Dated: October 25, 2000.

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Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1571]

Enrofloxacin for Poultry; Opportunity For Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM), is proposing to withdraw approval of the new animal drug application (NADA) for use of the fluoroquinolone enrofloxacin in poultry. This action is based on CVM's determinations that the use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a human pathogen, in poultry; this resistant *Campylobacter* is transferred to humans and is a significant cause of the development of resistant *Campylobacter* infections in humans; and resistant *Campylobacter* infections are a human health hazard. Therefore, CVM is proposing to withdraw the approval of the new animal drug application for use of enrofloxacin in poultry on the grounds that new evidence shows that the product has not been shown to be safe as provided for in the Federal Food, Drug, and Cosmetic Act (the act).

DATES: Submit written appearances and a request for a hearing by November 30, 2000. Submit all data and analysis upon which a request for a hearing relies by January 2, 2001.

ADDRESSES: Written appearances, requests for a hearing, data and analysis, and other comments are to be identified with Docket No. 00N–1571 and must be submitted to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Linda R. Tollefson, Center for Veterinary Medicine (HFV–200), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6647.

SUPPLEMENTARY INFORMATION:

I. Fluoroquinolones Approved for Poultry Use

The following are approved uses for fluoroquinolones in poultry:

A. Sarafloxacin Hydrochloride

NADA 141–017, SaraFlox® WSP, approved August 18, 1995, for the control of mortality in growing turkeys and broiler chickens associated with *Escherichia coli* organisms, Abbott Laboratories, 1401 Sheridan Rd., North Chicago, IL 60064.

NADA 141–018, SaraFlox® Injection, approved October 12, 1995, for the control of early chick mortality associated with *E. coli* organisms in chickens and turkeys, Abbott Laboratories, 1401 Sheridan Rd., North Chicago, IL 60064.

B. Enrofloxacin

NADA 140–828, Baytril® 3.23% Concentrate Antimicrobial Solution, approved October 4, 1996, for the control of mortality in chickens associated with *E. coli* organisms and control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms, Bayer Corp., Agriculture Division, Animal Health, Shawnee Mission, KS 66201.

Abbott Laboratories has requested withdrawal of NADA's 141–017 and 141–018 for use of sarafloxacin hydrochloride in poultry. By doing so, the company has waived its right to a hearing. Therefore, only NADA 140–828 is covered by this notice.

II. Summary of the Bases for Withdrawing the Approval

CVM is providing notice of an opportunity for a hearing on a proposal to withdraw approval of the NADA for enrofloxacin for use in poultry and to revoke the new animal drug regulations reflecting the approval of the NADA (21 CFR 520.813). Enrofloxacin belongs to the class of antimicrobial drugs called fluoroquinolones. Fluoroquinolones also are approved for use in humans. Fluoroquinolones 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. This class of drugs is effective against a wide range of human diseases and is used both in treatment and prophylaxis of bacterial infections in the community and in hospitals. Fluoroquinolones are essential to the treatment of foodborne diseases. These diseases have a major public health impact in the United States.

Enrofloxacin oral solution for each of its uses in poultry is a new animal drug as defined in section 201(v) of the act (21 U.S.C. 321(v)). As such, the drug cannot be legally marketed in interstate commerce in the absence of an approved NADA (sections 301, 501, and 512 of the act (21 U.S.C. 331, 351, and 360b)). The requirements for approval of NADA's are set out in section 512 of the act. Section 512 of the act requires that a new animal drug must be shown to be safe and effective for its intended uses. Section 201(u) of the act provides that ''safe'' as used in section 512 ''has reference to the health of man or animal.'' The determination of safety requires CVM to consider, among other relevant factors, ''the probable consumption of such drug and of any substance formed in or on food because of the use of such drug'' (section 512(d)(2)(A)). Accordingly, CVM must consider not only safety of the new animal drug to the target animal but also safety to humans of substances formed in or on food as a result of the use of the new animal drug.

FDA approved the NADA's for fluoroquinolones for use in poultry in 1995 and 1996 (see section V.A.3 of this document). After the approvals, CVM instituted several strategies intended to prevent or mitigate the development of resistance (see section V.A.4 of this document). However, resistance still quickly developed to the fluoroquinolones among the human foodborne pathogen, *Campylobacter* (see section V.B of this document). The resistance developed from use of fluoroquinolones in poultry under the approved, labeled conditions of use (see section V.B.1 of this document).

By 1998, Centers for Disease Control and Prevention (CDC) testing found that 13.6 percent of *Campylobacter* human isolates were resistant to fluoroquinolones. Fluoroquinolone resistance rose to 17.6 percent among *Campylobacter jejuni* and 30 percent among *Campylobacter coli* isolated from ill humans in 1999. In 1998, testing established that approximately 9.4 percent of the *C. jejuni* isolated from chicken carcasses at federally inspected slaughter plants in the United States were fluoroquinolone resistant. Higher levels of fluoroquinolone resistance are observed in retail chicken (see section V.B of this document).

After thoroughly analyzing all the data and evidence, CVM has determined the following: The primary cause of the emergence of domestically-acquired fluoroquinolone-resistant *Campylobacter* infections in humans is the consumption of or contact with contaminated food (see section IV.B of this document). Moreover, poultry is the most likely source of campylobacteriosis

in humans (see section V.C.2 of this document), poultry is also a source of fluroquinolone-resistant *Campylobacter* (see sections V.B.3 and V.B.4 of this document), and administration of fluoroquinolones to chickens leads to development of fluoroquinolone-resistant *Campylobacter* in chickens.

CVM has concluded, based on data from surveillance programs, published literature and other sources, that the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses, and therefore a significant cause of fluoroquinolone-resistant *Campylobacter* infections in humans. CVM's conclusion is supported by data establishing a temporal association between the approvals of these drugs for use in poultry in the United States and the increase in resistant *Campylobacter* infections in humans. Fluoroquinolones have been available for human use since 1986 and are commonly prescribed for persons with gastrointestinal illness. Yet resistance to fluoroquinolones did not increase among *Campylobacter* organisms above a very low level until 1996 or 1997, or soon after the approval and use of these drugs in poultry (see section V.B.5 of this document).

CVM's conclusion is also supported by comparison of fluoroquinolone use in poultry with the two most likely other possible causes of fluoroquinolone-resistant human infections—exposure to resistant *Campylobacter* during foreign travel, and direct use of fluoroquinolones in humans. People are exposed to fluoroquinolone-resistant *Campylobacter* during travel to developing countries (Ref. 1). However, a risk assessment conducted by CVM (see section V.C.3 of this document) demonstrates an unacceptable human health impact from domestically-acquired *Campylobacter* infections from use of fluoroquinolones in chickens (Ref. 2). These domestically acquired infections are much more likely to come from exposure to resistant *Campylobacter* through food than as a result of direct treatment with fluoroquinolones in humans (see section IV.B of this document). This is due in part to the fact that even if fluoroquinolone treatment results in resistant *Campylobacter* in an individual, the resistant organisms are unlikely to be transmitted to other people in the United States because generally the numbers of organisms present are low and fecal-oral transmission is required (Ref. 3). Therefore, the level of fluoroquinolone-resistant *Campylobacter* now seen in human isolates in the United States is

not plausibly due to fluoroquinolone use in humans or the spread of resistant *Campylobacter* from one human to another.

