What is ceftiofur?
Ceftiofur is a veterinary antibiotic approved by the U.S. Food and Drug Administration (FDA). It is in the class of drugs called cephalosporins. Ceftiofur is a third-generation cephalosporin. Cephalosporin antibiotics are also used in human medicine, and there are a total of four generations of cephalosporins. Later-generation (third- and fourth-generation) cephalosporins have been deemed critically important antibiotics in human and animal medicine because they are used to treat serious diseases in both.

What types of cephalosporins are used in animal agriculture and how are they used?
In veterinary medicine, only first- and third-generation cephalosporin products are used in the United States. Zoetis produces several product formulations that contain ceftiofur to address specific conditions in food animals. All are administered by injection or intramammary infusion. No cephalosporin antibiotics used in food-producing animals are administered orally, and none has label approval for use in promoting growth or preventing disease.

Is ceftiofur safe?
Ceftiofur is a safe, effective and on-label option for veterinarians who need to treat difficult diseases. Ceftiofur is one of the most extensively evaluated veterinary antibiotics. Since 1988, the FDA has approved new ceftiofur formulations and claims more than 20 times for the treatment and control of specific serious diseases in livestock.

How much ceftiofur is used in food-animal production?
Cephalosporin products (both first- and third-generation) comprise less than 0.3% of all medically important antibiotics sold (by weight) for use in animals, both companion and food animals. The 2011 and 2012 data for veterinary antibiotics sold and distributed at:

Why do government reports say cephalosporin use in animals has increased by 37%?
Cephalosporins sold for use in animals have increased since 2009 (the year for which this comparison was made), but it is a percentage increase of a very small number (well under 1% of total antibiotic sales). This statistic refers to the entire cephalosporin category for both food and companion animals. Also, the FDA has approved additional uses for cephalosporins since 2009, including some received for ceftiofur for treatment of specific serious conditions in food animals.

Are there alternatives to using ceftiofur in food animals?
For some classes of livestock and livestock diseases, the number of FDA-approved treatment options is limited. It is important that veterinarians have a range of alternatives because certain drugs work, or work better, only in certain cases. Ultimately, veterinarians need to have many therapeutic options available as they consider the herd health history, expected efficacy and recovery rates for those treated. Ceftiofur is a safe, on-label option and target pathogens remain nearly 100% susceptible to ceftiofur.1,2
What is Zoetis doing to address food safety questions?
The FDA’s approval process for ceftiofur hinges on whether food from the treated animal is safe for human consumption. One component of the approval process is a science-based microbial safety assessment, which is an evaluation of the potential for the antibiotic to contribute to antibiotic treatment failures due to resistance in humans. Another component is a determination of the safe ingestion levels of antibiotic residues in meat or milk without impact on human gut flora. These assessments and others form the basis for the human food safety assessment for all antibiotic approvals through the FDA. The FDA has confirmed the safety of ceftiofur many times; most recently, the FDA approved a Zoetis ceftiofur product in 2013.

Are cephalosporin-resistant *Salmonella* infections in people increasing? No. Data collected by the government’s National Antimicrobial Resistance Monitoring Surveillance (NARMS) confirms the level of these infections in people is low and has not been increasing.³

What guarantee do producers have that they will not have residues when using ceftiofur products? Producers must use ceftiofur according to label directions. In addition, Zoetis offers its customers a Residue Free Guarantee™ on ceftiofur products. This guarantee, introduced by Zoetis in 2011, backs all ceftiofur products used by dairy, cattle and swine farmers. It is the only guarantee of its kind in animal health. Not only that, we support our veterinary and livestock producer customers with the training and tools needed to use ceftiofur — and any of our antibiotic products — properly and responsibly to help protect animal and human health and the safety of the food supply.

What is the prevalence of residue violations in meat? There is good news. As part of the government’s food safety monitoring umbrella, the U.S. Department of Agriculture (USDA) has a multi-tiered program to detect residues in the food supply; this includes “scheduled sampling” that is statistically designed to gain insights about the level of residues in animals going into the food chain through random sampling. This program finds the prevalence of antibiotic residue violations across the meat supply is very, very low, and ceftiofur has not been identified among those antibiotic medicines with the greatest frequency of drug residues.⁴ For example, there were three violations in the scheduled sampling program in first half of 2014 (275,000 assays from more than 3,000 samples), none of which involved ceftiofur.

But I’ve read that USDA has found some ceftiofur residue violations in meat? What are the details? There is a second component of the residue monitoring system called the “inspector-generated program.” The intent of this component is not to estimate prevalence of residues but it rather “targets suspect animals and suspect populations of animals.”⁵ In the case of cattle and swine, inspectors observe EVERY animal as it is presented for harvest. If inspectors have concerns about the health of an animal, it is pulled from the line. Meat from the animal is evaluated, and tests for antibiotic residue are run. If the meat contains residue violations or if the animal is condemned for other reasons, it does not enter the food chain.

