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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

FDA Docket No. FDA-2008-N-0326 - New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition

Dear Sir/Madam:

I am writing on behalf of the American Veterinary Medical Association (AVMA), with comments for the U.S. Food and Drug Administration's (FDA) consideration, regarding its recent Order of Prohibition of Extralabel Animal Drug Use dated July 3, 2008. As a not-for-profit association established to advance the science and art of veterinary medicine, the AVMA is the recognized national voice for the veterinary profession. The association's more than 76,000 members represent approximately 86% of U.S. veterinarians, all of whom are involved in myriad areas of veterinary medical practice including private, corporate, academic, industrial, governmental, military, and public health services.

The AVMA has thoughtfully and carefully reviewed the FDA's order prohibiting the extralabel use of cephalosporin antimicrobial drugs in food-producing animals, including the cited scientific literature[1,2,3,4,5,6,7,8,9,10,11,12,13] and additional peer-reviewed scientific literature. The Association has consulted colleagues across the face of veterinary medicine and public health. The AVMA is committed to judicious antimicrobial use, ensuring the efficacy of antimicrobials, and upholding animal and public health. While we admire the FDA's intent, the AVMA has reached scientific conclusions that differ greatly from those offered by the FDA.

The AVMA strongly recommends that the FDA postpone its final rule prohibiting all extralabel use of cephalosporin antimicrobials in food-producing animals, in order to perform a risk assessment characterizing the hazard, evaluating the risk, and ascertaining the impact of any risk management recommendations should extralabel cephalosporin use be prohibited.

The AVMA bases its recommendations on the following:

- **The lack of scientific evidence showing any significant risk to human health by extralabel use of cephalosporins in food-producing animals**
- **The lack of any demonstrated benefit of the rule to human health**
- **The rule's potential for unintended consequences on animal health and welfare, on food safety, and on the practice of veterinary medicine**
- **The misinterpretation of federal regulation**

Analysis of Public Health Hazard: Analyzing FDA's Basis for Prohibiting the Extralabel Use of Cephalosporins

In the final rule, the FDA concludes:

- the extralabel use of cephalosporin antimicrobials in food producing animals is likely to lead to the emergence of cephalosporin-resistant strains of foodborne bacterial pathogens,
- if these drug-resistant bacterial strains infect humans, it is likely that cephalosporins will no longer be effective for treatment in those people, and
- such extralabel drug use will likely cause an adverse event and as such presents a risk to public health.

The FDA believes that the negligible increase in cephalosporin resistant human pathogens is a result of specific cephalosporin use in animals and is supported by the surveillance data cited (National Antimicrobial Resistance Monitoring System (NARMS)[14,15], Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)[16], and European Antimicrobial Resistance Surveillance System (EARSS)[17]. However, in our evaluation of the same data, we find little to no association between cephalosporin use in animals and the negligible increase in cephalosporin resistant human pathogens.

The AVMA supports the preservation of effective treatments for critically important human infections; however, our analysis demonstrates neither significant risk nor causality, between the extralabel use of cephalosporins in food animals and the effectiveness of human therapy. Most importantly, no definitive benefit to human health is scientifically demonstrated by the Order of Prohibition.

1) **We have found no evidence establishing causality between extralabel use of cephalosporin antimicrobials in food animals and the negligible increase in cephalosporin resistant *Salmonella* isolates from humans.** NARMS data paints a confusing picture of trends of resistance making any clear conclusions difficult, and determining causality virtually impossible.

We agree NARMS data does show a slight increase in cephalosporin resistance of some *Salmonella* serotypes[a] isolated from humans[18] and an increase in some of the same cephalosporin resistant *Salmonella* serotypes isolated from food animals[19,20]. However, during the same period of time the majority of serotypes showed no resistance or no increase in resistance in either human or animal isolates. Not only do these data refute the association between cephalosporin use in food animals and increasing cephalosporin resistance, they suggest that clonal spread of a particular serotype may be of greater significance than a slight trend that is not closely paralleled in human and animal isolates.

- Of the individual non-Typhi serotypes[b] identified in NARMS data, only *Salmonella typhimurium* show a slight increase in cephalosporin resistance in human isolates.
    - *Salmonella enteriditis* isolates from humans with the MDR-Amp C type resistance had **decreased** from 0.4% (1/269) in 1999 to 0% (0/271) in 2004.

[a] NARMS data only shows detailed resistance information for *Salmonella typhimurium, enteriditis*, and *newport* serotypes. These serotypes are all included in data classified as non-Typhi.