Development of resistance to fluoroquinolones among *Campylobacter* has important consequences for human health (see section V.C of this document). Foodborne diseases have a major public health impact in the United States, and *Campylobacter* is the most common known cause of foodborne illness in the United States (Ref. 3). Fluoroquinolones are considered to be one of the most valuable antimicrobial drug classes available to treat a wide variety of human infections, including infections resistant to other drugs, and have been particularly important in the treatment of foodborne infections.

Patients with severe enteric disease such as campylobacteriosis are usually treated empirically. Therefore, *Campylobacter* resistance presents a dilemma for the physician. If fluoroquinolone treatment is given based on symptoms, and the patient is infected with resistant *Campylobacter*, there is a risk that the treatment will not be effective or will be less 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. That is, the disease may be prolonged or result in complications, especially in vulnerable patients with underlying health problems (Refs. 1 and 4). Use of an alternative drug to treat the patient empirically may be less desirable because that drug may have a narrower spectrum of activity or greater or more toxic side effects.

Isolation of fluoroquinolone-resistant *Campylobacter* organisms from humans means that fluoroquinolone therapy—if administered—would be ineffective or less effective in these humans. The current level of resistance to fluoroquinolones among human *Campylobacter* isolates attributed to the use of fluoroquinolones in poultry represents a harm to human health.

Furthermore, a risk assessment conducted by CVM demonstrated the magnitude of the adverse impact that the use of fluoroquinolones in chickens has on human health. The risk assessment determined that in 1999 a mean estimate of 11,477 persons (5th and 95th percentiles: 6,412 and 18,978) infected with campylobacteriosis and prescribed a fluoroquinolone would have had a fluoroquinolone-resistant illness due to the use of fluoroquinolones in chickens. These people are likely to have had prolonged illnesses or complications. Furthermore,

CVM believes that the adverse human health effects were underestimated due to limitations in study methods and data.

Finally, CVM is concerned that the harm from fluoroquinolone-resistant *Campylobacter* infections will continue to increase such that more people will be unable to be effectively treated with fluoroquinolones when those drugs are needed for foodborne illness. With respect to the harm presented by resistant foodborne pathogens, it is especially important to take action as soon as a problem is detected since the nature of the problem is dynamic and relatively large shifts in the prevalence of resistance can occur within short timeframes (Refs. 5 and 6).

III. Legal Context of the Proposed Action

Section 512(e)(1)(B) of the act, requires withdrawal of approval of an NADA if:

* * * new evidence not contained in [an approved] application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved * * *.

Under this clause, to meet its initial burden to support withdrawal of an approval CVM must provide ''a reasonable basis from which serious questions about the ultimate safety of [the drug] may be inferred.'' *See* Diethylstilbestrol: Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision (Commissioner's DES Decision), 44 FR 54852 at 54861, September 21, 1979, *aff'd Rhone-Poulenc, Inc.*, *Hess & Clark Div.* v. *FDA*, 636 F.2d 750 (D.C. Cir 1980). *See also* Nitrofurans: Withdrawal of Approval of New Animal Drug Applications; Final Rule; Final Decision Following a Formal Evidentiary Public Hearing, 56 FR 41902, August 23, 1991. '''Serious questions' can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect'' (44 FR 54861). Once this threshold burden has been satisfied, the burden passes to the sponsor to demonstrate safety. *Id.*

Section 201(u) of the act provides that for purposes of section 512 of the act, ''safe'' has ''reference to the health of man or animals.'' In determining whether a drug is ''safe,'' section

512(d)(2)(A) of the act requires FDA to consider ''the probable consumption of such drug and any substance formed in or on food because of the use of such drug.''

''Safe,'' in the context of human food safety, can be defined as ''reasonable certainty of no harm.'' The definition is derived from language in H. Rept. 2284, 85th Cong., 2d. sess. 4095, 1958, defining the term ''safe'' as it appears in section 409 of the act (21 U.S.C. 348), which governs food additives. Substances formed in or on food due to the use of animal drugs were regulated under the food additive provisions in section 409 of the act until passage of the Animal Drug Amendments in 1968 (the 1968 amendments). The 1968 amendments merely consolidated all of the existing statutory authorities related to animal drugs into section 512 of the act, and the legislative history shows that the consolidation in no way changed the authorities with respect to the regulation of new animal drugs (S. Rept. 1308, 90th Cong., 2d. sess. 1, 1968). CVM has applied the ''reasonable certainty of no harm'' standard in determining the safety of substances formed in or on food as a result of the use of a new animal drug during the new animal drug application review process. CVM has done so by determining the level at which a substance formed in or on food as a result of the use of a new animal drug has no effect on humans (Ref. 75).

IV. Development of Antimicrobial Resistance As a Result of Drug Use in Animals

A. Development of Antimicrobial Resistance That Can Compromise Human Therapy

Antimicrobial drugs are products that affect bacteria by inhibiting their growth or by killing them outright. Antimicrobial drugs are used to treat bacterial disease in humans and since their discovery have prevented countless deaths worldwide. In animals, these drugs are used to control, prevent, and treat infection, and to enhance animal growth and feed efficiency.

That antimicrobial agents could select for resistant bacterial populations became apparent soon after the first antimicrobial drug, penicillin, was discovered. Antimicrobial use promotes antimicrobial resistance by selecting for resistant bacteria (Refs. 7 and 8). When an antimicrobial drug is used to treat an infection, the bacteria most sensitive to the drug die or are inhibited. Those bacteria that have, or acquire, the ability to resist the antimicrobial persist and replace the sensitive bacteria. If these

bacteria that have developed resistance are disease causing (pathogenic) in humans, they may cause disease resistant to treatment (Refs. 7 and 9).

Selective pressure resulting from the use of antimicrobial drugs is the underlying force in the development and spread of resistant bacterial populations. The association between antimicrobial use and resistance has been documented in various settings (Ref. 7), for nosocomial infections (Ref. 10) as well as for community-acquired infections (Ref. 11).

B. Antimicrobial Resistance in Foodborne Pathogens of Animal Origin

In industrialized countries, the major foodborne pathogens, *Campylobacter* and *Salmonella*, are infrequently transferred from person to person (Refs. 3 and 12). In these countries, epidemiological data have demonstrated that the primary source of antibiotic resistant foodborne infections in humans is the acquisition of resistant bacteria from animals via food (Refs. 3, 13, and 14). This has been demonstrated through several different types of foodborne disease followup investigations, including laboratory surveillance, molecular subtyping, outbreak investigations, and studies on infectious dose and carriage rates (Refs. 15, 16, 17, and 18).

