

**DOCKET NO. 2008N-0326: NEW ANIMAL DRUGS;
CEPHALOSPORIN DRUGS; EXTRALABEL ANIMAL DRUG USE;
ORDER OF PROHIBITION**

PFIZER ANIMAL HEALTH COMMENTS TO THE PROPOSED ORDER

Executive Summary

This document provides Pfizer's comments to FDA Docket No. 2008N-0326: New Animal Drugs: Cephalosporin Drugs; Extralabel Animal Drug use; Order of Prohibition.

Pfizer is a pioneer sponsor for antimicrobial drugs used to treat diseases in humans and animals, including cephalosporin drugs approved for use in food-producing livestock. Pfizer understands and shares the FDA's concerns regarding the challenges that antimicrobial resistance poses to both human and animal health. Pfizer also appreciates that the FDA has a unique role in protecting public health, using the best scientific knowledge available.

With this mandate in mind, Pfizer respectfully submits the following comments and suggestions to this proposed order. Our objective is to improve the proposed Order's consistency with science and with the FDA's own risk assessment guidance and policy to achieve the result that CVM seeks. This consistency is key to gaining veterinarians' support of the final Order that, left unchanged, may otherwise be viewed as a sweeping, unjustified government curtailment of their obligation to treat their patients with what is, in many cases, the only option for relieving animal suffering and disease. Lacking veterinarian support, CVM runs the risk of having a very broad ban which achieves nothing when a more targeted, science-based approach may achieve not only support by the profession, but foster progress in addressing certain improper uses of cephalosporins while protecting human and animal health.

First and foremost, Pfizer supports the efficacy and safety of the approved uses of its ceftiofur formulations in livestock. Ceftiofur is a prescription-only, injection-only (including intramammary infusion), 3rd-generation cephalosporin approved for therapeutic use in several livestock species for the treatment or control of bacterial diseases in sick animals and in animals at known risk of infection. FDA/CVM has conducted microbial safety risk assessment evaluations for all beef cattle, dairy cattle, and swine treatment and control indications for ceftiofur approved since 2003. There are no approvals of ceftiofur for the prevention of disease or for the use of ceftiofur via oral administration in feed or water.

Studies show that ceftiofur is a drug that exerts very transient, low selection pressure for resistant organisms during treatment and that it does not persist upon excretion by the animal. Furthermore, microbiologically active residues are not detected in feces of treated animals. All *in vivo*, *in situ*, and *in vitro* studies suggest that ceftiofur's persistence in the immediate animal environment is minimal, since ceftiofur and its residues are rapidly inactivated in feces, mixtures of feces and urine, and even in soil. In summary, the science shows that ceftiofur has many attributes that are ideal for treating very sick animals while carrying low risks to the environment and consumers.

Pfizer is concerned that the process by which the FDA concluded the need for this proposed Order was neither transparent nor risk-based. The emergence and dissemination of resistant *Salmonella* is a complex phenomenon that benefits from systematic evaluation of a number of variables (only one of which is drug use).

Cephalosporin-resistant *E. coli* and *Salmonella* are cross-resistant to many β -lactam drugs and, typically, co-resistant to other antimicrobial drug classes. Therefore, the use of any one of a number of antibiotic classes may exert a selective pressure for cephalosporin-resistant *Salmonella* because these organisms are multi-drug resistant. In addition, multi drug resistant bacteria can occur without any apparent antibiotic use, such as through clonal spread. As a result, the FDA should consider all factors that may select for resistance dissemination (management factors, biosecurity procedures, animal transport, and all antimicrobial drug class use) prior to drawing a conclusion regarding the impact of a single class, e.g. cephalosporins.

Pfizer questions the Order's reliance on NARMS data alone to make a decision on a mitigation strategy. The NARMS data, while useful in context, are only one component in monitoring for resistance in the food chain. The presence of cephalosporin resistance in *Salmonella* isolates, as the NARMS data indicate, does not in any way prove that the cephalosporin antibiotics are the sole culprits, especially in the face of overwhelming evidence that many other antimicrobials and other classes of antimicrobials that are much more widely used and may select for these multi-drug resistant organisms.