[b] Individual non-Typhi serotypes are identified in NARMS based upon incidence. The 3 most common non-Typhi serotypes in descending order are Typhimurium, Enteriditis, and Newport.

    - *Salmonella newport* isolates from humans with the MDR-Amp C type resistance had **decreased** from 18.2% (18/99) in 1999 to 14.7% in 2004 (28/190).
    - *Salmonella typhimurium* isolates from humans with the MDR-Amp C type resistance[c] had increased from 0.6% (2/362) in 1999 to 2.6% in 2004 (10/382).
- *Salmonella typhi* isolates[d] from humans with the MDR-Amp C type resistance has remained **unchanged** at 0% (0/166) from 1999 to 2004 (0/304)
- Of the major serotypes identified in USDA Agricultural Research Service NARMS[21] data, only *Salmonella typhimurium* and *heidelberg* have shown slight increasing trends.[e]
    - *Salmonella typhimurium* and *heidelberg* in chicken.
    - *Salmonella typhimurium* in cattle.
    - *Salmonella typhimurium* shows a clearly **declining** trend in cephalosporin resistance in turkeys.
- *E. coli* isolates in animals showed an increase in cephalosporin resistance, and yet no cephalosporin resistance in *E. coli* isolates in humans in most of the years evaluated[f].

Additional studies are needed to determine if or how human antimicrobial resistance is conferred through food products derived from animals treated with cephalosporins:

Although the direct transmission of these resistant organisms through food is the primary concern, we also recognize that resistance determinants must be further studied to determine the impact of those determinants.

- In evaluation of the full continuum of the food chain, it is important to recognize the most likely route of transmission of either antimicrobial resistant organisms or their resistance determinants [such as the extended spectrum β-lactamases (ESBLs)] from animals to humans is through the food chain.
    - In our evaluation of available information from FoodNet[g], only two of the foodborne outbreaks reported were linked to a resistant strain of bacteria. Although any foodborne disease outbreak is a public health concern, two outbreaks in the span of a decade is not a public health crisis. In addition, it is probable that the outbreaks would have been prevented through appropriate food handling procedures (thoroughly cooking the beef and pasteurizing the milk).
        - In the 2002 outbreak of *Salmonella newport* from ground beef, it is still unclear how the resistance (present in only 2 of the 47 cases) developed.[22]
        - In the more recent outbreak of a resistant *Salmonella newport*, all cases were epidemiologically traced back to consumption of raw milk cheeses.[23]

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[c] The values for MDR Amp C resistance are reported here, as they are very similar to values of ceftiofur resistance, and cited as an area of concern.

[d] *Salmonella typhi* is not known to be a foodborne pathogen. Such data is included to indicate that there is no obvious transfer of resistance determinants to a non-foodborne serotype of *Salmonella*.

[e] Other serotypes and swine show no clear trend data.

[f] NARMS data evaluated from 1996-2004 showed a few years with 4 or less isolates resistant to ceftiofur. In corresponding years, NARMS veterinary diagnostic samples show an increase or low prevalence and no identifiable trend in ceftiofur resistance.

[g] FoodNet is the only active surveillance and monitoring system we have in the US for foodborne diseases and related epidemiological studies.

- Unanswered questions include:
  - What is the efficiency of transfer of resistance determinants?
    - while it is commonly understood that genetic elements can be transferred amongst live bacteria, it is still unclear if or how efficiently those elements can be transferred if food is properly cooked and handled to destroy harmful bacteria.
    - bacterial species and serotype differences can affect genetic transfer.
  - What are the factors and how much do they influence expression of resistance genes?
  - What contribution do other gene donor and recipient factors such as bacterial environment, pathogenicity, and survivability have?
  - What other unknowns exist along the food continuum?
  - It still remains unclear how or if cephalosporin use has any contribution at all to the emergence and spread of ESBLs. A study conducted by the FDA Center for Veterinary Medicine in conjunction with the University of Maryland, University of Georgia, and Iowa State University[24] on *E. coli* and *Salmonella* isolated from food animals and ground meat determined that although there was a presence of the β-lactamase *CMY* genes, and those isolates did show decreased susceptibility to ceftiofur and ceftriaxone, it did not show any evidence that the use of cephalosporins or cephamycin contributed to increased expression or transferability of those genes. In fact, the study very clearly states that the majority of the *Salmonella* and *E. coli* isolates recovered from animals did not have a history of cephamycin or cephalosporin exposure.

