, or likely will cause, an adverse event. Furthermore, as discussed in section III.B of this document, the regulations permit a prohibition order to be either a general ban on the extralabel use of the drug or

class of drugs, or a ban limited to one or more of the uses described in the definition of *extralabel use* cited previously.

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 FDA revokes or modifies the order, or extends the period of public comment. The list of drugs prohibited from extralabel use is found in § 530.41.

At this time, FDA is concerned that certain extralabel uses of cephalosporins in food-producing major species are likely to lead to the emergence and dissemination 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. The Agency is particularly concerned about the extralabel use of cephalosporin drugs that are not approved for use in food-producing major species because very little is known about their microbiological or toxicological effects when used in food-producing animals. Therefore, FDA is issuing an order prohibiting, with limited exceptions, the extralabel use of cephalosporins in food-producing major species because, as discussed in this document, the Agency has determined that such extralabel use likely will cause an adverse event and, therefore, presents a risk to the public health.

B. Importance of Cephalosporins in Veterinary and Human Medicine

Cephalosporins are members of the beta-lactam (β-lactam) class of antimicrobials. Members of the cephalosporin class have a β-lactam ring fused to a sulfur-containing ring-expanded system (Ref. 1). These antimicrobials work by targeting synthesis of the bacterial cell wall, resulting in increased permeability and eventual hydrolysis of the cell.

Introduced into clinical use in 1964, cephalosporins are widely used antimicrobial agents in human medicine. Beta-lactams make up 40 percent of total prescriptions in the outpatient setting, and cephalosporins contribute 14 percent of the total outpatient antibiotic prescriptions. This use accounts for over 50 million prescriptions per year (Ref. 2). In the inpatient setting, cephalosporins are most commonly used to treat pneumonia. Older cephalosporins 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. Approved indications for newer cephalosporins include the treatment of lower respiratory tract infections, acute bacterial otitis media, skin and skin structure infections, urinary tract infections (complicated and uncomplicated), uncomplicated gonorrhea, pneumonia (moderate to severe), empiric therapy for febrile neutropenic patients, complicated intra-abdominal infections, pelvic inflammatory disease, septicemia, bone and joint infections, meningitis, and surgical prophylaxis. Indicated pathogens include, but are not limited to, *Acinetobacter calcoaceticus, Bacteroides fragilis, Enterobacter agglomerans, Escherichia coli, Haemophilus influenzae* (including β-lactamase producing strains), *Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Streptococcus pneumoniae,* and *Streptococcus pyogenes* (Ref. 3). Newer cephalosporins (for example, third generation cephalosporins such as ceftriaxone) are used in the hospital setting to treat seriously ill patients with life-threatening disease, many of which are due to organisms that reside in the gastrointestinal tract. These 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 (Ref. 4).

Two cephalosporin drugs are currently approved for use in food-producing animal species: Ceftiofur and cephapirin. Injectable ceftiofur products are approved for the treatment and control of certain diseases, including: (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.* Cephapirin is only approved as an intramammary infusion for the treatment of lactating cows having bovine mastitis caused by susceptible strains of *Streptococcus agalactiae* and *Staphylococcus aureus.*

C. Mechanism of Cephalosporin Resistance

In general, there are three major 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. 5).

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). CMY–2 (a type of AmpC) enzymes are found on the chromosome of most *Enterobacteriaceae,* and are also currently found on promiscuous plasmids in *Salmonella, E. coli,* and other members of the *Enterobacteriaceae.* These enzymes provide resistance to first, second, and third generation cephalosporins. CMY–2 is currently the predominant β-lactamase associated with *Salmonella* collected from animals and humans in the United States displaying resistance to ceftiofur and decreased susceptibility or resistance to ceftriaxone (Refs. 6–8), both third generation cephalosporins.

''Fourth generation'' cephalosporins are active *in vitro* against bacteria producing AmpC type β-lactamases, but there is some disagreement as to the clinical significance of that activity. Recently, three *E. coli* producing variant CMY–2 β-lactamases were isolated from patients in Pennsylvania. Two of the three patients from whom these isolates were obtained had undergone treatment with cefepime, a fourth generation cephalosporin, within the 2 months preceding isolation of the organisms. These isolates were shown to have reduced susceptibility to fourth generation cephalosporins, suggesting that CMY–2 has the potential to evolve to provide resistance to fourth generation cephalosporins when exposed to selective pressure (Ref. 9).

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. In 2010, the CLSI revised

the cephalosporin resistance breakpoints to more accurately reflect *in vivo* susceptibility. Prior to this time, a particular ESBL strain that might not raise the minimum inhibitory concentration (MIC) for a given cephalosporin to a level above the breakpoint for resistance would commonly prove to be resistant *in vivo* (Ref. 5). Therefore, there were specific guidelines for screening bacterial isolates for the presence of ESBLs when MICs fell in the susceptible range. Any bacterial isolate which produced either an AmpC enzyme or an ESBL was reported to clinicians as resistant to all cephalosporins even though susceptibility testing may have shown *in vitro* susceptibility to some of the cephalosporins (Ref. 10).

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 caused by *Salmonella* serovar 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 the United States do TEM and SHV still predominate, although CTX–M enzymes are now rising in prevalence (Refs. 12–19). 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.

Serious infections caused by cephalosporin-resistant bacteria may be empirically treated with ineffective antibacterial regimens, significantly increasing the likelihood of death. Urinary tract infections caused by community-acquired cephalosporin-resistant *E. coli* may be associated with bloodstream infections, and these infections may also be resistant to most or all antibiotics commonly used to treat such infections. Empirical treatment of such infections is often with a fluoroquinolone, amoxicillin-clavulanate, or a cephalosporin; however, these *E. coli* are likely to be resistant to all of these agents, making treatment of these infections more difficult (Ref. 11).