CDC published an extensive review of epidemiological studies that focused on human foodborne infections caused by drug-resistant *Salmonella* and concluded that the resistant infections were acquired through contaminated foods of animal origin (Refs. 12 and 19). Transfer of *Campylobacter* from poultry to humans through food was demonstrated as early as 1984 (Ref. 15).

Recent emergence of a resistant foodborne pathogen that has a food-producing animal reservoir is illustrated by *Salmonella enterica* serotype Typhimurium Definitive Type 104 (DT104). DT104 is a multidrug resistant pathogen that is currently epidemic in human and food-producing animal populations in the United Kingdom and has been isolated in several countries in Europe (Refs. 20, 21, and 22). This organism has also been identified in livestock and poultry in the United States (Refs. 23, 24, and 25). Also, a report from the United Kingdom suggests that infections caused by DT104 may be associated with greater morbidity and mortality than infections by less resistant serotypes of *Salmonella* (Ref. 26).

C. Role of Animal Drug Use in the Development of Resistant Foodborne Pathogens

Scientific evidence demonstrates that the use of antimicrobials in food-producing animals can select for resistant bacteria of human health concern. Repeated dosing of food-producing animals can also contribute to the selection of resistant bacteria (Refs. 27 and 28). When an antimicrobial drug is administered to an animal, the most susceptible bacteria will be eliminated, while the least susceptible organisms will survive. These surviving bacteria will proliferate and become the predominant population. With additional exposure to the drug, the resistant populations of bacteria will expand and have an increasing probability of survival and dissemination.

The resistant bacteria that develop as a result of antimicrobial drug use in food-producing animals can then be transferred to humans via food. The contaminated food may cause disease in persons handling or consuming the food or in persons consuming food contaminated from the animal-derived food.

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 are pathogenic to humans (Refs. 15, 29, 30, 31, and 32). For example, *Salmonella* and *Campylobacter* are ubiquitous and can exist in the intestinal flora of various food-producing animals without causing disease in the animals. However, these bacteria can cause severe, even fatal, foodborne illness in humans. If using an antimicrobial in a food-producing animal causes resistance to occur in such bacteria, and the resistant bacteria cause an illness in a consumer who needs treatment, that treatment may be compromised (Ref.9).

The link between antimicrobial resistance in foodborne pathogenic bacteria and use of antimicrobials in food-producing animals has been demonstrated in a number of studies (Refs. 25, 33, 34, and 35). For example, an association has been noted between loss of susceptibility to fluoroquinolones among *Salmonella enterica* Typhimurium DT104 isolates (see section IV.B of this document) and the approval and use of a fluoroquinolone for veterinary therapeutic use in the United Kingdom (Refs. 14, 30, and 36). Moreover, fluoroquinolone administration to chickens infected with fluoqoquinolone-sensitive *C. jejuni* has been shown to

result in the development of fluoroquinolone-resistant *C. jejuni* in those chickens (Ref. 35).

Epidemiological evidence shows that resistant foodborne pathogens are present on or within animals as a result of antimicrobial drug use in food-producing animals and can result in drug-resistant infections in humans (Refs. 1, 16, 37, 38, and 39). Holmberg et al. were the first to establish this by documenting an outbreak of salmonellosis in people caused by multi-drug-resistant *Salmonella* from eating hamburger originating from South Dakota beef cattle fed the antibiotic chlortetracycline for growth promotion (Ref. 16). As explained more fully in section V.B of this document, researchers in Minnesota recently reported on fluoroquinolone-resistant *Campylobacter* infections in humans acquired from poultry treated with fluoroquinolones (Ref. 1).

V. Antimicrobial Resistance Resulting From the Use of Fluoroquinolones in Poultry

As discussed below, during its evaluation of the NADA's for use of fluoroquinolones in poultry, CVM carefully considered the issue of potential resistance development due to the use of the drugs in poultry. When CVM approved the NADA's for use of fluoroquinolones in poultry, it believed that the fluoroquinolones could be used safely in poultry and that resistance development could be limited by certain restrictions placed on the use of the drugs. Resistance, however, has developed such that CVM now believes that its only option to protect human health is withdrawal of the approval of the NADA's for use of fluoroquinolones in poultry.

A. Circumstances Surrounding the Approval

1. Human Health Concern Related to Fluoroquinolone Resistance

Prior to FDA's approval of fluoroquinolones for use in food-producing animals, several scientific organizations and individual scientists expressed concern that the use of fluoroquinolones in food-producing animals would result in the selection of fluoroquinolone-resistant foodborne bacterial pathogens in humans (Refs. 7, 33, and 40). There were several reasons for these concerns.

First, as explained more fully in section V.C of this document, fluoroquinolones are very important for human therapy. Bacteria resistant to veterinary fluoroquinolones exhibit resistance to other compounds within the class. Thus, resistance to a fluoroquinolone used only in animals, such as enrofloxacin, confers resistance to all other fluoroquinolones, including ciprofloxacin and other fluoroquinolones used only in humans. The veterinary fluoroquinolone enrofloxacin is structurally similar to ciprofloxacin and a portion of it is metabolized to ciprofloxacin in the animal (Ref. 41).

Second, reports of studies conducted after approvals of fluoroquinolones for poultry in other countries had shown a relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter* in animals and humans. For example, the approval and use of these drugs in poultry in the Netherlands (Refs. 33, 35, and 42), and Spain (Refs. 43 and 44) preceded increases in fluoroquinolone resistance in *Campylobacter* isolates from treated animals and ill humans. In the Netherlands, *Campylobacter* isolates from humans and poultry were examined for resistance to the human fluoroquinolone ciprofloxacin between the years 1982 and 1989 to determine the influence of licensing of enrofloxacin for veterinary use in 1987 (Ref. 33). In 1982, none of the *Campylobacter* isolates from either human or poultry sources was resistant to ciprofloxacin. In 1989, fluoroquinolone resistance among the *Campylobacter* isolates was 11 percent in humans and 14 percent in poultry (Ref. 33).

Third, there was a concern about use of fluoroquinolones as water-soluble products. This use raised the possibility of development of resistant organisms in greater numbers than if the drugs were to be administered in an individually administered injectable dosage form. Due to the nature of animal production, the most efficient way to treat herds or flocks is to administer drugs through the water supply or the feed. When disease is detected in a herd of animals or a flock of poultry, the product is put into the animals' water supply, thereby exposing greater numbers of animals than just the few with clinical signs of the disease. The practice of treating an entire herd or flock is more likely to result in resistant pathogens than individual animal treatment due to the inability to control each animal's dose and the widespread contamination by water leakage and animal waste that occurs when large numbers of animals are treated, which result in untreated animals being exposed to the drug.