2) Evidence for increased cephalosporin resistance in animals is based on non-representative sampling strategies.

There are many reports indicating an increase in β-lactam resistance[25,26,27,28] ; however, there is no evidence that an increase in reports equates to an increase in prevalence. Many reports refer to the same data or may be generated as a result of increased monitoring and detection and therefore should not be interpreted as prevalence or incidence data.

FDA cites a perceived rise in ceftiofur resistance in *Salmonella* isolates at slaughter as a risk to public health. However, sampling protocol for the animal arm of NARMS confounds interpretation of that data, and may artificially inflate the observed increase in resistance.

- The 2006 NARMS Veterinary Isolates Final Report very clearly states "The animal component of NARMS comprises the testing of isolates obtained from diagnostic animal specimens, healthy on-farm animals, and food-producing animals at slaughter." However, specific data for healthy on-farm animals is unavailable within that report. It is unclear how data from slaughter samples that are confounded by sampling and comingling during processing[29] can be representative of the animal population.
- The NARMS report further states "*Salmonella* isolates were recovered from food animals at slaughter: carcass rinsates (chicken), carcass swabs (turkey, cattle and swine), and ground products (chicken, turkey, and beef) collected through USDA FSIS's *Salmonella* Pathogen

Reduction/HACCP[h] verification testing program from all federally inspected plants throughout the United States."

- *Salmonella* isolates were specifically isolated from slaughter samples to increase sensitivity and detection of positive samples.
  - In 1997, only 214 samples were taken throughout plants in the US. Of those samples (from plants that were known to have a higher likelihood of detection as a result of HACCP-based sampling), 1 sample was found to be ceftiofur resistant.
  - In 2006, 1380 samples were taken from plants that were known to have a higher likelihood of detection as a result of HACCP-based sampling, and 23 samples were found to be ceftiofur resistant.
  - It is unclear if an increase from 1 sample in 1997 to 23 samples in 2006, potentially co-mingled in ground meats or pooled from rinsates, and targeted specifically for increased sensitivity and detection over the past decade, truly presents a public health risk.

- The animal component of NARMS (National Antimicrobial Resistance Monitoring System) is based upon HACCP (Hazard Analysis and Critical Control Point) guidelines, while human NARMS data are obtained from diagnostic samples.
- As a result of the structure of HACCP surveillance, the presence of a positive sample increases sampling and subsequently reporting.[30,31] This increase in sampling provides results that are not representative of the animal population, would likely result in higher numbers of positives than the true prevalence and has the potential to introduce bias in evaluation of the available data.

<u>Data are lacking from unbiased sampling protocols</u>. If an actual increase in prevalence exists (versus increased sampling and reporting), it remains unclear how or if this presents a significant public health risk.

- Winokur et al[32] report similar genes exist in isolates from both food animals and humans, potentially showing a genetic linkage of those genes.
  - However, the isolates from food animals were obtained from clinically diseased animals within a localized geographic region.
  - It is unclear if sampled animals were treated with cephalosporins or any other antimicrobials. Thus it is impossible to determine from these data whether the similarities were due to selective pressures resulting from antimicrobial use or clonal spread of a specific serotype.
  - It remains unclear if any sampled animals entered the food chain. Diseased animals are prohibited from entering the food chain in a clinically diseased state. Consideration of the above factors is critical for appropriate conclusions regarding cause or source of resistance.
- European Antimicrobial Resistance Surveillance System[33] data
  - Evaluate only human isolates of *E. coli* for cephalosporin resistance.

[h] HACCP (Hazard Analysis and Critical Control Point) programs require a hazard analysis to determine food safety hazards that are likely to occur to indentify the preventative measure that can be applied to control those hazards. If a hazard such as resistant *Salmonella* has been found historically, or there is a reasonable probability that it will occur, controls to minimize the contamination are implemented and critical limits are established. Violations of those limits will prompt increased and repeated sampling.

- Increasing trends of resistance are categorized by individual country reporting. It is unclear if the data represent true prevalence or simply clusters of cases within regions. If the cases are clustered, the data may suggest clonal spread within a geographic area. These data cannot be interpreted without more detailed information such as identification of bacterial serotype and genetic determinants; sampling protocol; and history of antimicrobial use.
  - The rise of *CTX-M* ESBLs in Europe likely reflects a series of independent events (hospital acquired, clonal spread, human migration) and not simply a result of foodborne mechanisms.[34]
- Do not differentiate between human serotypes of *E. coli*[i] and those that are monitored in the US as foodborne pathogens (*E. coli O157*) therefore no indication of any epidemiological study to indicate the source of those human infections exists.
- Although EARSS[35] does state that newly emerging *CTX-M* and *CMY-2* genes are of concern, there are no data describing prevalence of the genes.