D. Cephalosporin-Resistant Zoonotic Foodborne Bacteria

In regard to antimicrobial drug use in animals, the Agency considers the most significant risk to the public health associated with antimicrobial resistance to be human exposure to food containing antimicrobial-resistant bacteria resulting from the exposure of food-producing animals to antimicrobials, including cephalosporins. Resistance to certain cephalosporins is of particular public health concern in light of the evidence of cross-resistance among drugs in the cephalosporin class. Importantly, resistance to ceftiofur compromises the efficacy of ceftriaxone, a first-line therapy for treating salmonellosis in humans. 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 CMY–2 and CTX–M β-lactamases (Ref. 6), which confer cephalosporin resistance and are transmissible between enteric bacteria. Acquired resistance to β-lactams in animal and human isolates has been observed in surveillance programs such as the U.S. National Antimicrobial Resistance Monitoring System (NARMS) and the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS).

Because food-producing animals are a known source of resistant *Salmonella* infections in humans (Ref. 20), the NARMS program has monitored ceftiofur resistance among *Salmonella* isolates from food-producing animals at slaughter since 1997. In 1997, no *Salmonella* 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 2009, the prevalence of ceftiofur resistance among *Salmonella* slaughter isolates increased to 14.5 percent for cattle, 4.2 percent for swine, 12.7 percent for chickens, and 12.4 percent for turkeys (Ref. 21).

Among food animal *Salmonella* isolates in NARMS, ceftiofur resistance has been identified in more than 20 different serotypes, and it has increased substantially in several serotypes commonly found in humans (Ref. 22). Ceftiofur resistance among all *Salmonella* Typhimurium isolates from chickens was 0.0 percent in 1997 and 33.3 percent in 2009. Among all *Salmonella* Typhimurium isolates from cattle, ceftiofur resistance was 3.0 percent in 1998 and 27.8 percent in 2009. Ceftiofur resistance rose from 12.5 percent in 1998 to 58.8 percent in 2009 among *Salmonella* Newport isolates from cattle. There was no ceftiofur resistance among *Salmonella* Heidelberg isolates from poultry in 1997, but resistance rose to 17.6 percent in chicken isolates and 33.3 percent in turkey isolates in 2009 (Refs. 22, 23).

The NARMS program has also monitored ceftiofur resistance among *Salmonella* isolates from humans since 1996. Ceftiofur resistance among non-Typhi *Salmonella* isolates from humans rose from 0.2 percent in 1996 to 3.4 percent in 2009. Resistance to ceftiofur also rose in several *Salmonella* serotypes commonly isolated from humans. In 1996, ceftiofur resistance among *Salmonella* isolates from humans was 0.0 percent, 0.0 percent, and 1.4 percent for serotypes Typhimurium, Newport, and Heidelberg, respectively. In 2009, ceftiofur resistance among isolates from these serotypes was 6.5 percent, 6.4 percent, and 20.9 percent, respectively (Refs. 23, 24).

The CIPARS program revealed an increase in Quebec of resistance to cephalosporins among *Salmonella* Heidelberg isolates from humans reaching a level of 36 percent of isolates in 2004. This increase was accompanied temporally by an increase in ceftiofur resistance in *Salmonella* Heidelberg isolates from retail chicken, which rose to 62 percent in 2004. Hatcheries in Quebec voluntarily stopped the use of ceftiofur in eggs and day-old chicks in February 2005. This action was followed temporally by a dramatic decline in the prevalence of ceftiofur resistance in *Salmonella* Heidelberg isolates from humans and retail chicken in Quebec, which by 2008 had declined to 12 percent and 18 percent, respectively. These trends in *Salmonella* Heidelberg were accompanied by similar trends in ceftiofur resistance in *E. coli* isolates from retail chicken (Ref. 25).

Ceftiofur is not used in human medicine in the United States, but after the 2010 CLSI change in the cephalosporin breakpoint, resistance to this agent largely coincides with resistance to ceftriaxone, a third generation cephalosporin that is a critically important antimicrobial approved for use in humans (Ref. 23). As discussed earlier, this resistance trait conferred by the CMY–2 enzyme. CMY–2 provides resistance to first, second, and third generation cephalosporins. In addition to conferring ceftiofur and ceftriaxone resistance, CMY–2 also imparts resistance to several other β-lactams, including ampicillin and amoxicillin/clavulanate (Ref. 26). The prevalence and spread of CMY–2 is reflected in the surveillance data on ceftriaxone and ceftiofur susceptibility

(Ref. 27) and supports the finding that cephalosporin use in food-producing animals is likely contributing to an increase in cephalosporin-resistant human pathogens.

E. Extralabel Uses of Greatest Concern

1. Dairy Cattle

The U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) conducts both ante-mortem and post-mortem inspection of livestock and poultry presented for slaughter at each official establishment. As part of ante-mortem inspection, FSIS personnel inspect animals to determine whether they exhibit behaviors or conditions that are indicative of illegal chemical use. If such behaviors or symptoms are exhibited, the animals are tagged and further examined at post-mortem inspection. During post-mortem inspection, FSIS veterinarians examine carcasses and their organs to determine whether the animals they came from had pathological diseases or other conditions that could have warranted the use of drugs or other chemicals and whether there are any indications of illegal chemical use. In addition, FSIS conducts laboratory analysis of sample tissues that have been taken from carcasses that have pathologies or other conditions indicative of chemical use to determine whether they contain violative chemical residues. FSIS transmits to FDA information about the violative chemical residue found, including the name of the official establishment where the livestock or poultry was presented for slaughter.

During the 1-year period ending June 25, 2009, FSIS reported 113 instances of violative ceftiofur residues in dairy cows and an additional 22 instances of violative ceftiofur residues in other food-producing animals, including beef cattle and veal calves. The FSIS reports include quantitative drug residue levels for each violation. In most instances, the violative residue levels of ceftiofur detected in dairy cows were significantly above the allowable tolerance of 0.4 ppm (kidney) in tested tissues and are summarized as follows:

- Up to 2x above the tolerance = 12 violations
- Between 2x and 5x above the tolerance = 17 violations
- Between 5x and 10x above the tolerance = 16 violations
- Between 10x and 20x above the tolerance = 30 violations
- Over 20x above the tolerance = 38 violations

An examination of 25 recent inspections of farms responsible for violative ceftiofur residues identified a number of factors that resulted in the misuse of ceftiofur animal drug products. These factors 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. Most of the violations involved culled dairy cows. More than half of the violations involved ceftiofur residue levels more than 10 times the established tolerance level.