Selective pressure exerted by fluoroquinolone use is the driving force for the development and spread of the genetic mutations in *Campylobacter* that lead to fluoroquinolone resistance. Administering fluoroquinolones to large numbers of animals through water or feed could substantially increase the selective pressure on the organisms and facilitate the spread of resistant pathogens. An additional problem arises when the dose administered to each bird is variable, which is the case when the antimicrobial is administered *ad libitum* in the water. This practice may result in ineffective dosing in some animals and increase the probability of selecting for resistant zoonotic bacteria in both healthy and diseased animals.

2. Advisory Committee Review

Because of the concerns surrounding the use of fluoroquinolones in food-producing animals, CVM consulted with a panel of experts comprised of its Veterinary Medicine Advisory Committee and FDA's [Human] Anti-Infective Drug Advisory Committee in May 1994 to address the issue of use of fluoroquinolones in food-producing animals in light of concerns about antimicrobial resistance. The panel supported several restrictions on the use of the drugs in food-producing animals in order to minimize the human health risks related to the development of resistant bacteria in animals (Ref. 45). Frequently expressed recommendations of committee members included approval for therapeutic use by veterinary prescription only, prohibition of extra-label use, and establishment of a nationally representative surveillance system to prospectively monitor resistance trends of selected enteric bacteria of animals that can cause disease in humans (Ref. 45).

3. Approval of Enrofloxacin

The NADA for Baytril® 3.23% Concentrate Antimicrobial Solution (enrofloxacin) was approved October 4, 1996, for broiler chickens and growing turkeys. The approval is for therapeutic use: Enrofloxacin is approved for the control of mortality in chickens associated with *E. coli* organisms and control of mortality in turkeys associated with *E. coli* and *P. multocida* organisms.

At the time this drug was approved, microbial safety studies were not required for therapeutic uses of antimicrobial new animal drugs in food-producing animals. Thus, no studies were required of the drug sponsor, and none was performed, demonstrating the safety of the use of fluoroquinolones in poultry with respect to antimicrobial resistance and the potential for resistant pathogens to be transferred from poultry

to humans. At that time, the agency believed that such studies were necessary only for certain subtherapeutic feed uses in food-producing animals (21 CFR 558.15). However, increasing evidence that therapeutic as well as subtherapeutic use of antimicrobials in food-producing animals may select for resistant bacteria of human health concern led the agency to issue final guidance addressing this concern in December 1999 (Ref. 46). The guidance addresses how FDA intends to consider the potential human health impact of all uses, therapeutic as well as subtherapeutic, of all classes of antimicrobial new animal drugs intended for use in food-producing animals. The guidance states that preapproval studies to answer questions regarding the human health impact of the microbiological effects of an antimicrobial product may be needed for therapeutic as well as subtherapeutic products (Ref. 46).

4. Approval Restrictions, Surveillance, and Educational Activities

Certain actions were taken at or near the time of approval of the fluoroquinolones to help ensure that resistance to fluoroquinolones did not develop in bacteria that are transferred from poultry to humans, and to detect any trend towards the development of resistance at an early stage. First, CVM imposed two restrictions on the use of the fluoroquinolones. CVM limited the drugs to use by or on the order of a licensed veterinarian. Also, FDA issued an order to prohibit all extra-label uses of fluoroquinolones in animals, which became effective in August 1997 (21 CFR 530.41).

Second, the agency took steps to gather surveillance data on the development of antimicrobial resistance among foodborne pathogens, including resistance to fluoroquinolones. In 1996, FDA, CDC, and the U.S. Department of Agriculture (USDA) established the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS) to prospectively monitor changes in antimicrobial susceptibilities of selected zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter (Ref. 47). Nontyphoid *Salmonella* was initially selected as the sentinel organism and the program has been expanded each year since its inception. NARMS is currently monitoring susceptibilities of human and animal isolates of *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus*. NARMS is set up as two equal parts, human and animal, that use

the same methodology for isolating and testing the organisms.

Animal isolate testing is conducted at the USDA Agricultural Research Service Russell Research Center. Human isolate testing is conducted at the CDC National Center for Infectious Diseases Foodborne Disease Laboratory. Goals and objectives of the monitoring program include: Providing descriptive data on the extent and temporal trends of antimicrobial susceptibility in enteric organisms from the human and animal populations; providing information to veterinarians, physicians, and public health authorities so that timely action can be taken; prolonging the life span of approved drugs by promoting the prudent use of antimicrobials; identifying areas for more detailed investigation; and guiding research on antimicrobial resistance.

Third, CVM has supported efforts by the American Veterinary Medical Association (AVMA) and several practitioner and producer groups to define and promote the appropriate use of antimicrobial drugs in food-producing animals to try to minimize the occurrence of resistant foodborne pathogens that may be transferred to humans through food. CVM is supporting the development of printed material and videotapes based on the prudent use guidelines developed by the AVMA to educate producers and veterinarians about food-producing animal drug use. CVM is also committed to help develop other educational strategies to be disseminated to veterinarians and food-producing animal producers via symposia and exhibits at scientific meetings. Veterinary medical schools may also use these educational materials as part of a food safety curriculum.

B. Development of Resistance After FDA Approvals of Fluoroquinolones for Use in Poultry

1. Overview

Despite the previously described restrictions placed by FDA on the use of the approved poultry fluoroquinolone products, fluoroquinolone resistance among *Campylobacter* developed and increased after the 1996 approvals. CVM believes, based on research, that prior to 1995, there was very little, if any, fluoroquinolone-resistant *Campylobacter* in the United States among domestically acquired foodborne disease (see section V.B.5 of this document). After the approval, however, fluoroquinolone resistance was observed in *Campylobacter* from human clinical cases, and in poultry isolates taken from slaughter plants and retail

establishments. The results were obtained from NARMS and a key study by the Minnesota Department of Health. In the 4 years since approval of the fluoroquinolones, CVM has found very little evidence of extra-label use of these drugs in food-producing animals, based on information derived from regulatory inspections. Nor has CVM found evidence of over-the-counter sales of the poultry fluoroquinolones. Therefore, the agency's attempts to prevent the development of fluoroquinolone-resistant human pathogens through limiting these drugs to prescription use and by prohibiting extra-label use have not been sufficient.

2. Human Isolate Data from NARMS

CDC began routinely testing human *Campylobacter* isolates for resistance to fluoroquinolones in 1998, 2 years after approval of enrofloxacin for use in poultry. In 1998, CDC tested 346 human *Campylobacter* isolates and found 13.6 percent of the *Campylobacter* isolates were resistant to fluoroquinolones (Ref. 48). In 1999, CDC tested 315 human isolates of *Campylobacter*; fluoroquinolone resistance had risen to 17.6 percent among *C. jejuni* and 30 percent among *C.* coli, a statistically significant increase (Ref. 49).