3) Substantial amounts of data exist suggesting mechanisms of cephalosporin resistance may be entirely unrelated to use of cephalosporins.

Given these data, it is likely that the increased cephalosporin resistance seen in some human *Salmonella* isolates is the result of a route or mechanism unrelated to veterinary use of cephalosporins. In fact, antimicrobial resistance is a dynamic process affected by many factors not limited to selective pressures from the use of a particular antimicrobial.[36]

Several factors other than the use of cephalosporins are implicated:

- Clonal spread
  - NARMS data do show a few trends that parallel both human and animal levels of resistance. However, there are many more trends indicating no parallels in levels of resistance. (See above noted NARMS data).
  - Geographical clustering of resistant isolates as evidenced by EARRS data and other studies.[37,38]
- Other non-foodborne organisms as a source of resistant determinants
  - *Citrobacter freundii*, a commensal organism of the human intestinal tract has been suggested as a reservoir of ESBLs[39] and there has been strong evidence that the *CMY* genes have been translocated from *Citrobacter* to other bacterial species.[40,41]
  - AmpC cephalosporinases were present in enterobacteriae prior to the discovery of antibiotics and the introduction of antibiotic usage. [42]
- Antimicrobials other than cephalosporins (potential cross selection) [43, 44, 45,46,47,48,49]
  - EARSS data show aminopenicillin resistance (often exhibiting coresistance with 3rd generation cephalosporins) is also rising by the same mechanisms as the cephalosporins and extended spectrum β-lactamases (ESBLs), while resistance to 3rd generation cephalosporins alone is 0%.
  - The same phenomenon can be observed in NARMS data annually over the past decade wherein percent resistance to cephalosporins is identical or nearly identical to percent resistance to aminopenicillins in all veterinary diagnostic isolates of *Salmonella*.

[i] A commensal organism routinely found in the intestinal tracts of many animals and humans.

- Other studies also indicate similar patterns of resistance wherein all isolates carrying the bla_{CMY2} gene are co-resistant to other antimicrobials in addition to cephalosporins.[50]

- Plasmid dissemination, hospital cross-infections, and human migration are additional important mechanisms for the spread of antibiotic resistance which must be considered beyond foodborne mechanisms.[51,52,53,54]
- Unknown factors or a combination of factors

  - A study from Japan, a country in which cephalosporins are only approved for parental use in cattle and swine, found cephalosporin resistant strains of *E. coli* in broilers[55].
  - Antibiotic resistance and corresponding genes were found in similar proportions from untreated controls as well as from animals treated with antimicrobials[56, 57].

Our review of current available literature, including those references cited by FDA, **provides no evidence to specifically support that extralabel use of cephalosporin antimicrobials in food animals leads to an emergence of cephalosporin resistant foodborne bacterial pathogens in animals.** There are reports of extended spectrum β-lactamases (ESBLs) and the Amp-C plasmid mediated *CMY-2* gene in foodborne bacterial pathogens. We recognize that use of antimicrobials may create selection pressure, though not always. Further, how selection pressure is exerted and by which specific antimicrobial remains to be quantified. It has yet to be demonstrated whether cephalosporin use is a contributing factor to the development of resistance genes such as ESBLs. In fact, organisms found to have these resistance determinants tend to exhibit co-resistance to additional β-lactams. Thus, while some may make the assumption that cephalosporin use would exert increased selective pressure on these organisms, the scientific picture is much more complex.

Whether or not a true increase in β-lactam resistance prevalence exists (versus increased detection and reporting), particularly the ones for which FDA expresses a concern (*CTX-M* and other ESBLs), **the cause of resistance, factors influencing expression of those genes if they are present, and human health impacts have yet to be determined (or "identified").**

- Data[58] show that although organisms having this type of β-lactam resistance are resistant to cephalosporins, they are also almost always resistant to many other β-lactams as well. This co-resistance is indicative of a result, not a causal factor.
- The causal factor for this type of antimicrobial resistance remains unknown. Because nearly all of the organisms possessing the ESBLs are also co-resistant to drugs other than cephalosporins as suggested by data including EARSS and NARMS, the true selective pressure may be due to a β-lactam other than cephalosporins.

