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Cephalosporin Order of Prohibition Questions and Answers

On January 6, 2012, the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) issued an order prohibiting certain uses of the cephalosporin class of antimicrobial drugs in food-producing animals.

A copy of the Federal Register document is available at <http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf>¹. Although the basis for the order is fully described in the January 6, 2012 final rule, CVM has provided the following questions and answers.

What is FDA announcing today?

FDA's Center for Veterinary Medicine is issuing an order that prohibits the extralabel use of cephalosporin drugs (not including cephalixin) in cattle, swine, chickens, and turkeys. In its order, FDA is prohibiting what are called "extralabel" or unapproved uses of cephalosporins in cattle, swine, chickens and turkeys, the so-called major species of food-producing animals. Specifically, the prohibited uses include:

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

The following exceptions to the prohibition apply:

- Extralabel use of approved cephalixin products in food-producing animals;
- Use to treat or control an extralabel disease indication, as long as this use adheres to a labeled dosage regimen (i.e., dose, route, frequency, and duration of administration) approved for that particular species and production class; and
- Extralabel use in food-producing minor species, such as ducks or rabbits.

Does the new order mean that all cephalosporin drug use in food-producing animals is prohibited?

No, the rule only applies to the extralabel use of certain cephalosporins in cattle, swine, chickens and turkeys. Use of cephalosporin drugs for their approved indications in food animal species is not prohibited under this rule.

Why is FDA doing this?

The cephalosporin class of drugs is important in treating human diseases, such as pneumonia, skin and tissue infections, pelvic inflammatory disease, and other conditions. It is critical to preserve the effectiveness of these drugs.

FDA is concerned that certain extralabel uses of cephalosporins in cattle, swine, chickens and turkeys are likely to contribute to cephalosporin-resistant strains of certain bacterial pathogens. If cephalosporins are not effective in treating human diseases from these pathogens, doctors may have to use drugs that are not as effective or that have greater side effects.

The Agency is particularly concerned about the extralabel use of cephalosporin drugs that are not approved for use in cattle, swine, chickens and turkeys because little is known about their microbiological or toxicological effects when used in these food-producing animals.

How does this action relate to FDA's overall strategy to address the public health concern of antibiotic use in food producing animals?

Addressing antimicrobial resistance is a challenging task that requires the expertise and collaborative efforts of many entities. The order to prohibit certain extralabel uses of cephalosporin drugs in major species of food-producing animals addresses the use of one class of antimicrobial drugs used in animal agriculture for therapeutic purposes. This action is among a number of ongoing FDA activities and initiatives intended to address concerns about the use of antimicrobial drugs in animal agriculture, including:

- Monitoring resistance trends in foodborne bacteria through the National Antimicrobial Resistance Monitoring System (NARMS)
- Assessing antimicrobial resistance risks for new antimicrobial drugs as part of the new animal drug approval process.
- Promoting the judicious use of medically important antimicrobials currently approved for use in food-producing animals in a draft guidance entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" draft Guidance for Industry #209 ("draft GFI #209"). The agency is working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders to address antimicrobial resistance concerns in a manner that is protective of both human and animal health.

What are some examples of extralabel uses of cephalosporins that are prohibited by this order?

- In ovo chick injections (injections into chicken eggs) is an unapproved use and is prohibited
- The use of biobullets in beef cattle is an unapproved use and is prohibited
- The extralabel use of human cephalosporin drugs in food-producing major species is an unapproved use and is prohibited
- Prevention uses in food-producing major species are prohibited

What is not prohibited by this order?

- Extralabel use of approved cephalixin products in food-producing animals;
- Use to treat or control an extralabel disease indication, as long as this use adheres to a labeled dosage regimen (i.e., dose, route, frequency, and duration of administration) approved for that particular species and production class; and
- Extralabel use in food-producing minor species, such as ducks or rabbits

Why didn't FDA prohibit extralabel use of cephalixin products in food-producing major species?

Currently there are no cephalixin drug products approved for use in humans. Cephalixin also has a narrow spectrum of activity compared to newer cephalosporins like ceftiofur. For these two reasons, cephalixin is less likely to cause cross-resistance to drugs in other cephalosporin classes. Furthermore, cephalixin is currently only approved for use in food-producing animals as an intramammary infusion formulation for dairy cattle. Therefore, because the impact of cephalixin 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 determined that it was

appropriate to exclude cephalosporin drug products from the prohibition order.

When does the order go into effect and is there an opportunity for the public to comment?

The order of prohibition that published as a final rule on January 6, 2012, will go into effect on April 5, 2012. However, the public can submit comments during a 60-day comment period that closes on March 6, 2012. CVM intends to review and consider all submitted comments prior to the effective date of the order.

You may submit written or electronic comments to <http://www.regulations.gov>². Comments are to be identified with the docket number FDA-2008-N-0326.

How does today's order differ from the previous proposed order of July 2008?

The 2008 proposal prohibited all extralabel use of cephalosporins in food producing animals with no exceptions. Today's order was based on the agency's review of comments and additional information submitted in response to the July 3, 2008 order, including comments asserting that the order was too broad in that it unnecessarily prohibited certain extralabel uses that are not likely to present a risk to the public health. The agency re-examined the basis for the original order and reconsidered its approach in three specific areas: extralabel use of cephalosporins, extralabel use for unapproved indications, and extralabel use in food-producing minor species.

Historical Context

What action is FDA taking on cephalosporins?

Today's order prohibits all extralabel use of cephalosporin drugs in food-producing animals except for the following uses:

- (1) *Cephapirin*: Extralabel uses of approved cephalosporin 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 use in food-producing minor species is excluded from the prohibition.