Based on investigations conducted by FDA, the majority of residue violations were the result of poor recordkeeping and other management practices. Among the provisions required for extralabel drug use in animals under 21 CFR part 530, the client (the owner of the animal or animals or other caretaker) must agree to follow the instructions of the veterinarian, the veterinarian must institute procedures to assure that the identity of the treated animal or animals is carefully maintained, and the veterinarian must take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment.

Adhering to the ELU requirements is particularly important for extralabel drug use in dairy cattle because treatment often occurs in sick adult dairy cows close to the time of potential slaughter and introduction into the food supply. Evidence of this practice is the fact that 67 percent of all tissue residue violations reported by FSIS at slaughter are attributed to adult dairy cattle. In comparison, antimicrobial drug treatment in swine and beef cattle more often occurs earlier in the life of the animal, typically at some transition point that is well before slaughter. This aspect of dairy husbandry is not only a concern regarding violative drug residues, it is also a concern in the context of antimicrobial resistance. Recent evidence suggests that administration of ceftiofur crystalline-free acid (CCFA) in cattle will cause a transient increase in the population of ceftiofur-resistant isolates in gut bacteria that lasts approximately two weeks before a return to more normal susceptibility patterns (Ref. 28). Because of this, the Agency is concerned that improper extralabel use of ceftiofur in culled dairy cows just prior to slaughter could result in increased levels of cephalosporin resistance in carcass bacteria.

Ceftiofur use in dairy herds has been shown to increase herd prevalence of ceftriaxone resistant *E. coli* over that in herds without ceftiofur use. Herds reporting ceftiofur use were 25 times more likely to have cows from which ceftriaxone resistant *E. coli* were isolated than those that did not use ceftiofur (Ref. 29). In addition, a ceftiofur-resistant fecal *E. coli* isolate expressing CTX-M-type extended-spectrum β-lactamase was recovered from a sick dairy calf that was treated in an extralabel manner for diarrhea with ceftiofur (Ref 17). *Escherichia coli* are considered good indicators of the selective pressure imposed by antimicrobial use in food-producing animals and, as such, may reflect what might occur in *Salmonella* spp. under the same conditions (Ref. 30). *Salmonella* Newport has been shown to be the predominant serotype among cases of clinical salmonellosis in dairy cattle, followed by *S.* Typhimurium, including the *S.* Typhimurium variant, 4,5,12:i:- (Refs. 31, 32). Over 68 percent of all isolates were resistant to five or more antimicrobials in these studies. In one study, 97 percent of *S.* Newport isolates were multi-drug resistant (MDR), exhibiting an MDR-AmpC phenotype (Ref. 31). The proportion of multi-drug resistance was significantly higher ($p < 0.0001$) among *S.* Newport and *S.* Typhimurium, both serotypes of human importance, than among all other serotypes. MDR-AmpC *S.* Newport resistant to third generation cephalosporins has also been shown to persist in the dairy environment and can be shed from individual cows for up to 190 days (Ref. 33). Studies have also shown that recent antimicrobial treatment, including ceftiofur, can increase the probability of isolating *Salmonella* in calves, heifers, and cows (Refs. 34, 35).

It is estimated that just over one million cases of human salmonellosis occur every year in the United States (Ref 36). *Salmonella* serovars Typhimurium and Newport are often multi-drug resistant and appear to be associated with more severe human disease than other serovars (Refs. 37, 38). These infections can lead to treatment failures, greater hospitalization or death rates, and higher costs than infections with susceptible strains. Consumption of

dairy products, as well as dairy farm contact, represents important risk factors for human *S.* Newport MDR-AmpC infection (Ref. 39). Additionally, a number of outbreaks of *S.* Newport MDR-AmpC have been linked to dairy product consumption (Refs. 40, 41). NARMS data indicate that in 2006, 42.6 percent of diagnostic *Salmonella* isolates from cattle were ceftiofur resistant. *S.* Typhimurium and *S.* Newport were the second and third most frequently isolated serovars from human infections in that year, and *S.* Newport was the third most frequently isolated serovar from cattle. Thirty-four percent of *S.* Newport isolated from humans and 32 percent of *S.* Newport isolated from cattle were resistant to ceftiofur, making this serovar the leading source of ceftiofur-resistant isolates for both hosts.

2. Poultry

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. 42). For example, ceftiofur was being administered at unapproved dosing levels or via unapproved methods of administration. In particular, ceftiofur was being administered via egg injection, rather than by the approved method of administering the drug to day-old chicks. The Agency 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. As a result, FDA believes human exposure to food containing cephalosporin-resistant bacteria would be significantly higher as well. Therefore, considering the large amount of food produced by the poultry industry each year, the Agency believes such extralabel use presents a risk to the public health.

3. Other Extralabel Uses That Increase Drug Exposure

One of the goals of this order of prohibition is to reduce the amount of cephalosporins used in food-producing animals for uses that have not been evaluated for safety and approved by FDA. This is particularly important for uses that result in significant increases in cephalosporin drug exposure such as the injection of chick eggs previously noted. Other extralabel uses that significantly increase drug exposure include certain deviations from an approved dosage regimen. This would 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.

4. Biobullets

The Agency received 35 comments on the July 3, 2008, order of prohibition that documented the extralabel use of ceftiofur in a compounded new animal drug product known as Biobullets. According to the manufacturer's Web site, Biobullets deliver a solid pellet of ceftiofur sodium (NADA 140–338) 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. Furthermore, based on these comments, and on past regulatory actions regarding Biobullets (Ref. 43), FDA continues to have concerns that the manufacture, distribution, and use of this product may violate the compounding and valid veterinary-client-patient-relationship provisions of AMDUCA and 21 CFR part 530.