Antibiotic violations are higher among the unhealthy animals pulled from the line by inspectors, including violations related to ceftiofur. And although these animals identified by inspectors represent a small percentage of the total and do not make it into the food supply, if issues are confirmed, it is important to understand and address why the violations are occurring.
FREQUENTLY ASKED QUESTIONS ABOUT CEFTIOFUR

Why are animals with violative levels of antibiotics showing up in the inspector generated program?
Investigations of farms where the animals originate suggest these violations are the result of inadequate veterinarian involvement, often because producers fail to meet the labeled guidelines for the withholding period. Other common reasons include using drugs in ways that are not approved (off-label) and inaccurate record keeping.

Why did FDA impose restrictions on ceftiofur use in 2012?
In 2012, the FDA deemed that certain extra-label use (ELDU) of third-generation cephalosporin antimicrobial drugs in food-producing animals is not appropriate. Specifically, the order prohibits the following:
- Extra-label use of cephalosporin drugs at unapproved doses, frequencies, durations, routes of administration, or in approved livestock species
- Use of cephalosporin drugs for disease prevention
- *In ovo* use in poultry. (This use was never approved for poultry.)

The ELDU order by the FDA does **not** affect the FDA’s approved indications for ceftiofur. The veterinarian’s ability to prescribe ceftiofur for FDA-approved uses in food animals is unchanged. The order allows veterinarians extra label prescribing privileges of cephalosporin drugs in cattle, swine, chickens and turkeys for non-labeled disease indications, but in those cases, veterinarians must follow approved routes of administration, dosage and withdrawal times for the treatment and control of disease. These approved uses of ceftiofur have undergone and met the scientific rigor required by the FDA and, when used according to label directions, are safe and effective in treating disease while protecting the safety of the food supply.

What is Zoetis’ position on those ELDU restrictions?
Zoetis supports these ELDU restrictions. We strongly support the responsible use of all antibiotics to protect animal and human health and strongly advocate veterinary involvement whenever antibiotics are used. We also acknowledge the intent of the proposed order to respect veterinary discretion in determining the appropriate and responsible use of cephalosporin antibiotic medicines in the interest of animal health and human health.

Based on the paper by Lowrance, et al, would Zoetis support a withdrawal time based on microbial safety factors, in other words, determining the time when zoonotic pathogens would likely resume their susceptibility to medically important antibiotics?
No. Keep in mind, drug sponsors do not set withdrawal times. Sponsors provide an extensive and required group of studies to regulatory agencies to provide a full understanding of the toxicology, metabolism and microbial safety of a proposed compound. The agency evaluates all relevant data. This evaluation includes an assessment of the potential effect of a compound on human gut flora (otherwise called a microbial ADI) as well as selection pressures for resistant organisms. In total, antibacterial resistance is one portion of the full human food safety assessment, and the drivers for the final assessment are dependent on the drug. Regulatory agencies use all data to establish a withdrawal period that will ensure safe meat, milk and eggs for human consumption.

Can veterinarians continue to recommend ceftiofur products for approved label uses?
Yes. If a diagnosis and a treatment plan is made under the supervision of the veterinarian consistent with the labeled use of ceftiofur, veterinarians should feel confident recommending ceftiofur as a safe and effective treatment of serious animal diseases.
What is Zoetis doing to help support responsible use of ceftiofur and why?

Responsible use of ceftiofur on the farm will help preserve its effectiveness against target pathogens as well as help to ensure safe food. The Zoetis Field Force and technical services team has invested 26 years in ongoing education and training so veterinarians and farmers understand how to use ceftiofur products appropriately and within the label guidelines outlined by the FDA. The team advocates for, advises and trains veterinary and livestock farmer customers on sound practices on the farm, such as proper nutrition, vaccination and veterinary oversight, all of which reduce the need for disease treatment. Additional information about our programs may be found at www.zoetisus.com and www.avoidresidues.com.

Whom should we call if we have questions?

Producer and veterinarian customers may call Zoetis’ Veterinary Medical Information and Product Support (VMIPS) at 800-366-5288.

Residue Free Guarantee: If you use a Zoetis-branded ceftiofur product according to label indications, and experience a violative ceftiofur milk or meat residue, Zoetis will compensate you for the market value of the animal or purchase the tanker of milk at fair market value. You must purchase the product from a Zoetis-approved supplier, use the product according to label indications, have documentation of the product purchase and treatment records, and have conducted training on appropriate use to ensure proper dose and route of administration of the product. Extra-label use as prescribed by a veterinarian is excluded from the guarantee. If you experience a ceftiofur residue violation after following label indications and the above steps, contact Zoetis VMIPS (Veterinary Medical Information and Product Support) at 800-366-5288 to report the situation.

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