Finally, a complete ban of extra-label use for cephalosporin drugs undermines the veterinarian's role in determining the best treatment for their patients, particularly in situations where there are no viable, FDA approved, treatment alternatives. This may result in the inability to effectively treat sick animals, raising a significant concern for animal welfare and potential misuse of other antimicrobial drugs. Indeed, the proposed Order places the veterinarian in the position of letting patients die when no good treatment options are available, except ceftiofur. Moreover, we strongly believe that the Order, if finalized without revision, could create unintended consequences, such as weakening the health of the herd, and predisposing the animals for further dissemination of pathogens. Any strategy related to concerns with antimicrobial resistance must address and avoid such unintended consequences.

Given all of these considerations, we at Pfizer brought together our scientists and veterinarians to discuss ways to amend the Order to be more effective. We reviewed the existing science; judicious use principles; current cephalosporin approvals in livestock, and the risk assessments supporting those approvals; as well as the policy construct of the Agency's risk assessment process and guidance. Given these parameters and information, we developed the following proposals for CVM's consideration.

First, the administration of cephalosporins not approved for use in food animals, should be banned in food animals. Cephalosporins researched and approved for human use are being used in food animals, even via water, and that simply runs counter to the AMDUCA law and creates a high public health risk.

Second, veterinary cephalosporins should be allowed to be prescribed in an extralabel manner in the species for which a label has already been approved, only via the approved dose and routes of administration, and only for treatment and control of diagnosed diseases in individual animals. This would address CVM's concern of *in ovo* injections in poultry and address concerns that cephalosporins are being used more widely, i.e. to prevent disease, than the approvals allow.

Third, Pfizer recommends that appropriate veterinary professional oversight and resistance monitoring is needed for the use of all antimicrobial drugs, not just cephalosporins.

Fourth, Pfizer proposes that any extralabel use of cephalosporins outside these requirements requires a microbial safety risk assessment by the FDA/CVM for that extralabel use to be allowed.

Finally as a longer term goal in tackling this complex issue of multi-drug resistance, FDA and the animal health industry very much need to find the answers to critical questions that involve antimicrobial use issues across key classes as well the role of clonal spread, animal handling/processing and final food processing. Science is starting to show that each has a role yet we know very little about them and how they interact. Indeed, what we don't know is fairly extensive given the complexity of these factors. It is important to continue working together on the various task forces that the government has created as well as continue our own research efforts here at Pfizer. Pfizer pledges to work with FDA, and other interested parties, on a strategy to address these points.

General Comments

Pfizer's Focus on Human Health and Safety

At Pfizer, protecting human health is our top priority and protecting animal health is a critically important link to human health. Pfizer is motivated by the fact that 11 of the last 12 significant epidemics since 1993 emerged in animals and subsequently spread among humans.

Antimicrobial agents for human and veterinary use are usually derived from the same drug classes. Given the difficulty in discovering antimicrobial drugs, it is fortunate that the same drug classes are effective in both animals and humans. Indeed, given the priority of human health, there are very few classes that cannot be used in humans. With this reality, it is almost inevitable that cross-resistance to entire classes of antimicrobial drugs can develop in bacteria which can then be transmitted between people and animals.

Pfizer understands the urgency and priority placed on developing antimicrobial drugs for human use to treat serious bacterial infections, including those caused by resistant bacteria. Reflective of our commitment, within the last 10 years Pfizer introduced linezolid (Zyvox®), the first of a new class of antimicrobials (i.e., oxazolidinones) for use in the treatment of serious infections, such as respiratory and complicated skin and soft tissue infections, including those due to resistant strains of gram-positive bacteria. Pfizer continues to invest in the discovery and development of new antimicrobial agents for both humans and animals.