5. Human Cephalosporins

Another concern is the extralabel use in food-producing animals 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 July 3, 2008, 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.

III. Response to Comments

A. Revised Scope of the Order

Many of the comments received on the July 3, 2008, order of prohibition said the scope of the original order was too broad in that it unnecessarily prohibited certain extralabel uses that do not significantly contribute to the development of antimicrobial resistance.

As is recognized for the use of antimicrobial drugs in general, the use of cephalosporins provides selection pressure that favors expansion of resistant variants of bacteria. 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, as stated in the July 2008 order of prohibition, FDA believes that it is necessary to take action to limit the extent to which extralabel use of cephalosporins in food-producing animals may be contributing to the emergence and dissemination of resistant variants. However, as noted earlier, FDA also agrees with many of the comments received on the July 3, 2008, order of prohibition that said the scope of the original order was too broad in that it unnecessarily prohibited certain extralabel uses that are not likely to cause an adverse event and present a risk to the public health. As discussed below, based on the comments and additional information submitted in response to the July 3 order, the Agency has reconsidered its position on the following three specific areas: extralabel use of cephapirin, extralabel use for unapproved indications, and extralabel use in food-producing minor species.

1. Cephapirin

FDA considered the possibility of limiting the order of prohibition to certain generations of cephalosporins, or to certain individual cephalosporin drugs. FDA recognized that not all cephalosporin drugs necessarily posed the same level of risk. But given the

potential for confusion regarding the classification of individual cephalosporin drugs into various generations, FDA concluded in the July 3, 2008, final rule, that it would be problematic to define the scope of the prohibition based on cephalosporin ''generation.'' Although FDA continues to believe that a ''generation-based'' prohibition would be problematic, the Agency has given further consideration to excluding certain cephalosporin drugs from the order of prohibition. Therefore, based on the comments received on the July 3, 2008, order of prohibition, the Agency now believes that it is not necessary to prohibit the extralabel use of approved cephapirin drug products in food-producing animals.

Several factors contribute to cephapirin drug products being of a lesser concern for promoting antimicrobial resistance in bacteria of significant public health concern. First, there are currently no cephapirin drug products approved for use in humans and, since cephapirin has such 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 (Refs. 26, 28). Furthermore, target organisms for approved uses of cephapirin include those not normally considered to cause serious human infections through the foodborne route.

Second, cephapirin is currently only approved for use in food-producing animals as intramammary infusion drug products for dairy cattle. These products are formulated and dispensed in a manner that limits their suitability for other uses or routes of administration, thus restricting their potential for extralabel use significantly.

Therefore, because the impact of cephapirin on antimicrobial resistance among bacteria of public health concern is substantially less than other, newer cephalosporins, and its unique dosage form restricts the extent of its extralabel use significantly, the Agency believes that it is appropriate to exclude cephapirin drug products from the prohibition order.

2. Extralabel Indications for Use

People often think of extralabel use only in terms of unapproved indications for use, that is, diseases or conditions not included in the approved labeling. However, as noted earlier, the definition of ''*extralabel* use'' includes several aspects of drug use not described in the approved labeling including, but not limited to:

(1) Use in species not listed in the labeling;

(2) Use for indications (disease or other conditions) not listed in the labeling;

(3) Use at dose levels, frequencies, or routes of administration other than those stated in the labeling; and

(4) Deviation from the labeled withdrawal time based on these different uses.

For example, if a veterinarian uses a drug for an approved therapeutic indication, but administers it at twice the labeled dose, such use would represent an extralabel use. Alternatively, if a veterinarian uses a drug for an approved therapeutic indication, and administers the drug at the approved dosage regimen for that indication, but there is a failure to observe the labeled withdrawal time before the treated animal is sent to slaughter, such use would also represent an extralabel use. It is important to understand that there are many ways to use an approved drug in an extralabel fashion.

As noted earlier, a prohibition order can be either a general ban on all extralabel use of a drug or class of drugs, or a lesser ban limited to one or more of the individual extralabel uses. Many commenters were concerned that a blanket prohibition of all extralabel use of cephalosporins would have a negative impact on animal health and welfare because, by prohibiting all extralabel use, therapeutic use for unapproved indications would also be prohibited, thereby eliminating effective treatment options for many life-threatening diseases for which there are limited or no approved therapies. However, while the vast majority of the comments objected to a blanket prohibition, few expressed an objection to prohibiting extralabel dosage regimens. Only those comments regarding intramammary use of cephalosporins expressed a need for extralabel dosage regimens. In fact, several comments explicitly suggested FDA narrow the order to only allow extralabel use for unapproved therapeutic indications, but still prohibit most other extralabel use, including modifications to approved dosage regimens.

An important tenet of the Agency's microbial food safety assessment for antimicrobial drugs in food-producing animals is its focus on conditions of use. When the microbial food safety hazard associated with the use of an antimicrobial drug in food-producing animals is evaluated as part of the new animal drug approval process, the evaluation takes into consideration the proposed conditions of use, including:

(1) Dosage regimen (dose level, frequency of administration, duration, and route of administration), and

(2) Indications for use (purpose of treatment, species, class or age of the target animal, and the number of animals likely to be treated).

As such, it is the approved conditions of use that help mitigate antimicrobial resistance risks associated with a particular drug's use by controlling the overall drug exposure in treated animals. Although all aspects of the conditions of use contribute to some extent to drug exposure, FDA believes, after re-examining the basis for this order of prohibition, that extralabel uses of cephalosporins that involve modifications of the approved dosage regimen are likely to pose the greatest risk of increasing the extent to which animals are exposed to the drug. Such extralabel uses allow for greater exposure of individual animals through modification of dose levels, duration of administration, and/or frequency of administration. Furthermore, using the drug by unapproved routes of administration (*e.g.,* via drinking water) can also increase exposure levels by facilitating administration of the drug to a significantly larger number of animals.

