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**NARRATIVE STATEMENT OF THE DIRECTOR OF THE CENTER FOR
VETERINARY MEDICINE PURSUANT TO 21 C.F.R. 12.85 ON THE PROPOSAL
TO WITHDRAW ENROFLOXACIN (NADA 140-828) FOR USE IN POULTRY**

Introduction

The Center for Veterinary Medicine (CVM) submits this narrative statement as required by 21 C.F.R. 12.85(a)(4). This statement sets out the Center's position on the factual issues for hearing and identifies the type of supporting evidence that the Center intends to introduce at hearing.

Background

The Center is proposing to withdraw approval of the new animal drug application (NADA) for use of the fluoroquinolone enrofloxacin in poultry, NADA 140-828. New evidence shows that enrofloxacin use in poultry has not been shown to be safe as required by the Federal Food, Drug, and Cosmetic Act (the Act). A Notice of Opportunity for a Hearing (NOOH) in this matter was published on October 31, 2000 (See 65 FR 64954, as amended 66 FR 6623 (January 22, 2001)).

This action is based on CVM's determination that: (1) the use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter* spp. (a human pathogen) in poultry; (2) these fluoroquinolone-resistant *Campylobacter* spp. are transferred to humans and are a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans; and (3) fluoroquinolone-resistant *Campylobacter* infections in humans are a human health hazard.

Issues for Hearing

The primary factual issues for hearing are:

Whether new evidence shows that enrofloxacin is not now shown to be safe for use in poultry under the conditions of use upon which the application was approved. This issue includes:

- a. Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred, such as:
 - i. Whether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in poultry?
 - ii. Whether fluoroquinolone-resistant *Campylobacter* spp. in poultry are transferred to humans and whether they contribute to fluoroquinolone-resistant *Campylobacter* infections in humans?
 - iii. Whether fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?
- b) Whether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe?

Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred?

CVM's position is that there is a reasonable basis from which serious questions about the safety of enrofloxacin may be inferred. CVM published its rationale for proposing to withdraw the approval of the enrofloxacin NADA for use in poultry in the October 31, 2000, NOOH. The references listed in that notice illustrate the type of evidence the Center intends to introduce at the hearing, and provide a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred.

Whether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in poultry?

CVM's position is that enrofloxacin use in poultry causes the development of fluoroquinolone-resistant *Campylobacter* spp., a human pathogen, in poultry.

When an antimicrobial drug is administered to an animal, the most susceptible bacteria affected by the drug will be eliminated, while the least susceptible organisms will survive. These surviving bacteria will proliferate and become the more predominant population. When antimicrobial drugs are administered to food-producing animals, they promote the emergence of resistance in bacteria that may not be pathogenic to the animal, but may be pathogenic to humans.

The Center intends to introduce scientific papers, studies, and the testimony of experts supporting CVM's position that fluoroquinolone use in poultry acts as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in poultry. This evidence includes, but is not limited to: data on *Campylobacter* spp. colonization in poultry; data on fluoroquinolone use in poultry; testimony on biological processes of selective pressure and emergence and dissemination of resistant organisms; laboratory test results showing that poultry harboring *Campylobacter* spp. quickly develop fluoroquinolone-resistant *Campylobacter* spp. once fluoroquinolones are administered; and sensitivity testing of *Campylobacter* isolates from poultry to fluoroquinolones.

Whether fluoroquinolone-resistant *Campylobacter* spp. in poultry are transferred to humans and whether they contribute to fluoroquinolone-resistant *Campylobacter* infections in humans?

CVM's position is that fluoroquinolone-resistant *Campylobacter* spp. from poultry are transferred to humans and are a significant cause of the development of fluoroquinolone-

resistant *Campylobacter* infections in humans.