3. Poultry Isolate Data From NARMS and Other Sources

Approximately 9.4 percent of the *C. jejuni* isolated from chicken carcasses at federally inspected slaughter plants in 1998 were fluoroquinolone resistant (Ref. 50). The *Campylobacter* isolates were collected in a pilot study during the latter 3 months of the year. The 1999 data set, collected for the entire year, shows that approximately 9.3 percent of the *C. jejuni* were resistant to fluoroquinolones (Ref. 51). However, the 1999 data when segregated by State show that several areas of the country had significantly higher than the 9.3 percent average level (Ref. 2). When the isolate test results are weighted by the level of chicken production in each State, the level of resistance among *C. jejuni* is approximately 12 percent for 1999 (Ref. 2).

Campylobacter isolates from retail chicken products show even higher levels of fluoroquinolone resistance. In January-June 1999, public health laboratories in Georgia, Maryland, and Minnesota, under the direction of the CDC, tested 180 chickens with 23 distinct brand names that were purchased from 25 grocery stores (Ref. 52). *Campylobacter* were isolated from 80 (44 percent) of the chickens. Nineteen (24 percent) of the samples had *Campylobacter* isolates resistant to

fluoroquinolones and 25 (32 percent) were resistant to nalidixic acid, a quinolone antimicrobial drug that serves as a precursor to fluoroquinolone resistance development (Ref. 52). These retail chicken findings are consistent with those from an earlier, independent study by the Minnesota Department of Health, described in the next subsection.

4. Human and Poultry Isolate Data From the Minnesota Study

Researchers at the Minnesota Department of Health studied quinolone and fluoroquinolone resistance among Minnesota residents, and evaluated chicken as the source of the resistance. They found that the proportion of fluoroquinolone-resistant *C. jejuni* isolates from humans increased from 1.3 percent in 1992 to 10.2 percent in 1998 (Ref. 1).

The proportion of resistant *C. jejuni* collected from all reported cases of illness increased only slightly from 1992 to 1994. Although researchers found that increases between 1996 and 1998 were predominantly associated with foreign travel, the percentage of resistant infections that were acquired domestically also increased from 0.3 percent to 3 percent between 1996 and 1998 (Ref. 1).

As part of the study, the Minnesota Department of Health in cooperation with the Minnesota Department of Agriculture collected 20 different brands of retail chicken products from 18 markets in the Twin Cities metro area in 1997. *Campylobacter* were isolated from 88 percent (80/91) of the samples; 20 percent of these were *Campylobacter* resistant to fluoroquinolones. The products with resistant strains had been processed in five States (Ref. 1).

Molecular subtyping revealed a strong association between resistant *C. jejuni* strains from the retail chicken products and *C. jejuni* strains from the domestically acquired human cases of campylobacteriosis. The study used polymerase chain reaction with restriction length polymorphism flagellin gene typing to identify strains of fluoroquinolone-resistant *C. jejuni* among isolates from the domestically acquired human cases and locally available retail chicken products. The investigators attributed the 1996 to 1998 increase in resistant domestic cases among humans to poultry treated with fluoroquinolones (Ref. 1). The investigators concluded that ''the use of fluoroquinolones in poultry, which began in the United States in 1995, has created a reservoir of resistant *C. jejuni*'' (Ref. 1).

5. Summary of Fluoroquinolone Resistance Data

The most recent data on fluoroquinolone resistance among *Campylobacter* isolates (1999) show 17.6 percent resistance among *C. jejuni* in humans, and 9.3 percent resistance among *C. jejuni* on chickens sampled at slaughter plants. Retail samples taken in 1999 indicate even higher levels of fluoroquinolone-resistant *Campylobacter* on chickens (Ref. 52).

After thoroughly analyzing all the data and evidence, CVM has determined that a significant cause of the emergence of domestically-acquired fluoroquinolone-resistant *Campylobacter* infections in humans is the consumption of, or contact with, contaminated food (see section IV.B of this document), that poultry is the most likely source of campylobacteriosis in humans (see section V.C.2 of this document), and that poultry is also a source of resistant *Campylobacter* (see section V.B.3 and V.B.4 of this document). CVM has also concluded that the administration of fluoroquinolones to chickens leads to development of fluoroquinolone-resistant *Campylobacter* in the chickens (see section IV.C of this document). Fluoroquinolone-resistant *Campylobacter* have been found in broiler chicks that had been administered fluoroquinolone drugs (Ref. 35). Further, resistant *Campylobacter* found on chicken carcasses would not have resulted from use of a nonfluoroquinolone drug because fluoroquinolone resistance in *Campylobacter* arises exclusively from clonal expansion, rather than by the transfer of plasmids or resistance determinants (Ref. 53). Also, the fluoroquinolone resistance results only from drug use; that is, the resistance could not have developed naturally since fluoroquinolones are totally synthetic antimicrobials with no known natural analogues. (See also discussion in section IV.A of this document.) Consequently, CVM has concluded, based on a careful study of all relevant data and information, that use of fluoroquinolones in poultry is a significant cause of domestically acquired resistant *Campylobacter* infections in humans.

CVM's conclusion is supported by the establishment of a temporal association between the approval of the fluoroquinolones for poultry and the emergence of fluoroquinolone-resistant *Campylobacter* in humans. Although most of the data cited above were collected after the approval, CVM believes that there was very little, if any,

fluoroquinolone-resistant *Campylobacter* in the United States among domestically acquired foodborne disease cases before the approvals. Fluoroquinolones have been available for human use since 1986 when ciprofloxacin was approved in the United States (Refs. 1 and 54). Ciprofloxacin soon was one of the most commonly used antimicrobials to treat infections caused by a variety of bacterial infections in humans, including *Campylobacter* infections. However, emergence of domestically acquired fluoroquinolone-resistant human foodborne infections in numbers large enough to be detected by national surveillance systems did not occur until sometime between 1996 and 1998 Ref. 1).

Only rare, sporadic, and isolated incidents of fluoroquinolone-resistant *Campylobacter* infections were reported in humans prior to 1995.[1] (NARMS was not initiated until January 1996 and *Campylobacter* were not tested until 1998.) In addition, as shown in section V.B.4 of this document, only very low levels of resistance were detected among isolates from human *Campylobacter* cases collected by the Minnesota Department of Health from 1992 to 1994 (Ref. 1). Additional data from Minnesota demonstrated an increase in fluoroquinolone resistance among *Campylobacter* collected from domestically-acquired cases of human illness after the approval of the poultry fluoroquinolones (Refs. 1 and 54). The researchers were able to conclude that the 1996 to 1998 increases in domestic cases were due to the use of fluoroquinolones in poultry. That conclusion is supported by the association found between molecular subtypes of resistant *C. jejuni* strains that were acquired domestically in humans and those found in chicken products (Ref. 1). (See section V.B.4 of this document.)