It is in this context that FDA concluded that extralabel uses that conform to the approved dosage regimen, but involve use for unapproved therapeutic indications, pose a significantly lower risk with respect to increasing overall drug exposure than uses at unapproved dose levels, unapproved duration and/or frequency of administration, or unapproved routes of administration. Accordingly, the Agency also concluded that an exception to the order of prohibition could be made on this basis. However, FDA also took into account the extralabel uses of cephalosporin drugs in food-producing animals of greatest concern (see discussion in section II.E of this document regarding prevention use) and concluded that this exception to the prohibition should only be for the treatment and control of disease.

Therefore, the Agency thinks it is appropriate to narrow the scope of the prohibition order somewhat by only allowing extralabel use in food-producing major species for treatment or control of unapproved disease indications, but continuing to prohibit most other extralabel use in these species including unapproved dosage regimens and use to prevent extralabel disease indications.

For the reasons described previously, FDA does not at this time believe that extralabel use in food-producing major

species to treat or control an unapproved disease indication presents a risk to the public health as long as the drug is used at a labeled dose, frequency, duration, and route of administration approved for that species and production class.

3. Food-Producing Minor Species

In accordance with the act, minor species means animals other than cattle, swine, chickens, turkeys, horses, dogs, cats, and humans. Many comments requested that food-producing minor species, particularly small ruminants, be excluded from the order of prohibition. Most of these comments cited the limited availability of approved animal drug products for these species and several comments also noted that small ruminants represent only very limited uses of cephalosporin drug products compared to cattle, swine, and poultry. Based on these comments, the Agency reconsidered the decision to include food-producing minor species in the prohibition on the extralabel use of cephalosporin drugs in food-producing animals.

As noted earlier, in regard to the use of antimicrobial drugs in animals, the Agency considers the most significant risk to the public health associated with antimicrobial resistance to be human exposure to food containing antimicrobial-resistant bacteria resulting from the exposure of food-producing animals to antimicrobials. However, when considering the foodborne pathway, the potential for human exposure to antimicrobial-resistant pathogens is significantly less for food derived from minor species than it is for food derived from the food-producing major species. The exposure potential is less in part because the amount of food derived from cattle, swine, and poultry is much greater than the amount of food derived from sheep, goats, and aquaculture, the minor species from which the most food is derived. Furthermore, the amount of food derived from any of the other food-producing minor species, such as deer, bison, elk, rabbit, duck, goose, quail, pheasant, partridge, pigeon, ostrich, or emu is considerably less than the amount of food derived from sheep, goats, and aquaculture. In addition, cephalosporins are approved for use in sheep and goats, thereby reducing the potential for extralabel use in these species, and there is little or no practical use for cephalosporin drugs in aquaculture.

Therefore, for the reasons described previously, FDA does not at this time believe that extralabel use in food-producing minor species presents a risk to the public health.

Please note that all the provisions of AMDUCA remain applicable to the exceptions noted above. This includes provisions making it unlawful for the permitted extralabel use of a cephalosporin drug to result in a residue above an established tolerance or safe level. See 21 U.S.C. 360b(a)(4)(B) and FDA regulations at 21 CFR 530.11.

B. Legal Standard

Several comments questioned the legal standard applied by FDA in implementing the order of prohibition. Some comments referred to the Agency's approach as involving the ''precautionary principle,'' an apparent reference to a principle used in the European Union in some environmental and regulatory decision-making. Two comments suggested that, in order to support an order of prohibition, it would be necessary for FDA to demonstrate ''either a demonstrative negative impact on human health or an imminent danger to human health.'' Some comments suggested that FDA must perform a risk assessment that would characterize the hazard, evaluate the risk, and ascertain the impact of any risk management recommendations associated with the order.

One comment suggested that a link between the use of cephalosporins in the treatment of animals and the development of bacterial resistance in humans would not meet the criterion of the AMDUCA implementing regulation that the extralabel use of cephalosporins has caused or will likely cause an adverse event. That comment appears to make a technical argument that an adverse event in the context of the regulation can only be an adverse event in animals, as opposed to humans. (The commenter acknowledged that the lack of drug efficacy when used for a labeled pathogen in target animals would be considered an adverse event.)

AMDUCA was enacted in 1994, and its provisions became effective upon FDA's issuance of final regulations implementing those provisions in 1996. Prior to the passage of AMDUCA, Federal law prohibited the use of a new animal drug in a manner other than in accordance with the approved label directions, *i.e.,* extralabel use. Recognizing the reality that veterinarians are often confronted with situations in which there are no approved drugs for the species of animal that they are treating, or for particular diseases or conditions afflicting those animals, Congress enacted AMDUCA to allow licensed veterinarians to prescribe extralabel uses of approved animal drugs and approved human drugs for animals without violating the law.

The provisions of AMDUCA relating to extralabel use in animals of approved new animal drugs and approved human drugs, sections 512(a)(4) and 512(a)(5) of the FD&C Act, respectively, provide that such extralabel use must be in compliance with conditions specified in implementing regulations promulgated by FDA. (21 U.S.C. 360b(a)(4) and 360b(a)(5)). Section 512(a)(4) further provides that if FDA finds, after extending an opportunity for public comment, that the extralabel use of a new animal drug ''presents a risk to the public health * * * [FDA] may, by order, prohibit any such use.'' (Section 512(a)(4)(D) (21 U.S.C. 360b(a)(4)(D)).

Although the express language relating to prohibiting extralabel use appears in the provisions of AMDUCA that deal with extralabel use of approved new animal drugs, in its implementing regulations at part 530, FDA has interpreted the statute as applying the same standard to extralabel use of approved human drugs in food-producing animals. FDA's implementing regulations state that a prohibition may occur if FDA determines that ''[t]he extralabel use of the drug or class of drugs presents a risk to the public health.'' 21 CFR 530.21(a)(2). See also 21 CFR 530.25(a)(2). The regulations permit a prohibition to be either a general ban on the extralabel use of the drug or class of drugs, or a ban limited to particular species, indications for use, dosage forms, routes of administration, or a combination of those factors. 21 CFR 530.21(b).