4) We find a lack of evidence associating a human health benefit or a decline in resistance with the withdrawal of cephalosporins.

An isolated report from Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)[59] concludes a voluntary withdrawal of cephalosporins resulted in a decline of resistance in human and chicken isolates. We believe that the CIPARS data and the report on the decrease of resistance in *Salmonella heidelberg* isolates in Quebec is an interesting case report but only provides trend data and no scientific evidence supporting a causal conclusion.

- This single CIPARS report suggests causality through a decline in the resistance of *Salmonella heidelberg* isolates from humans and poultry concurrent with a voluntary withdrawal of extralabel cephalosporin use of ceftiofur in hatcheries. **A similar decline in resistance was seen in the absence of cephalosporin withdrawal in nearby Ontario, making it difficult to discern the effect of the voluntary ban.**
- Data collected in Ontario show that the two provinces were extremely similar in their trends of decline in resistance in human isolates and human use of cephalosporins, as well as decline in resistance of chicken isolates.
- Upon close evaluation of the trend data provided in the report, there is evidence that human use of cephalosporins in both provinces also decreased during the same period of time, further confounding any interpretation of the trend data.

If cephalosporin resistance is truly significant, we have not identified factors causing the resistance, nor ramifications of any such resistance affecting human health.

- Some studies indicate resistant strains of *Salmonella* are actually less virulent than susceptible strains[60], and thus may not have any impact on human treatment failures.
- The use of antimicrobials to treat *Salmonella* gastroenteritis cases is typically contraindicated. Therefore, if antimicrobial treatment is contraindicated, prevention of human treatment failures through the Order of Prohibition would be minimal at best.

We are deeply concerned with the scientific soundness of the information utilized by the FDA in its justification to advance prohibition of extralabel cephalosporin use in food animals. In our research, we have found no consistent trends demonstrating associations between extralabel cephalosporin use in food animals and increased resistance/health hazards in humans. We assert that both a substantial level of additional research and a complete risk assessment are warranted at this time.

Misinterpretation of Federal Regulation

The AVMA believes the FDA **should not and cannot treat the changes in antimicrobial susceptibility patterns or the presence of resistance determinants in non-labeled foodborne pathogens isolated from animals or humans as adverse events for the approved animal drug.** Extralabel drug use may be prohibited under 21 USC § 360b(a)(4)(D), which requires the finding that a use presents a risk to the public health. Under implementing regulations, 21 CFR § 530.21(a)(2), FDA may prohibit that extralabel drug use in animals which presents a risk to public health. FDA defines "presents a risk to the public health" in various permutations in 21 CFR § 530.3(c), (d), and (e), to mean having caused or is likely to cause an adverse event. Thus, an adverse event is a prerequisite to action. The term "adverse event" is not defined in the Act or the regulations. However, other FDA publications indicate that the correct definition for adverse events are "reports of injury, toxicity, sensitivity reaction, unexpected incidence or severity of side effects associated with use, or failure of the drug to exhibit expected pharmacological action."[61]. Further, FDA Guidance # 117 defines an adverse event as "any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of [Veterinary Medicinal Product] VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy according to approved labeling or noxious reactions in humans after being exposed to VMP(s)." A lack of human antimicrobial drug effectiveness because

of bacterial resistance would not be reported to veterinary drug companies and FDA would not have such documentation.

The AVMA believes that a lack of drug efficacy when used for labeled pathogens in target animals would be considered an adverse event. However, in contrast, it appears that in its prohibition order, FDA is defining hypothetical human treatment failures based upon non-statistically evaluated shifts in the antimicrobial susceptibility patterns of non-labeled, foodborne pathogens such as *Salmonella* and the presence of resistance determinants as the adverse event. The AVMA simply does not believe that FDA can define such concerns as adverse events in order to use the ELDU provisions of AMDUCA in such an unsupported broad manner. Moreover, even if it were appropriate for FDA to define human antimicrobial drug treatment failures as an animal drug adverse event within the meaning of the extralabel drug use regulations, **we find no data demonstrating transmission of cephalosporin resistant foodborne pathogens from animals to humans, no evidence illustrating that such events are likely to occur, and no evidence supporting actual human treatment failures due to the use of veterinary cephalosporins.** Therefore, the action to prohibit the extralabel use of cephalosporins in animals is an arbitrary exercise of the agency's discretion.