Because there was no food-producing animal fluoroquinolone use other than use in poultry until late 1998 (when CVM approved fluoroquinolones for use in cattle), CVM believes that the data presented in this section V.B of the document) provide strong evidence that the increase in domestically acquired fluoroquinolone resistance observed in people since 1996 (Ref. 1) is largely associated with the use of fluoroquinolones in poultry. Data from other countries, which showed

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[1] In two surveys encompassing 474 human isolates from 1982 to 1992 in the United States, only a single ciprofloxacin resistant isolate was identified. This isolate was subsequently speciated as *C. lari*, which is intrinsically resistant to fluoroquinolones (Ref. 54).

increases in *Campylobacter* resistance following approval of fluoroquinolones for use in poultry, support this conclusion as to temporal association (Refs. 33, 43, and 55). (See section V.A.1 of this document.)

CVM's conclusion is also supported by an examination of the two most likely other possible causes of fluoroquinolone-resistant *Campylobacter* in humans. One possible cause is the direct use of fluoroquinolones in humans. Although fluoroquinolone-resistant *Campylobacter* may develop in the intestinal tract of persons with these infections who are treated with fluoroquinolones, spread of the organisms to other persons is uncommon because person-to-person transmission of these organisms is rare in developed countries (Ref. 3). As a result, the resistance due to direct human use is likely to be limited (Refs. 12 and 19). (See section IV.B of this document.) The lack of an increase in fluoroquinolone-resistant human cases from the time when fluoroquinolones were first used in human medicine, the high level of human use since their approval, and the emergence of fluoroquinolone resistance in human cases of *Campylobacter* infections soon after the approval of fluoroquinolones for poultry, all support the conclusion that the resistance observed in humans is due to the use of fluoroquinolones in poultry.

Exposure to *Campylobacter*-contaminated food can occur during foreign travel and, indeed, some of the fluoroquinolone resistance identified among humans is due to acquiring an illness while traveling outside the United States. However, a risk assessment conducted by CVM demonstrates a significant human health impact from domestically acquired fluoroquinolone-resistant *Campylobacter* infections due to the use of fluoroquinolones in chickens (Ref. 2). (See section V.C.3 of this document.)

CVM therefore believes that a significant cause of the emergence of fluoroquinolone-resistant *Campylobacter* infections in humans is the consumption of, or contact with, contaminated poultry that had been administered fluoroquinolones, had contact with other poultry treated with this drug, or had contact with the environment contaminated directly or indirectly with this drug.

C. Human Health Implications

1. Importance of Fluoroquinolines in Human Medicine

Fluoroquinolones are considered to be one of the most valuable antimicrobial drug classes available to treat human infections because of their broad spectrum of activity, pharmacokinetics, safety, and ease of administration (Ref. 56). This class of drugs is effective against a wide range of human diseases and is widely used both in treatment and prophylaxis of bacterial infections in the community and in hospitals (Ref. 56). Fluoroquinolones are important because they are active against a variety of organisms resistant to most other classes of antibiotics or for which alternative agents are more toxic and/or not available for oral administration. They have been very effective in treating or preventing serious, often life-threatening, infections in a number of major areas of human medicine, both in the hospital and in the community. In the hospital setting, the fluoroquinolones are very often life-saving drugs of choice for a wide variety of common resistant and serious infections because of both their activity and their favorable safety profiles.

Fluoroquinolones are particularly important in the treatment of gram negative infections, including those caused by *Campylobacter*, but also including *Shigella*, *Salmonella*, *E. coli*, *Klebsiella* and other Enterobactericiae. These type of enteric bacteria cause a wide variety of infections and are frequently resistant to agents such as ampicillin, tetracycline, trimethoprim-sulfa and many cephalosporins (Ref. 56). In addition, the fluoroquinolones are often less toxic and more convenient to administer than alternative treatments that may be available for resistant organisms.

Fluoroquinolones are the agents most frequently used as the drugs of choice in the empiric treatment of patients presenting to a physician with serious gastrointestinal symptoms such as acute diarrhea or possible enteric fever (e.g., typhoid fever) because they traditionally have exhibited a very high level of clinical effectiveness against most enteric pathogens (Refs. 4 and 57). Severity of illness is one of the most important criteria physicians use in determining which patients require immediate treatment for a presumed infectious enteric illness. Other criteria include having a complicating medical condition and belonging to a high-risk group such as persons who are immunocompromised. Upon presentation to the physician, the patient is examined and if treatment is

deemed necessary, treatment is usually prescribed empirically, that is, without having the results of culture and sensitivity testing available prior to the selection of the treatment. Culture and sensitivity testing of *Campylobacter* can take 48 to 96 hours before results are available to provide guidance to the physician in selection of a treatment regimen. Thus, the physician needs to be able to confidently prescribe an agent likely to be immediately effective against the array of organisms most likely to be causing the patient's severe symptoms.

Treatment of serious susceptible enteric infections with an effective fluoroquinolone (e.g., ciprofloxacin) can reduce the duration of illness and most likely prevent complications and adverse outcomes, including hospitalization (Refs. 19 and 58). The magnitude of the benefit of antibiotic treatment is directly related to the early initiation of therapy (Refs. 19 and 58). For example, effective treatment of campylobacteriosis with fluoroquinolones has been shown to decrease the duration of illness from 10 days to 5 days and the mean duration of diarrhea from 5 to 1.3 days (Refs. 7, 19, and 58).

2. Foodborne Diseases

a. *Introduction.* Foodborne diseases have a major public health impact in the United States. Recent estimates describe 5,000 deaths and 76 million foodborne illnesses annually (Ref. 59). The causes of foodborne illness are varied and include bacteria, parasites, viruses, toxins and novel agents. Clinical severity of foodborne disease also varies and ranges from mild gastroenteritis to life-threatening neurologic, hepatic, and renal syndromes as well as septicemia (Ref. 59). Development of resistance in foodborne bacterial pathogens to safe and effective antimicrobials complicates the medical and public health concern as important treatment options are compromised or lost (Refs. 7, 19, 61, and 62).

b. *Campylobacteriosis.* The three primary causes of bacterial foodborne disease in the United States are *Campylobacter*, *Salmonella*, and some pathogenic strains of *E. coli*. *Campylobacter* infections are predominantly foodborne infections associated with animal-derived food products (Refs. 59, 63, and 64). *Campylobacter* is the most common known cause of foodborne illness in the United States (Ref. 3), causing an estimated 2 million cases every year (Ref. 60). Compared to patients with typical noninvasive salmonellosis, patients with *C. jejuni* or *Campylobacter*

coli gastroenteritis often experience more severe illness and are ill longer. Gastroenteritis caused by *Campylobacter* commonly causes severe diarrhea, often bloody, fever, severe abdominal pain, and can mimic acute appendicitis, which may result in unnecessary surgery (Ref. 65). While these symptoms usually improve within several days, they persist or recur in 15 to 25 percent of patients and can be confused with chronic bowel diseases (Ref. 65). For example, among 460 sporadic (not associated with an epidemic) cases of campylobacteriosis recently reported in 19 representative U.S. counties, the mean duration of illness was 10 days, with 7 lost workdays, and one-half hospitalization day. Five patients (1 percent) died (Ref. 66). Effective treatment of campylobacteriosis with fluoroquinolones within the first 2 days of illness decreased the duration of illness from 10 days to 5 days (Refs. 7, 19, and 58).