Our priority is protecting human health, in part by developing high quality veterinary medicines that are safe to the food supply and the consuming public. Pfizer devotes technical resources to educate veterinarians and producers on the appropriate use of our approved drugs, monitors antimicrobial susceptibility of major cattle and swine pathogens and supports the government's monitoring of the antimicrobial susceptibility of important food-borne enteric pathogens. We support these steps to protect human health and to maintain the efficacy of our antimicrobial drugs.

Overview of Ceftiofur

Ceftiofur is a prescription-only, injection-only, 3rd-generation cephalosporin approved for therapeutic use in beef cattle, lactating and non-lactating dairy cattle, swine, sheep, goats, horses, day-old chicks, day-old poults and dogs. In these species, ceftiofur is only approved for the treatment or control of bacterial diseases in sick animals and in animals at known risk of infection. Specifically, ceftiofur is approved for treatment of respiratory disease in cattle, swine, horses, sheep and goats, as well as bovine metritis, bovine pododermatitis (“foot rot”), early chick and turkey poult mortality, and canine urinary tract infections. Ceftiofur is also approved for use via intramammary infusion in both lactating and non-lactating dairy cattle for the treatment of clinical and subclinical mastitis. Microbial safety risk assessment evaluations have been conducted by FDA/CVM for all beef cattle, dairy cattle, and swine indications for ceftiofur approved since 2003. There are no FDA-approved uses of ceftiofur products via oral administration in feed or water. There are also no label indications for preventative use of these products or growth promotion.

Studies show that ceftiofur is a drug that exerts very transient, low selection pressure for resistant organisms during treatment and that it does not persist upon excretion by the animal. Given the number of different antimicrobial drugs that may exert selection pressure for cephalosporin resistant *Salmonella* and *E. coli* (see below), ceftiofur’s characteristics of transient exposure are a very desirable property. Indeed, the metabolic pathway of ceftiofur has been examined extensively, and found to be the same in all livestock studied, regardless of the ceftiofur salt or ceftiofur product formulation. The principal metabolites of ceftiofur, desfuroylceftiofur (DFC) are formed within minutes of injection. These DFC metabolites retain microbiological activity against label pathogens, and are present in an active form at the infection site. However, microbiologically active residues are not detected in feces of treated animals. All *in vivo*, *in situ*, and *in vitro* studies suggest that ceftiofur persistence in the immediate animal environment is minimal, since ceftiofur and its residues are readily inactivated in feces, mixtures of feces and urine, and even in soil mixtures [1, 2]. These scientific studies have demonstrated the microbial safety attributes of ceftiofur in multiple species for which FDA has granted approvals.

Risk Assessment and Management of Ceftiofur

Pfizer fully agrees with and supports FDA’s science-based risk assessment approach to making decisions that can affect public health, such as the evaluation of a new veterinary antimicrobial drug or a new drug claim. This includes assurance that there is a high level of protection for antimicrobials considered “critically important” for treating human diseases. We have submitted risk assessments for antimicrobial agents in these drug classes and the FDA/CVM has approved their use with specific restrictions. We concur with the FDA that approved uses of ceftiofur when used according to label instructions are safe and effective.

The FDA has determined that 3rd-generation cephalosporins are critically important to human health. The World Organization for Animal Health (also known as the ‘OIE’) has also determined that 3rd-generation cephalosporins such as ceftiofur are critically important antibiotics to animal health (http://www.oie.int/download/Antimicrobials/OIE_list_antimicrobials.pdf). Because of its importance to the veterinary profession, Pfizer Animal Health has worked with the National Research Support Program Region 7 (NRSP-7) of the USDA to gain FDA/CVM approvals in several minor species. This reflects Pfizer’s desire to respond to the unmet needs of the veterinary patient, and the high value the veterinary community places on

ceftiofur as a key therapeutic agent for livestock species. The broader implications of eliminating extralabel use of cephalosporins have not been addressed in the proposed Order, and may have unintended consequences such as increased animal morbidity and mortality due to a lack of approved veterinary drugs and increased use of other, possibly less effective, antimicrobial drugs which can cross- and co-select for cephalosporin resistance.