Why was the first order of July 2008 revoked?

In response to the July 2008 order, FDA received many substantive comments and additional information related to the extralabel use of cephalosporins in veterinary practice. FDA revoked the July 2008 order in order to allow FDA scientists the time necessary to fully consider the substantive comments from the public.

How many comments were received?

The Agency received comments from approximately 170 organizations or individuals on the July 3, 2008, order of prohibition.

Who submitted comments?

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.

Did FDA receive comments in support of the order of prohibition?

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.

Can you summarize the types of comments received?

The comments can be summarized into two general categories:

- (1) Comments that 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) Comments that 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.

Did the FDA agree with the comments?

FDA does not agree with comments alleging that the Agency did not meet the legal standard for issuing an order of prohibition; however, the Agency does agree with comments that the scope of the original order of prohibition could have been more targeted.

Background

What is antimicrobial resistance?

Antimicrobial drugs have been widely used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. Antimicrobial resistance occurs when an antimicrobial drug loses its ability to effectively control or kill bacterial growth; the bacteria become resistant to the drug and these resistant bacteria continue to multiply in the presence of therapeutic levels of an antibiotic. The development of resistance to antimicrobial drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. Misuse and overuse of antimicrobial drugs can create selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increase the opportunity for individuals to become infected by resistant bacteria. Because antimicrobial drug use contributes to the emergence of drug resistant organisms, these important drugs must be used judiciously in both animal and human medicine to slow the development of resistance.

What are cephalosporins?

Cephalosporins are widely used antimicrobial agents in human and veterinary medicine. They were introduced into human clinical use in 1964.

Are cephalosporins used for growth promotion in herds or flocks of food-producing animals?

No, they are only used for therapeutic use in individual animals. Cephalosporins are not available for herd-wide or flock-wide use via medicated feed or medicated drinking water.

What diseases in humans are cephalosporins used to treat?

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*.

Why are cephalosporins important for human medicine?

Newer cephalosporins (for example, third generation cephalosporins such as ceftriaxone) are used in the hospital setting to treat seriously ill patients with life-threatening diseases, 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.

What diseases in animals are cephalosporins used to treat?

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 *Escherichia 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 *Escherichia 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*.

What is extralabel drug use?

The term "extralabel use" refers to use of an approved drug in an animal in a manner that does not follow the approved labeling. Extralabel drug use should only occur in circumstances when an animal's health is threatened, or suffering or death may occur if treatment is not administered.

Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), extralabel use of drugs in animals is permitted only by, or on the order of, a licensed veterinarian within the context of a valid veterinarian-client-patient relationship. A valid veterinarian-client-patient relationship has several specific components. First, a veterinarian takes responsibility for making medical judgments regarding the animal's health and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) agrees to follow the veterinarian's instructions. Second, the veterinarian is familiar with the animal and can provide a general or preliminary diagnosis for the animal's medical condition. Third, the veterinarian is available for follow-up in the event of adverse reactions or treatment failure. Therefore, a valid veterinarian-client-patient relationship exists only when the veterinarian has recently seen, and is personally familiar with, how the animal is cared for by virtue of physically examining the animal during medically-appropriate or routine visits to the location where the animal is kept.

Extralabel drug use in food-producing animals carries additional requirements because of the potential for drug residues in edible animal products. The complete extralabel use requirements are found in Title 21 of the U.S. Code of Federal Regulations, Part 530 (21 CFR part 530). Some of the requirements for extralabel drug use in food-producing animals include:

- A valid veterinarian-client-patient relationship must exist.
- There is no approved animal drug labeled for the treatment need which has the same active ingredient in the required dosage form and concentration; or, the approved animal drug is clinically ineffective for its approved use and an effective substitute is needed.
- The veterinarian must carefully evaluate and diagnose the condition requiring treatment.
- The veterinarian must establish a scientifically appropriate withdrawal period, based on appropriate scientific information, if available.
- The veterinarian must ensure that the treated animal's identity is carefully documented and maintained.
- The veterinarian must ensure that the assigned withdrawal times are observed and no illegal drug residues occur in any food-producing animal receiving extralabel drug treatment.

Have other drugs been prohibited from extralabel use in food-producing animals?

Yes. Under the provisions AMDUCA and 21 CFR part 530, FDA can prohibit the extralabel use in animals of approved animal or human drugs, or an entire class of drugs, if FDA determines that: (1) an acceptable analytical method needs to be established and such a method has not or cannot be established; or (2) the extralabel use of the drug or drug class presents a public health risk. FDA can also limit the prohibition on extralabel use to specific species, indications, dosage forms, routes of administration, or a combination of these. In the case of cephalosporins, FDA is prohibiting extralabel use of the entire class of cephalosporin drugs, with certain exceptions, to avoid risks to public health.

When the Order of Prohibition takes effect, cephalosporins will be added to the current list of drugs and other substances found in 21 CFR part 530 that are prohibited from extralabel use in food-producing animals as follows:

- Chloramphenicol
- Clenbuterol
- Diethylstilbesterol (DES)
- Dimetridazole
- Iprnidazole
- Other nitroimidazoles
- Furazolidone
- Nitrofurazone
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxyypyridazine)
- Fluoroquinolones
- Glycopeptides
- Phenylbutazone in female dairy cattle 20 months of age or older
- Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys: (i) For disease prevention purposes; (ii) At unapproved doses, durations, or routes of administration; or (iii) If the drug is not approved for that species and production class.

In addition, the extralabel use of adamantanes and neuraminidase inhibitors used to treat or prevent influenza A in humans is prohibited in chickens, turkeys, and ducks.

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U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)





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