Analysis of Unintended Adverse Impacts of the Order of Prohibition

We have found numerous examples illustrating adverse impacts that could result from this Order of Prohibition. While unintended, these impacts have significant ramifications on animal health and welfare and on the practice of veterinary medicine. Moreover, human health could be significantly affected by a compromised food safety system.

Animal Health and Welfare Impacts

The Veterinarian's Oath compels veterinarians to use our scientific knowledge and skills for "the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of animal resources, the promotion of public health and advancement of medical knowledge." Consequently, veterinarians must examine both the human health impact of food borne disease and antimicrobial resistant pathogens, and the animal health and welfare impacts of drug use in animals. Veterinarians are well acquainted with and supportive of judicious antimicrobial use in food producing animals.

Extralabel drug use is necessary in veterinary medicine. Any deviation from labeled use of an antimicrobial, no matter how slight, is extralabel use. Because labeled indications for animal drugs are limited, **extralabel drug use is a medically necessary provision authorized by the U.S. Congress to relieve the pain and suffering of millions of animals**. Specifically, in 1994, the U.S. Congress passed the Animal Medicinal Drug Use Clarification Act (AMDUCA). Regulations resulting from the AMDUCA govern how veterinarians treat food-animal patients and mandate that any extralabel drug use must be accompanied by appropriate medical rationale and must ensure the safety of food derived from treated animals.

It is important to recognize that extralabel drug use is not misuse. Extralabel drug use is prudent drug use when it optimizes therapeutic efficacy and minimizes resistance to antimicrobials to protect public and animal health. Extralabel drug use is a legal tool for veterinarians to use in their professional practices to relieve animal pain and suffering. After passage of the AMDUCA, extralabel drug use became an FDA-regulated professional activity. In addition, extralabel drug use must be utilized within a Veterinarian-Client-Patient Relationship (the veterinarian's equivalent of

the physician's "doctor-patient relationship"), only for therapeutic uses, and only when such use does not present a risk to the public health.

Extralabel drug use plays a critical role in veterinary medicine because veterinarians have a relatively limited number of FDA approved drugs for treatment of the numerous animal species, each with diverse disease conditions. Drug sponsors cannot reasonably be expected to generate labels for all conditions of all animals, though FDA approved labeled indications are very beneficial. Specifically, while there are a number of commercially available FDA-approved cephalosporin drugs, the FDA drug review and approval process tends to generate very specific drug labels limited to one or a few indications substantiated by data and some tightly specified conditions of use including species, age or class of animal, disease condition, pathogen, dosage, duration and route of therapy. Consequently, **extralabel cephalosporin use is medically necessary to relieve animal pain and suffering** and allow veterinarians discretion to use drugs judiciously.

Under the FDA order, if an animal's medical needs do not fit within the confines of the approved label, yet treatment with a cephalosporin is medically indicated, a veterinarian is left only to recommend a sub-optimal treatment or possibly no treatment.

This has several negative consequences:

- The veterinarian's ability to uphold his/her Oath to relieve animal pain and suffering is in conflict as he/she must refrain from use of a historically beneficial therapy.
- Early mortality increases. Also, animal welfare is jeopardized as the animal(s) experience greater pain and suffering in the absence of effective treatment.
- With fewer pharmaceutical options the veterinarian's benefit to the producer is reduced, decreasing the amount of veterinarian interaction on the farm and the veterinarian's supervisory role in judicious antimicrobial use on the farm.
- Decreased access to cephalosporins creates greater selection pressure on the fewer remaining approved drugs, potentially decreasing drug efficacy.
- The clinical effectiveness of the remaining antimicrobials may decrease for a particular medical need; in some cases reducing the chances the animal(s) will recover from the disease which is likely to increase morbidity and mortality.
- Use of alternative antimicrobials with various delivery systems could rise, leading to increased treatment of groups of animals versus individual animals.
- The net volume of cephalosporins used in animals may in fact increase, whereas current extralabel options include lower volumes, fewer doses, and more targeted treatment. Without these options the result could be less judicious use overall.
  For example:
  - Rather than treating juvenile animals at the first onset of disease in an extralabel manner, veterinarians would have to wait until animals achieved the labeled age for use. The result would be increased volumes of cephalosporins for larger animals.
  - Delaying increases the chances that disease may spread to additional animals, increasing the number of doses used.

These impacts could all be "costs" that veterinarians and animals would have to bear for the good of mankind if human health was actually being harmed by veterinarians' extralabel cephalosporin use.