Pfizer Animal Health supports the stewardship of this molecule by monitoring antimicrobial susceptibility among target pathogens, with that data on susceptibility available to support therapeutic decision-making. Pfizer encourages and supports ongoing training of veterinarians and end users in the treatment of infectious diseases and management practices that minimize disease and resistance determinant transmission. The use of Pfizer's products is recommended within the context of well-defined protocols that call for active veterinary involvement and oversight.

The Biology of Cephalosporin Resistance among Enteric Foodborne Pathogens in the United States

Pfizer believes the only way to beneficially impact antimicrobial resistance is to attack resistance from multiple fronts, not simply by banning uses of a specific class of antimicrobial agent. We agree with FDA that national efforts should strive to minimize the selection and dissemination of cephalosporin and other antimicrobial resistance traits associated with *Salmonella* and *E. coli*. The epidemiology of *Salmonella* and *E. coli* transfer among animals generally and cephalosporin-resistant *Salmonella* and *E. coli* specifically is complex. Mitigation strategies to minimize their dissemination should be multi-factorial, and an extralabel ban of cephalosporins cannot work by itself to contain the spread of these multi-drug resistant organisms.

Salmonella and *E. coli* most frequently become resistant to cephalosporins by acquiring a β -lactamase that is either an extended spectrum β -lactamase (ESBL) or an AmpC cephalosporinase. These β -lactamases can inactivate a very broad range of β -lactam drugs. The ESBLs can inactivate and confer decreased susceptibility or resistance to the penicillin group of β -lactams and their derivatives, the narrow-spectrum cephalosporins, and 3rd-generation cephalosporins. Some members of the CTX-M group of ESBLs additionally confer reduced susceptibility or resistance to 4th-generation cephalosporins. Members of the TEM-, SHV, and CTX-M groups of ESBLs have been demonstrated in *Salmonella* and *E. coli* isolated from animals in Europe. To date, there have been no reports of their isolation from food-producing animals in the US, and they have not been detected in the US NARMS program among animal isolates. The AmpC cephalosporinases confer cross-resistance to the same groups of β -lactams as the ESBLs, and additionally are active against the cephamycins (e.g., cefoxitin), but they are not considered active against 4th-generation cephalosporins. The CMY group of cephalosporinases is the most frequently reported β -lactamase in cephalosporin-resistant *E. coli* or *Salmonella* isolated from animals in the US. Cephalosporins and other antimicrobial agents are used in Europe. The fact that there is regional localization of CMY-carrying *Salmonella* (and *E. coli*) in animal isolates in the US underscores the underlying importance of clonal spread, independent of antimicrobial drug use of the multi-drug resistant organisms, and the complexity of this biology.

Surveys in the US and worldwide indicate that all *Salmonella* and *E. coli* isolates that are resistant to 3rd- and 4th-generation cephalosporins are both cross-resistant to other β -lactam drugs as well as, with few exceptions, co-resistant to other drug classes [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]. Frequently these resistance determinants are present on a multi-drug resistance plasmid along with determinants that code for the ESBL or AmpC cephalosporinase. In other cases, the other resistance determinants are encoded on the chromosome. Given multi-drug resistance, the use of any one of a number of antibiotic classes can exert a selective pressure for multi-resistant *Salmonella* or *E. coli* that produce an expanded-spectrum β -lactamase. The occurrence of cross- and co-resistance underscores the need for mitigation strategies that minimize clonal spread of these bacteria that can happen independent of antimicrobial use. Biosecurity control measures such as sanitation, segregation of diseased animals, management of the commingling of new animal introductions into the herd, separation of animals from manure, and abattoir sanitation and hygiene all can substantially impact dissemination of resistant as well as susceptible pathogens.