The regulations further define the phrase ''use of a drug presents a risk to the public health'' to mean that ''FDA has evidence that demonstrates that the use of the drug has caused or likely will cause an adverse event.'' 21 CFR 530.3(e). FDA has thus, by regulation, imposed upon itself the requirement that it have some evidence that demonstrates either that a drug has caused an adverse event or that it likely will cause an adverse event. FDA believes that, when the issue is, as with cephalosporins, a question of the development of antibacterial resistance in animals that may affect human health, an order of prohibition may be based on evidence that such development of antibacterial resistance—which could lead to serious adverse events in humans—is ''likely'' as a result of the extralabel animal drug use. The regulation is clear that there need not be evidence that such an event has actually occurred.

FDA rejects the apparent suggestion of one commenter, noted above, that an order of prohibition cannot be based on an adverse event in humans. Such a reading would be squarely inconsistent with the statutory provisions authorizing FDA to ban extralabel uses that present a risk to the public health. FDA addressed this issue in the preamble to the final AMDUCA implementing regulations, clarifying that ''[t]he agency did not intend for the term 'adverse event' to be interpreted as related only to animal 'adverse drug reactions.' '' (61 FR 57732 at 57737, November 7, 1996). Also, as made clear by the preamble, ''* * * the primary focus will be on human health.'' (61 FR at 57732 at 57737).

FDA also rejects the assertion by some commenters that FDA relied on the ''precautionary principle.'' As previously noted, the standard in the regulation does require the existence of evidence. In the preamble to the final rule, FDA addressed the question of what type of evidence would be necessary by saying that the risk determinations that would lead to prohibition of an extralabel use ''typically will involve documented scientific information. However, the Agency believes that it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate.'' (61 FR 57732 and 57738; November 7, 1996). In other sections of this preamble, FDA provides a detailed description of the evidence supporting its conclusion that the extralabel use that is being prohibited by this revised order does in fact present a risk to the public health, including a likelihood that the use would, if not prohibited, ultimately lead to adverse events in humans resulting from the development of resistance to antibiotic drugs needed to treat human infections.

IV. Conclusions

Based on information regarding cephalosporin resistance as discussed previously, FDA continues to believe, as it did in July of 2008, that it is likely that the extralabel use of cephalosporins in certain food-producing animal species is contributing to the emergence of cephalosporin-resistant zoonotic foodborne bacteria. Therefore, FDA has determined in accordance with the relevant provisions of 21 CFR part 530 that, with some exceptions, such extralabel use likely will cause an adverse event and, as such, presents a risk to the public health. As also noted earlier, FDA agrees with many of the comments received on the July 3, 2008, order of prohibition that said the scope of the original order was too broad and, in response, has narrowed the scope of this order accordingly. Specifically, this order prohibits all extralabel use of cephalosporin drugs in food-producing animals except for the following uses, provided they comply with AMDUCA and FDA's regulations implementing AMDUCA at 21 CFR part 530:

(1) *Cephapirin:* Extralabel uses of approved cephapirin products are excluded from the prohibition.

(2) *Extralabel Indications for Use:* Extralabel uses to treat or control an extralabel disease indication in food-producing major species when used at a labeled dose, frequency, duration, and route of administration approved for that species and production class, are excluded from the prohibition.

(3) *Food-Producing Minor Species:* Extralabel uses in food-producing minor species are excluded from the prohibition.

To restate in more practical terms, after this order becomes effective, the following extralabel use restrictions will apply to all cephalosporin drug products, except approved cephapirin products, when used in food-producing animals:

Major Species: Extralabel use of a cephalosporin drug product is permitted in food-producing major species to treat or control an extralabel disease indication, but only when it is approved and labeled for use in that particular species and production class, and only when the product is administered at dose levels, frequencies, durations, and routes of administration stated on the approved labeling for that particular species and production class. However, extralabel use for disease prevention purposes is prohibited.

Minor Species: All extralabel use of a cephalosporin drug product is permitted in food-producing minor species provided such use complies with the requirements of AMDUCA and 21 CFR part 530.

V. Comments

FDA is providing 60 days from the date of this publication for the public to comment on this document. For the effective date of the order, see the **DATES** section of this document, unless the Agency revokes or modifies the order, or extends the comment period. Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments 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.

VI. Order of Prohibition

Therefore, I hereby issue the following order under 21 CFR 530.21 and 530.25. FDA finds that certain 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, the Agency is prohibiting the extralabel use of the cephalosporin class of antimicrobial drugs as follows:

Cephalosporins (not including cephapirin) are prohibited from extralabel use in cattle, swine, chickens, or turkeys as follows: (1) For disease prevention purposes; (2) at unapproved doses, frequencies, durations, or routes of administration; and (3) if the drug is not approved for that species and production class.

VII. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**). You may view them between 9 a.m. and 4 p.m., Monday through Friday. FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.

1. Livermore, D.M. and L.D. Williams. β-Lactams: Mode of Action and Mechanisms of Resistance. In *Antibiotics in Laboratory Medicine;* Victor Lorian (ed.); Williams & Wilkins, Baltimore, pp. 502–578, 1991.
2. John H. Powers, M.D., Transcript—Official Meeting of the Veterinary Medicine Advisory Committee, New Drug Microbial Safety Review Under Guidance #152, *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm126971.htm* (accessed January 6, 2011), September 25, 2006.
3. U.S. Food and Drug Administration, MAXIPIME (cefepime hydrochloride) for Injection, NDA 50–679/S–021, *http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050679s028lbl.pdf* (accessed January 6, 2011).
4. Biedenbach, D.J. *et al.* Analysis of *Salmonella* spp. with resistance to extended-spectrum cephalosporins and fluoroquinolones isolated in North America and Latin America: report from the SENTRY Antimicrobial Surveillance Program (1997–2004). *Diagnostic Microbiology and Infectious Disease* 54:13–21, 2006.
5. Livermore, D.M. Beta-Lactamases in Laboratory and Clinical Resistance.