Campylobacter species are often found as commensal bacteria, which are bacteria that exist in an animal without causing harm to that animal. These bacteria are carried in the intestinal tract of food-producing animals and can contaminate food during slaughter and processing (Ref. 67). The USDA Food Safety Inspection Service has recently conducted surveys of recovery rates and estimated the mean number per unit (gram, cm^3) of product for some of the major foodborne pathogens found on raw animal products at slaughter and processing. Raw product isolation rates vary by species, with turkeys and chickens appearing to have the highest rates of *Campylobacter* recovery (Refs. 68, 69, 70, and 71).

Broiler chickens carry the highest carcass and ground product load of *Campylobacter* when compared to other food-producing animals at slaughter (Refs. 70 and 71). These data are consistent with the repeated observations in epidemiological studies of the increased risk of campylobacteriosis associated with exposure to poultry. In surveys of retail food products conducted by other organizations, *Campylobacter* was isolated from: 2 to 20 percent of raw beef, 40 percent of veal; up to 98 percent of chicken meat; low proportions of pork, mutton, and shellfish; 2 percent of fresh produce from outdoor markets and 1.5 percent of mushrooms (Refs. 15 and 72).

The symptoms exhibited by persons with an enteric foodborne illness include vomiting, diarrhea, abdominal pain, cramping, and fever. The causal agent of an enteric illness is not easily determined based upon symptoms alone. Empiric treatment of patients with serious enteric disease of presumed bacterial etiology is usual medical practice because when treatment is delayed (e.g., until the *Campylobacter* infection or another etiologic agent is confirmed by a medical laboratory), the therapy may be ineffective or less effective, and the illness is more likely to be prolonged or result in complications (Ref. 4). Also, the clinical signs of patients with campylobacteriosis are indistinguishable from enteric disease caused by *Salmonella*, which also is treated with fluoroquinolones. Relapses occur in approximately 5 to 10 percent of untreated patients with campylobacteriosis (Ref. 4) and have been associated with fluoroquinolone resistance (Ref. 74).

Antibiotic therapy is always indicated for patients who demonstrate symptoms of high fever, bloody diarrhea, or more than eight stools in 24 hours; who are immunosuppressed; who have bloodstream infections; or whose symptoms worsen or persist for more than 1 week (Ref. 4). More invasive disease such as blood-borne infections occur in less than 1 percent of patients with *C. jejuni* infections and are more common in the elderly or very young individuals as well as those with impaired immune systems (Ref. 65). Rare manifestations of campylobacteriosis can include meningitis, endocarditis, and septic abortion (Ref. 4).

Campylobacteriosis also carries the potential for serious sequelae as a result of immunologic reactions to the infection. The disease has been linked to reactive arthritis and Reiter's Syndrome as well as Guillain-Barre Syndrome (Ref. 65). Guillain-Barre Syndrome is an autoimmune-mediated disorder of the peripheral nervous system. Since the elimination of polio, this syndrome is now the most common cause of acute flaccid paralysis (Ref. 73). Many studies have shown a link between campylobacteriosis and Guillain-Barre Syndrome. Culture and serologic data indicate that 30 to 40 percent of patients with the syndrome have evidence of a preceding *Campylobacter* infection, but this may be an underestimate (Ref. 73). *C. jejuni* is the most common species identified from patients with Guillain-Barre Syndrome, but other species of *Campylobacter* may be involved (Ref. 73). It is not known whether resistant *Campylobacter* infections are more susceptible to developing sequelae such as Guillain-Barre Syndrome. There is also evidence suggesting that Guillain-Barre Syndrome may be more severe following infection with *Campylobacter* than other precipitating infections (Ref. 73).

3. Campylobacter Risk Assessment

The data on fluoroquinolone resistance levels, and the evidence leading to the conclusion that the use of fluoroquinolones in chickens is a significant cause of fluoroquinolone resistance in humans, establish an adverse effect on human health by fluoroquinolones. To assist in establishing the extent of the adverse human health impact of fluoroquinolone use in poultry, CVM developed a risk assessment model. The risk assessment estimates the extent of the risk to human health from resistant *Campylobacter* pathogens attributed to the use of fluoroquinolones in chickens in the United States. Specifically, the risk assessment model relates the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens (Ref. 2). The risk assessment addressed that portion of the risk that was quantifiable, which is the risk related to consumption of chicken. The unquantifiable portion, that portion due to spread of the pathogen from chicken to other foods through contamination during food preparation or from secondary spread to other animals, was not considered in the risk assessment.

As explained in section V.B.5 of this document, the presence of fluoroquinolone-resistant *Campylobacter* on chicken carcasses results from the use of fluoroquinolones in chickens. This conclusion was used as a parameter in the risk assessment. This does not mean, for purposes of the risk assessment, that every chicken carrying resistant *Campylobacter* had to have been treated with a fluoroquinolone. Resistant organisms could have been acquired from a contaminated environment due to fluoroquinolone drug use in a previous flock, through contact with other chickens during transportation to the slaughter plant and antemortem processing, or through contamination in the slaughter plant by other infected chicken carcasses.

The number of *Campylobacter* culture confirmed human cases in the U.S. population was used to estimate the total burden of campylobacteriosis. These data are collected from State public health laboratories that participate in FoodNet, the CDC's Foodborne Disease Active Surveillance

Network. FoodNet monitors the incidence of foodborne disease in humans and conducts studies to identify the sources and consequences of infection. Using the data on human *Campylobacter* cases reported in FoodNet, the risk assessment calculated a mean estimate of 1.7 million cases of campylobacteriosis (5th and 95th percentiles: 1.1 million and 2.7 million) for 1999 (Ref. 2).

The model also estimates the number of fluoroquinolone-resistant *Campylobacter* cases in humans attributable to chickens. This estimate excludes travelers to countries outside the United States, those patients who were prescribed a fluoroquinolone prior to stool culture, and those patients who were unsure of the timing of their treatment in relation to stool culture. For 1999, the mean estimate of the domestically-acquired fluoroquinolone-resistant *Campylobacter* cases in humans attributable to chickens is 190,421 (5th and 95th percentiles: 103,471 and 318,321) (Ref. 2). The model also estimated the number of humans with fluoroquinolone-resistant campylobacteriosis due to chickens who actually received a fluoroquinolone drug for therapy.

For 1999, the estimated mean number of people infected with fluoroquinolone-resistant *Campylobacter* from consuming or handling chicken and who subsequently received a fluoroquinolone as therapy is 11,477 (5th and 95th percentiles: 6,412 and 18,978) (Ref. 2). These people received less effective or ineffective therapy for their infections. Because their therapy was less effective or ineffective, these people would have had adverse health effects. Since the risk assessment was limited to resistance development due to use of fluoroquinolones in chickens only and the impact is a mean estimate, the actual risk to humans from fluoroquinolone-resistant *Campylobacter* infections from all foodborne sources is likely to be higher.