Dissemination of *Salmonella* and *E. coli*, whether MDR or pan-susceptible, occurs by means independent and dependent of drug use. While ceftiofur is among those drugs that can select for cephalosporin-resistant *Salmonella* or *E. coli*, there are also reports that cephalosporin-resistant, multi-drug resistant organisms occur in animal species where either cephalosporins are not used, or in species (chicken) where there is no approved use of cephalosporins [8, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. *Salmonella* can be introduced into herds and flocks by a number of non-drug mechanisms, including: introduction of new animals; contaminated feed; rodents or other wild mammals; birds; insects; water; humans (veterinarians, farm crew, farm site visitors); farm or trucking equipment; animal transport from the farm and pre-slaughter holding (lairage) at the slaughterhouse [29, 30, 31, 32, 33, 34, 35, 36]. In addition, cross-contamination of carcasses at the slaughterhouse can occur, leading to additional dissemination of organisms and resistance determinants [37, 38, 39, 40].

Antimicrobial Susceptibility Surveillance and Interpretation

In FDA's proposed order, NARMS data are cited as evidence of an increase in the prevalence of cephalosporin resistance among certain isolates in both human and animals. Pfizer contends that the unilateral ban of extralabel use of cephalosporins is an inappropriate use and translation of the data based on the NARMS program's protocols and operation. Simply put, the sampling scheme of NARMS slaughter isolate program is not designed to estimate *Salmonella* or *E. coli* prevalence or resistance in the animal population at large [41]. Rather, NARMS slaughter isolate surveys provide non-statistically based trends in susceptibility over time among isolates from the PR/HACCP program of the USDA FSIS program. Furthermore, the USDA/NARMS slaughter survey does not survey or determine the yearly prevalence of antimicrobial susceptibility among zoonotic, enteric bacteria associated with healthy animals. The slaughter isolates in the USDA/NARMS survey are collected according to the sampling scheme of a food hygiene compliance monitoring program (the USDA/FSIS PR/HACCP program). The slaughter isolates of *Salmonella* are collected from carcass swabs (pork, beef and turkey), carcass rinsates (chickens), and ground meat (beef, chicken and turkey isolates). The percentage of swabs from carcasses may vary according to year, only *E. coli* are isolated from chicken rinsates, and the extent of sampling across abattoirs nationwide has differed across years so use of these data to determine trends is tenuous at best. Finally, there are no yearly monitoring

programs for isolates from healthy animals in NARMS: The only isolates tested in the NARMS diagnostic isolate program are from animals that are clinically ill or dead (the worst of the worst, not those animals destined for the food chain). In addition, the NARMS data was not designed to monitor factors (e.g., drug use and herd management) which may be contributing to the emergence of resistance. Drug use and non-drug use practices, such as good animal husbandry and hygiene can affect the selection and dissemination of resistant bacteria, and NARMS is not set up to survey organisms associated with the livestock populations where antimicrobials are used. Even if use practices were available at the producer level, NARMS is not designed to scientifically link use practices with susceptibility patterns, as the Order suggests.

The proposed Order by FDA/CVM also does not take into account trends in diagnostic isolates of *Salmonella* from humans after 2004. It is concerning to note that the 2004 NARMS data for human isolates are the most contemporaneous data from the US being referenced in the proposed order, although NARMS data for humans from more recent years should be available to the FDA. Therefore, to base this Order on the USDA-NARMS data on slaughter meat and carcass isolates, with no analysis of recent (later than 2004) trends in human *Salmonella* infections, and to refer to a single 2001 study on hatchery practices in the US establishes a troubling precedent of a major regulatory action based upon a scientific interpretation that extends beyond the existing data.