Yet analysis of the data fails to document a relationship of harm to human health, and the FDA order creates untenable harm to animals, their owners, and their veterinarians, should this rule be implemented.

Food Safety Ramifications

Healthy animals make healthy food. For veterinarians to be effective in protecting our food supply, having the appropriate tools for preventing, controlling, and treating disease, including antimicrobials, is paramount. Veterinarians protect America's food supply by ensuring food animal health from "farm to fork," including their work in clinical practice, in state public health agencies, in the federal government, and in the corporate sector.

Antimicrobial use restrictions can adversely affect the safety and availability of the food supply:

- Decreased drug availability is a food security issue. At the farm level, veterinarians use their clinical expertise to develop disease prevention, control, and treatment strategies for production animals in all phases of life. Animals at certain stages of life have specific health concerns demanding veterinary medical interventions. For example, juvenile animals are at risk for early mortality and morbidity due to infections, an animal health and welfare concern. With limited labeled options for disease prevention, control, and treatment in some species, those mortality risks would be expected to increase. This is not only an animal health and welfare concern, but also a food security concern, in that it could decrease the number of animals available for the food supply. With the expansion of the world population, the demand for animal-derived protein is expected to increase by 50% by 2020. [62]
- Uncontrolled infections can increase bacterial contamination of animal carcasses. Infections in morbid animals can lead to secondary infections. These secondary infections increase animal pain and suffering, but also increase the risk of bacterial contamination of the processed carcasses resulting in increased risk to the food supply.
- Residue avoidance is essential for the safety of the meat, milk and eggs produced by food animals. More specifically, the short withdrawal time required with cephalosporin use makes the antimicrobial ideal when animals destined for slaughter require treatment. In addition, short withdrawal time is also important in milk producing animals. Antimicrobial alternatives tend to have longer withdrawal times, and while great precautions are taken to ensure food safety, the lack of cephalosporins could increase the risk of animals with volative tissue residues entering the food chain. Finally, this is especially troublesome considering the questionable future viability or demise of the Food Animal Residue Avoidance Databank (FARAD) program.
- In some species, cephalosporins are the only class of antimicrobial labeled for injection into non-edible tissue. Use of alternate antimicrobials may lead to increased carcass lesions.
- Decreased demand for veterinary medical services may result.
- Producers may elect over-the-counter treatments instead of those recommended by veterinarians. Consequently, such treatment would be administered without the veterinary medical intervention needed to ensure that clinically appropriate diagnostics and therapeutic agents are utilized. Greater numbers of animals may be treated in the absence of veterinary supervision.

The AVMA understands the Order of Prohibition is well-intended, however; it will not have the desired positive impact on human health. Moreover, **we believe the Order is more likely to compromise our food safety system.** Impacts on animal health as a result of antimicrobial use restrictions should not be overlooked in evaluation of public health risks, and we must not forget that animal health is a critical component of food safety and public health.

The Practice of Veterinary Medicine

Veterinarians provide numerous safeguards to the food supply. Having pharmaceutical options available helps veterinarians customize judicious antimicrobial recommendations to meet the clinical circumstances and ensure food safety. Reducing the availability of antimicrobials hampers such professional discretion. Many federal and state agencies recognize the pivotal role of veterinarians in supervising the use of potent agents.

Veterinarians evaluate whether a therapy's benefits would outweigh its risks to both the patients and to the public health. Veterinarians have been trained to "do no harm" as they make therapy recommendations, and they have the duty to utilize such agents to promote animal health and welfare in such a way that safeguards the public health.

Veterinarians continue to use the Veterinary-Client-Patient Relationship as the cornerstone of their clinical practice. Veterinarians assume responsibility for making clinical judgments regarding the health of animals and need for medical treatment. They also maintain personal acquaintances with their clients and patients and they have sufficient knowledge to diagnose and treat patients. Finally, veterinarians foster continual communications with their clients such that follow-up discussions and treatments are available to clients.

Veterinarians protect our nation's public health and animal health and well-being and are in the best position to prescribe and administer the most appropriate therapies for their patients. Veterinarians are licensed by state authorities to practice veterinary medicine and are authorized by both state and federal government entities to handle potent medical agents in the course of their professional practice.