Clinical Microbiology Review 8:557–584, 1995.
6. Li, X.Z. *et al.* β-Lactam Resistance and β-lactamases in Bacteria of Animal Origin. *Veterinary Microbiology* 121:197–214, 2007.
7. Centers for Disease Control and Prevention (CDC), National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report, 2008. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, 2010.
8. Glenn, L.M. *et al.* Analysis of Antimicrobial Resistance Genes Detected in Multidrug-Resistant *Salmonella enterica* Serovar Typhimurium Isolated from Food Animals. *Microbial Drug Resistance* 17:407–418, 2011.
9. Doi, Y. *et al.* Reduced Susceptibility to Cefepime among *Escherichia coli* Clinical Isolates Producing Novel Variants of CMY–2 β-Lactamase. *Antimicrobial Agents and Chemotherapy* 53:3159–3161, 2009.
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. *et al.* CTX–M: Changing the Face of ESBLs in Europe. *J. Antimicrobial Chemotherapy* 59:165–174, 2007.
12. Lewis, J.S. *et al.* First Report of the Emergence of CTX–M-Type Extended-Spectrum ß-Lactamases (ESBLs) as the Predominant ESBL Isolated in a U.S. Health Care System. *Antimicrobial Agents and Chemotherapy* 51:4015–4021, 2007.
13. Castanheira, M. *et al.* Rapid Emergence of *bla*CTX–M Among *Enterobacteriaceae* in U.S. Medical Centers: Molecular Evaluation From the MYSTIC Program (2007). *Microbial Drug Resistance* 14:211–216, 2008.
14. Sjölund-Karlsson, M. *et al.* Human *Salmonella* Infection Yielding CTX–M β-Lactamase, United States. *Emerging Infectious Diseases* 14:1957–1959, 2008.
15. McGettigan, SE. *et al.* Prevalence of CTX–M β-Lactamases in Philadelphia, Pennsylvania. *Journal of Clinical Microbiology* 47:2970–2974, 2009.
16. Sjölund-Karlsson, M. *et al. Salmonella* Isolates with Decreased Susceptibility to Extended-Spectrum Cephalosporins in the United States. *Foodborne Pathogens and Disease* 7:1503–1509, 2010.
17. Wittum, T.E. *et al.* CTX–M-Type Extended-Spectrum ß-Lactamases Present in *Escherichia coli* from the Feces of Cattle in Ohio, United States. *Foodborne Pathogens and Disease* 7:1575–1579, 2010.
18. Naseer, U. and A. Sundsfjord. The CTX–M Conundrum: Dissemination of Plasmids and *Escherichia coli* Clones. *Microbial Drug Resistance* 17:83–97, 2011.
19. Sjölund-Karlsson, M. *et al.* CTX–M-producing Non-Typhi *Salmonella* spp. Isolated from Humans, United States. *Emerging Infectious Diseases* 17:97–99, 2011.
20. Mølbak, K. Spread of Resistant Bacteria and Resistance Genes from Animal to Humans—The Public Health Consequence. *Journal of Veterinary Medicine* B51:364–369, 2004.
21. USDA, ''National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Animal Arm Annual Report, 2009,'' Athens, Georgia, U.S. Department of Agriculture, USDA, 2011.
22. FDA, ''National Antimicrobial Resistance Monitoring System-Enteric Bacteria (NARMS): 2009 Executive Report,'' Rockville, MD, U.S. Department of Health and Human Services, Food and Drug Administration, 2011.
23. FDA, ''National Antimicrobial Resistance Monitoring System-Enteric Bacteria (NARMS): 2007 Executive Report,'' Rockville, MD, U.S. Department of Health and Human Services, FDA, 2010.
24. CDC, ''National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report, 2009,'' Atlanta, Georgia, U.S. Department of Health and Human Services, CDC, 2011.
25. Dutil, L. *et al.* Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg in chicken meat and humans, Canada. *Emerging Infectious Diseases* 16:1, 2010.
26. Zhao, S. *et al.* Beta-Lactam Resistance in *Salmonella* Isolated From Retail Meats in the United States: National Antimicrobial Resistance Monitoring System (NARMS): 2002–2006. *Applied and Environmental Microbiology* Oct. 23, 2009.
27. Zhao, S. *et al.* Identification and expression of cephamycinase *bla*CMY genes in *Escherichia coli* and *Salmonella* isolates from food animals and ground meat. *Antimicrobial Agents and Chemotherapy* 45:3647–50, 2001.
28. Lowrance, T.C. *et al.* Changes in antimicrobial susceptibility in a population of *Escherichia coli* isolated from feedlot cattle administered ceftiofur crystalline-free acid. *American Journal of Veterinary Research* 68:501–507, 2007.
29. Tragesser, L.A. *et al.* Association between ceftiofur use and isolation of *Escherichia coli* with reduced susceptibility to ceftriaxone from fecal samples of dairy cows. *American Journal of Veterinary Research* 67:1696–1700, 2006.
30. van den Bogaard, A.E. and E.E. Stobberingh. Epidemiology of resistance to antibiotics. Links between animals and humans. *International Journal of Antimicrobial Agents* 14:327–335, 2000.
31. Cummings, K.J. *et al.* The incidence of salmonellosis among dairy herds in the northeastern United States. *Journal of Dairy Science* 92:3766–3774, 2009.
32. Cummings, K.J. *et al.* The duration of fecal *Salmonella* shedding following clinical disease among dairy cattle in the northeastern USA. *Preventive Veterinary Medicine* 92:134–139, 2009.
33. Cobbold, R.N. *et al.* Long-term persistence of multi-drug-resistant *Salmonella enterica* serovar Newport in two dairy herds. *Journal of the American Veterinary Medical Association* 228:585–591, 2006.
34. Warnick, L.D. *et al.* Effect of previous antimicrobial treatment on fecal shedding of *Salmonella enterica* subsp. enterica serogroup B in New York dairy herds with recent clinical salmonellosis. *Preventive Veterinary Medicine* 56:285–297, 2003.
35. Berge, A.C., D.A. Moore, and W.M. Sischo. Prevalence and antimicrobial resistance patterns of *Salmonella enterica* in preweaned calves from dairies and calf ranches. *American Journal of Veterinary Research* 67:1580–1588, 2006.
36. Scallan, E. *et al.* Foodborne Illness Acquired in the United States—Major Pathogens. *Emerging Infectious Diseases* January 2011.
37. Varma, J.K. *et al.* Antimicrobial-resistant nontyphoidal *Salmonella* is associated with excess bloodstream infections and hospitalizations. *Journal of Infectious Diseases* 191:554–561, 2005.
38. Varma, J.K. *et al.* Hospitalization and antimicrobial resistance in *Salmonella* outbreaks, 1984–2002. *Emerging Infectious Diseases* 11:943–946, 2005.
39. Varma, J.K., *et al.* Highly Resistant *Salmonella* Newport-MDRAmpC Transmitted through the Domestic US Food Supply: A FoodNet Case-Control Study of Sporadic *Salmonella* Newport Infections, 2002–2003. *Journal of Infectious Diseases* 194:222–230, 2006.
40. Centers for Disease Control and Prevention. Outbreak of multidrug-resistant *Salmonella* Newport—United States, January-April 2002. *Morbidity and Mortality Weekly Report* 51:545–548, 2002.
41. CDC, Outbreak of multidrug-resistant *Salmonella enterica* serotype Newport infections associated with consumption of unpasteurized Mexican-style aged cheese—Illinois, March 2006–April 2007. *Morbidity and Mortality Weekly Report* 57:432–435, 2008.
42. 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.
43. U.S. Food and Drug Administration, Dallas District, Warning Letter: The Veterinary Pharmacy, Inc. REF–2004–DAL–WL–29, August 6, 2004. *http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2004/ucm146544.htm* (accessed January 6, 2011).