Currently, there are no equivalent, publicly-funded, national surveillance programs for the monitoring of antimicrobial resistance among veterinary pathogens in the US. Pfizer Animal Health has, for more than 9 years, conducted an ongoing survey of label pathogens and has tested more than 20,000 on label bacterial isolates from across the US. Pfizer makes the results known to veterinarians through publications and presentations at veterinary conferences and has provided these data to CVM as part of INAD and NADA submissions. Veterinarians can consider these data when decisions on therapy need to be made, and when they do not have culture and sensitivity information on the pathogens.

Effective control of antimicrobial resistance requires that decision-making, whether for the determination of treatment for a sick animal or for expenditure of public funds, be based upon quality scientific data. The collection, analysis and reporting of data on antimicrobial use practices and resistance among enteric, zoonotic bacteria and important veterinary pathogens require considerable financial and personnel support. As antimicrobial resistance among pathogens has serious public health implications, adequate resources must be directed towards assuring that sufficient data are collected and are available as quickly as possible. Pfizer supports NARMS and its continuation as a publicly-funded tool for tracking antimicrobial resistance among enteric bacteria. A robust, well-designed surveillance system can identify the presence of resistant bacteria before they spread too far and at a time when there is a greater chance for mitigation strategies to be successful. In addition, using surveillance data, hypotheses about risk factors for resistance emergence and spread can be generated, which can then be tested scientifically. Robust surveillance programs are also very expensive, and Pfizer supports their continued refinement and support.

The Importance of the Veterinarian in Maintaining a Healthy Food Animal Supply

The application of Extralabel Drug Use (ELDU) via AMDUCA legislation plays an important role in the veterinarian's ability to provide producers with sound health care options for their animals. Unlike physicians, veterinarians have fewer FDA-approved medicines available to

treat diseases, making their right to use medicines in an extralabel, but judicious manner, essential. Congress acknowledged veterinarians rights in this legislation, but also included some limitations on these rights. FDA has a responsibility to ensure that its decisions do not unilaterally reverse these rights - the intent of the law - without a substantial scientific rationale for doing so.

It is important to recognize that there are significant bacterial diseases in livestock that require antibiotic treatment. For some of these diseases, there are no FDA approved antibiotics available and this necessitates the veterinarian's need to use antibiotics including the cephalosporin antibiotics in an extra label manner to treat these animals. As a result of this order, veterinarians will lose the privilege to use this class of antibiotics for such diseases. This will have unintended consequences for both livestock health and well being. The proposed order does not take this into account.

As animal health and livestock production industries, we need to challenge our current management practices and seek viable refinements that minimize dissemination of resistant organisms while continuing to supply the global demand for animal-derived protein, which is projected to increase to more than 300 million metric tons by 2020. Resistance of zoonotic pathogens to critically important antimicrobial agents can be influenced by many factors, including use of other antimicrobial agents and livestock management.

Judicious Use of Antimicrobial Drugs

It is vital that the veterinary profession and livestock producers maintain vigilance regarding judicious use of all antimicrobial drugs, not just cephalosporins. Use of approved products which have modern and contemporaneous data supporting safe and effective dosage regimens is only one of the pillars of responsible use of antimicrobial agents. Infection prevention is clearly the best approach, with disease prevention products (i.e., vaccines) and improvement of management practices being at the center of these efforts.

All FDA-approved ceftiofur formulations and indications are consistent with judicious use practices promulgated by the FDA/CVM in collaboration with the American Veterinary Medical Association (AVMA), including the following characteristics of this veterinary drug: 1) prescription only, 2) individual animal treatment by injection only, 3) approvals for use in treatment of clinically recognizable diseases, 4) available recent pharmacokinetic and pharmacodynamic data supporting the dose and duration on the label, and 5) available recent susceptibility data through diagnostic laboratories, NARMS surveys, and, for label pathogens, through Pfizer-supported programs. Pfizer believes that judicious use principles should be actively considered for every therapeutic decision regarding antibiotic use in livestock, irrespective of the antimicrobial drug.