- Specifically, the Drug Enforcement Administration (DEA) entrusts veterinarians to prescribe controlled substances for animals, i.e., those drugs that are available only within a closed system of distribution due to the potential for abuse and addiction.
- The Environmental Protection Agency (EPA) allows veterinarians to use both restricted-use and conventional pesticides in the course of their professional practice without specific restrictions or certifications.
- The United States Department of Agriculture (USDA) recognizes veterinarians as professionals who may vaccinate animals to advance national animal disease control and eradication programs.
- The US Food and Drug Administration authorizes veterinarians to prescribe, administer, and dispense prescription drugs for animals.

In summary, there is significant veterinary medical oversight over the use of drugs in food animals. Veterinarians hold clinical expertise through their professional training, with the cornerstone of veterinary clinical practice ensuring regular communications with clients and contact with patients, allowing veterinarians to monitor the health and well-being of those patients and to uphold public health principles. Moreover, veterinarians are seen by both the U.S. Congress and federal and state

agencies as the medical professionals with the judgment capacity to prudently utilize potent biologics and therapeutics in the course of their practice.

Although reasonable federal oversight is rational, the AVMA believes **veterinarians adequately and responsibly provide the safeguards to protect both human and animal health.** We assert the broad prohibition is unnecessary and would be deleterious to animal and public health and animal welfare.

Benefits of FDA/AVMA Communication and Outreach

The AVMA welcomes the opportunity to partner with the FDA Center for Veterinary Medicine (CVM) on issues of paramount importance. An example of an effective FDA-AVMA partnership was well illustrated in the co-development of AVMA's Judicious Therapeutic Use of Antimicrobials in 2000, which guides veterinarians on prudent and appropriate use of antimicrobials in their course of practice. The FDA CVM relayed to *Journal of the A VMA* News (August 15, 2000) that it "welcomes efforts undertaken by outside groups to help reduce the threat of antimicrobial resistance. In particular, we appreciate the initiative taken by AVMA to develop judicious use principles... AVMA's willingness to partner with us will result in greater food safety."

The AVMA asserts that had the FDA communicated with the Association and other stakeholders on its current concerns regarding cephalosporin use in food animals, those communications could have greatly facilitated the FDA's evaluation of the public health impact of extralabel cephalosporin use in food animals and administration of the Animal Medicinal Drug Use Clarification Act (AMDUCA) to protect public health. Likewise the veterinary profession would be alerted to the FDA's questions or concerns.

We encourage the FDA to communicate with the AVMA on this important issue as well as future matters involving the use of drugs in animals.

AVMA's Conclusions and Recommendations

In this correspondence to the FDA, it is the AVMA's intent to relay our significant concerns regarding the Order of Prohibition of Extralabel Animal Drug Use and to illustrate the need for its postponement, so that a risk assessment can be performed by the FDA to characterize the hazard, to evaluate the risk, and to ascertain the impact of risk management initiatives.

Our recommendations are based on our conclusions that:

- **The lack of scientific evidence showing any significant risk to human health by extralabel use of cephalosporins in food-producing animals**
- **The lack of any demonstrated benefit of the rule to human health**
- **The rule's potential for unintended consequences on animal health and welfare, on food safety, and on the practice of veterinary medicine**
- **The misinterpretation of federal regulation**

We urge that a risk-benefit analysis or a risk-risk analysis be conducted in order to assess the risk of using cephalosporins in an extralabel manner in food animals as well as the consequences of not using such drugs.

Specifically, we assert that **an FDA risk assessment include** the following:

- **Careful review and evaluation of all routes by which antimicrobial resistant bacteria and their genes can arise in the human population.** Any hazards characterized as having significant risk should be controlled through a collaborative effort by all stakeholders involved in animal health, public health, human clinical medicine, and food safety.
- **Utilization of a transparent science-based approach** to determine if the use of cephalosporins affects the number of antimicrobial-resistant organisms to which humans are exposed through food animal products, as well as to describe the magnitude and severity of any impacts to human health.
- Specific focus on the species prevalence rates and resistance rates for specific foodborne pathogens such as *Salmonella*, *E. coli*, and *Campylobacter* to allow **a more focused risk assessment and subsequent, more informed risk management scheme.**

The AVMA commends the FDA's intent to prevent public health risks, yet we have grave concerns about the justifications and ramifications of the FDA's Order of Prohibition. We hope that the comments offered by the AVMA assist the FDA in its reassessment. Please feel free to contact the AVMA should you need additional explanation of comments or other resources.

We look forward to continuing our collaborative efforts with the FDA to advance our nation's animal and public health.

Thank you for your time and consideration.

Respectfully,

for W. Ron DeHaven, DVM, MBA
Executive Vice President
American Veterinary Medical Association

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