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 (not including cephapirin) in cattle, swine, chickens, or turkeys:

(i) For disease prevention purposes;

(ii) At unapproved doses, frequencies, durations, or routes of administration; or

(iii) If the drug is not approved for that species and production class.

* * * * *

Dated: November 23, 2011.

Bernadette Dunham,

Director, Center for Veterinary Medicine.

[FR Doc. 2012–35 Filed 1–4–12; 11:15 am]

BILLING CODE 4160–01–P

DEPARTMENT OF DEFENSE

Office of the Secretary

[DOD–2010–OS–0043; RIN 0790–AI62]

32 CFR Part 222

DoD Mandatory Declassification Review (MDR) Program; Correction

AGENCY: Department of Defense.

ACTION: Final rule; correction.

SUMMARY: On December 27, 2011 (76 FR 80744–80747), Department of Defense published a final rule titled DoD Mandatory Declassification Review (MDR) Program, which assigns responsibilities and provides procedures for members of the public to request a declassification review of information classified under the provisions of Executive Order 13526, or predecessor orders. This rule corrects a paragraph identification error in the regulations.

DATES: This correction is effective January 26, 2012.

FOR FURTHER INFORMATION CONTACT: Patricia Toppings, (571) 372–0485.

SUPPLEMENTARY INFORMATION: On December 27, 2011, Department of Defense published a final rule titled DoD Mandatory Declassification Review (MDR) Program. Subsequent to the publication of that final rule, Department of Defense discovered that paragraph § 222.5(f) in the third column of page 80746 should have read § 222.5(j).

Correction

In the final rule (FR Doc. 2011–33104) published on December 27, 2011 (76 FR 80744–80747), make the following correction:

§ 222.5 [Corrected]

On page 80746, in § 222.5, in the third column, in the first line of the third paragraph, ''(f) *MDR Appeals.''* should read ''(j) *MDR Appeals.''*.

Dated: December 30, 2011.

Aaron Siegel,

Alternate OSD Federal Register Liaison Officer, Department of Defense.

[FR Doc. 2011–33857 Filed 1–5–12; 8:45 am]

BILLING CODE 5001–06–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[EPA–R09–OAR–2011–0547; FRL–9480–1]

Revisions to the California State Implementation Plan, San Joaquin Valley Unified Air Pollution Control District (SJVUAPCD)

Correction

In rule document 2011–33660 appearing on pages 214–217 in the issue of Wednesday, January 4, 2012, make the following corrections:

(1) On page 214, in the second column, in the DATES section, in the second line, ''February 3, 2011'' should read ''February 3, 2012''.

(2) On page 217, in the first column, in the last paragraph, in the fifth line, ''March 7, 2011'' should read ''March 5, 2012''.

[FR Doc. C1–2011–33660 Filed 1–5–12; 8:45 am]

BILLING CODE 1505–01–D

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2010–0944; FRL–9330–4]

Bacillus Amyloliquefaciens Strain D747; Exemption From the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes an exemption from the requirement of a tolerance for residues of the *Bacillus amyloliquefaciens* strain D747 (formerly known as *Bacillus subtilis* variant *amyloliquefaciens* strain D747) in or on all food commodities when used in accordance with good agricultural practices. Certis USA LLC submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting an exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of *Bacillus amyloliquefaciens* strain D747 (formerly known as *Bacillus subtilis* variant *amyloliquefaciens* strain D747).

DATES: This regulation is effective January 6, 2012. Objections and requests for hearings must be received on or before March 6, 2012, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2010–0944. All documents in the docket are listed in the docket index available at *http://www.regulations.gov.* Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information the disclosure of which is restricted by statute. Certain other material, such as copyrighted material, is not made available via the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic docket at *http://www.regulations.gov,* or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Susanne Cerrelli, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; telephone number: (703) 308–8077; email address: *cerrelli.susanne@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you are an agricultural