Pfizer Animal Health believes that appropriate professional oversight of the use of therapeutic antimicrobial agents is the critical linkage across all of these facets of judicious use. In our opinion, such oversight is essential for the use of therapeutic antimicrobial agents. This professional oversight should also include an awareness of the antimicrobial resistance occurring in label pathogens and zoonotic bacteria, regionally and nationally. By monitoring the antimicrobial susceptibility of pathogenic bacteria, rational and informed therapeutic decisions can be made including appropriate drug use, even when culture and sensitivity results are not immediately available at the time of clinical presentation. In addition, susceptibility monitoring can provide an early warning of the spread of antimicrobial

resistance among clinically relevant bacteria of veterinary interest through changes in the spatial and temporal distribution of resistant bacteria.

Pfizer Recommendations and Suggestions to the Order

Pfizer recommends FDA/CVM undertake the following actions:

1. FDA/CVM needs to devise a process that will enable the Agency with the ability to request and review microbial safety assessments for extralabel uses needed in livestock for unmet medical needs. Examples of unmet needs include duck septicemia, metritis in sheep and goats, *Actinobacillus suis* infections, sow mastitis, and joint infections in cattle. A revised review process would allow FDA/CVM to evaluate the microbial safety for specific extralabel uses of cephalosporins, with the intent to determine if such proposed use could be removed from the banned list of extralabel uses.
2. FDA/CVM should enhance the efficiency of the drug approval process by creatively addressing efficacy for new, previously extralabel indications in livestock. If there were specific, efficient approaches that would enable examination of particular extralabel uses, it would also allow the agency to review a broader array of antibiotics and use patterns within the context of Investigational NADAs without lowering the microbial safety standards and requirements of animal health antimicrobial agents. Conceivably, an unintended consequence of an extralabel use ban of one antimicrobial drug class is an increased use of other antimicrobials under conditions that may be of greater concern to human health. Clearly, having more agency scrutiny and approval of livestock antimicrobial products and indications to replace the extralabel uses of veterinary antimicrobials should enhance the safety of the human food supply. Industry financially supports the FDA/CVM through the Animal Drug User Fees Act (ADUFA) a user fees program initiated in 2003. Assuring the adequate staffing of FDA/CVM to facilitate the drug review process thus adding new tools to the veterinary armamentarium, is a primary reason the animal health industry was strongly supportive of renewing ADUFA for another five years.
3. Pfizer recommends that the scope of the proposed extralabel drug use ban in the final Order be narrowed to allow extralabel drug use of approved veterinary parenteral cephalosporin products (including intramammary products) in the approved species and by the approved routes of parenteral administration, with individual animal administration required. For any other extralabel uses of cephalosporins approved for use in food-animals, such use should be permitted only if a scientific microbial safety risk assessment has been reviewed and accepted by FDA/CVM.
4. Pfizer recommends that all antimicrobial agents labeled only for humans or companion animals (i.e., no livestock approved indication) be prohibited from use in livestock. This recommendation does not apply to extra-label cephalosporin use in companion animals.
5. Pfizer recommends that appropriate professional oversight that takes into account available label and food borne pathogen surveillance data is an essential component for the judicious use of all livestock antimicrobial agents, not just cephalosporins.

In summary, Pfizer believes that a multifaceted and science-based approach to deal with multi-drug resistant food borne pathogens such as *Salmonella* is essential. Pfizer believes that the total ban on the extralabel use of cephalosporin drugs in food animals alone will not

accomplish this task and may, indeed, be counterproductive. Pfizer believes that there is an absolute need for the veterinarian to utilize this drug class in an extralabel manner as there are many bacterial diseases that do not have approved therapies and failure to treat in an extralabel manner will have animal welfare ramifications. The data submitted to CVM in support of all food animal ceftiofur approvals continues to support the safety and effectiveness of this antibiotic in all available ceftiofur products when used on label. Pfizer firmly believes that these same data can be used to support select prudent extralabel uses of ceftiofur which should be allowed. Finally Pfizer believes that a more focused extralabel prohibition as describe above is justified.

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