Campylobacteriosis is one of the most common food borne illnesses in the United States. *Campylobacter* spp. are commonly found in the intestinal flora of poultry without causing disease in the birds. The increased risk, in humans, of campylobacteriosis associated with exposure to poultry has been repeatedly observed in epidemiological studies. These bacteria may cause severe food borne illness in humans. Likewise, fluoroquinolone-resistant *Campylobacter* spp. that develop as a result of antimicrobial drug use in food-producing animals can be transferred to humans via food. The contaminated food may cause disease in persons handling or consuming the food or in persons consuming other food contaminated by the animal-derived food.

The Center intends to introduce scientific papers, studies, and expert testimony supporting CVM's position that fluoroquinolone-resistant *Campylobacter* spp. in poultry are transferred to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans. This evidence includes, but is not limited to: poultry consumption data; epidemiological studies finding a strong association between eating poultry and acquiring human *Campylobacter* infections; epidemiologic studies finding a strong association between eating poultry and acquiring fluoroquinolone-resistant human *Campylobacter* infections; studies linking the genetic make-up of *Campylobacter* isolates from poultry and humans; the temporal relationship between the approval of fluoroquinolones for use in poultry in the United States and the rise in the level of fluoroquinolone-resistant human *Campylobacter* infections in humans in the United States; the temporal relationship between the approval of fluoroquinolones for use in poultry in other countries and the rise in the level of human fluoroquinolone-resistant *Campylobacter* infections in those countries; the biological implausibility that the level of fluoroquinolone-resistant human *Campylobacter* infections now seen in the United States is entirely due to fluoroquinolone use in humans or the spread of resistant *Campylobacter* infections from one human to another; and a risk assessment showing that a portion of fluoroquinolone-resistant *Campylobacter* infections in humans is attributable to consumption of poultry treated with fluoroquinolones.

Whether fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?

CVM's position is that fluoroquinolone-resistant *Campylobacter* infections in humans do have the potential to adversely affect human health.

The magnitude of the benefit of antibiotic treatment is directly related to the early initiation of therapy. Patients with severe enteric disease such as campylobacteriosis are often treated empirically. Fluoroquinolone-resistant *Campylobacter* presents a dilemma for the physician. If fluoroquinolone treatment is given based on symptoms, and the patient is infected with a fluoroquinolone-resistant *Campylobacter* infection, there is a risk that the treatment will not be effective, and valuable time will be lost. If treatment is delayed until the causative organism and susceptibility are confirmed by a medical laboratory, again valuable time will be lost. In these situations, the disease may be prolonged or result in complications, especially in vulnerable patients with underlying health problems. Fluoroquinolones are used routinely by physicians for the empiric treatment of food borne and diarrheal illnesses; they are considered to be one of the most valuable antimicrobial drug classes available to treat human infections because of their spectrum of activity, pharmacodynamics, safety and ease of administration. They have traditionally exhibited a very high level of clinical effectiveness against most enteric bacterial pathogens.

The Center intends to introduce scientific papers, studies and expert testimony supporting CVM's position that fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely affect human health. This evidence includes, but is not limited to: data on the duration of diarrhea in patients with fluoroquinolone-resistant infections compared to that for patients with fluoroquinolone-sensitive infections (whether or not the person is treated with a fluoroquinolone); expert opinions regarding potential complications stemming from

fluoroquinolone-resistant *Campylobacter* infections; and testimony on the recommended treatments for diarrheal diseases and the prescribing habits of physicians.

Whether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe?

CVM believes that the evidence that is outlined above and that it intends to introduce at the hearing provides a reasonable basis from which serious questions about the safety of enrofloxacin for use in poultry may be inferred. CVM asserts that the sponsor of the drug, Bayer Corporation, now has the burden of to prove that the use of enrofloxacin under the approved conditions of use in poultry is safe.

I certify that, to my best knowledge and belief, this submission complies with the requirements of 21 C.F.R. 12.85, which sets out the Food and Drug Administration's requirements addressing disclosure of data and information by the participants of formal evidentiary public hearings.

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