4. Summary of Human Health Impact

Foodborne diseases have a major public health impact in the United States, and *Campylobacter* is the most common known cause of foodborne illness. Fluoroquinolones are especially important in the treatment of foodborne diseases. Selection of *Campylobacter* resistance to fluoroquinolones is therefore a particular human health concern. Fluoroquinolones used in treating patients with enteritis are typically prescribed empirically because when treatment is delayed pending the results of culture and sensitivity, the

illness may be extended or therapy may be ineffective. Moreover, fluoroquinolone resistance in *Campylobacter* infections has been associated with relapses (Ref. 74).

Campylobacter resistance therefore presents a dilemma for the physician. If fluoroquinolone treatment is given based on symptoms, there is a risk that the treatment will not be effective or will be less effective and valuable time will be lost. If the physician waits for a culture to determine the organism and its susceptibility to antimicrobials, again valuable time will be lost. In either case, the illness may be prolonged and result in complications, including hospitalization and deaths. The physician could turn to another drug for empiric treatment, but alternatives with the spectrum of activity shown by the fluoroquinolones are not available or may be less desirable than the fluoroquinolone due to greater side effects associated with therapy or increased cost of treatment. Even if an acceptable alternative is available at the time, the public health is diminished by the loss of an effective drug from the physician's armamentarium. The *Campylobacter* risk assessment provides evidence of the extent of the adverse impact of fluoroquinolone use in poultry on human health. The risk assessment determined in 1999 a mean estimate of 11,477 people (5th and 95th percentiles: 6,412 and 18,978) infected with fluoroquinolone-resistant *Campylobacter* from consuming or handling chicken and who subsequently received a fluoroquinolone as therapy. The fact that fluoroquinolone use in poultry has resulted in increased resistance of *Campylobacter* infecting humans is clear, as is the risk to human health. Continued use will likely lead to even higher levels of resistance and additional adverse health effects.

VI. Other Considerations

Before issuing this notice of opportunity for a hearing on the withdrawal of the approval for use of fluoroquinolones in poultry, CVM considered requiring revisions to the labeling of the fluoroquinolones to exert more control over their use. Limiting use to individual bird treatment and requiring that the drugs not be used more than once in any individual animal in order to minimize the initial development of resistant enteric organisms were options considered. CVM determined, however, that these use limitations would be impractical for both the veterinary practitioners and poultry producers. The limitations would necessitate mandatory animal identification and maintenance of

extensive treatment records. Even if feasible, due to poultry production and processing practices, this approach would not prevent untreated poultry from picking up the resistant organism from treated poultry or from the environment, exposures that may be substantial during transportation to slaughter and antemortem containment.

CVM also considered establishing a drug registry requiring that veterinarians demonstrate the need for a fluoroquinolone through culture and antimicrobial susceptibility testing and request permission to use the drug in chickens or turkeys from CVM before doing so. This approach would greatly diminish the exposure of poultry to fluoroquinolones and could also be used to enforce a ''single use'' labeling provision. The treated animals could be tagged for followup testing at the slaughter plant and if resistant organisms were identified, the contaminated carcasses could be diverted to nonfood uses. CVM also determined that this alternative was impractical due to the cost of sampling, process control problems with accumulation of carcasses due to the prohibitive amount of time required for current resistance testing techniques, and the public health risk associated with the handling of contaminated carcasses.

VII. Notice of Opportunity for a Hearing

Therefore, notice is given to Bayer Corp., Agriculture Division, Animal Health, that CVM proposes to withdraw the approval of the fluoroquinolone enrofloxacin for use in poultry. This action is based on section 512(e)(1)(B) of the act in that new evidence not contained in the NADA or not available until after the application was approved, evaluated together with the evidence available when the application was approved, shows that enrofloxacin is not shown to be safe under the conditions of use upon the basis of which the application was approved.

In accordance with section 512 of the act and part 514 (21 CFR part 514) and under the authority delegated to the Director of the Center for Veterinary Medicine (21 CFR 5.84), CVM hereby provides an opportunity for a hearing to show why approval of the new animal drug application for enrofloxacin for use in poultry, NADA 141–828, should not be withdrawn. Any hearing would be subject to part 12 (21 CFR part 12).

If a sponsor decides to seek a hearing, the sponsor must file: (1) On or before November 30, 2000, a written notice of appearance and request for a hearing, and (2) on or before January 2, 2001, the

data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact to justify a hearing as specified in § 514.200.

Any other person may also submit comment on this notice. Procedures and requirements governing this notice of opportunity for a hearing, a notice of appearance and request for a hearing, submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing, are contained in § 514.200 and part 12.

The failure of a holder of an approval to file timely a written appearance and request for hearing as required by § 514.200 constitutes an election not to avail himself or herself of the opportunity for a hearing, and the Director of the Center for Veterinary Medicine will summarily enter a final order withdrawing the approvals.

A request for a hearing may not rest upon mere allegations of denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests a hearing, making findings and conclusions, and denying a hearing.

If a hearing is requested and is justified by the sponsor's response to this notice of opportunity for a hearing, the issues will be defined, an administrative law judge will be assigned, and a written notice of the time and place at which the hearing will commence will be issued as soon as practicable.

All submissions under this notice must be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m. Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (section 512 (21 U.S.C. 360b)) and under the authority delegated to the Director of the Center for Veterinary Medicine (21 CFR 5.84).

VIII. Environmental Impact

The agency has determined under 21 CFR 25.33(g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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Dated: October 24, 2000.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee; Renewals

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the renewals of certain FDA advisory committees by the Commissioner of Food and Drugs (the Commissioner). The Commissioner has determined that it is in the public interest to renew the charters of the committees listed below for an additional 2 years beyond charter expiration date. The new charters will be in effect until the dates of expiration listed below. This notice is issued under the Federal Advisory Committee Act of October 6, 1972 (Pubic Law 92–463 (5 U.S.C. app. 2)).

DATES: Authority for these committees will expire on the dates indicated below unless the Commissioner formally determines that renewal is in the public interest.

Name of committee	Date of expiration
Gastrointestinal Drugs Advisory Committee	March 3, 2002
Advisory Committee for Reproductive Health Drugs	March 23, 2002
Arthritis Advisory Committee	April 5, 2002
Veterinary Medicine Advisory Committee	April 24, 2002
Anesthetic and Life Support Drugs Advisory Committee	May 1, 2002
Blood Products Advisory Committee	May 13, 2002
Pulmonary-Allergy Drugs Advisory Committee	May 30, 2002
Drug Abuse Advisory Committee	May 31, 2002
Science Advisory Board to the National Center for Toxicological Research	June 2, 2002
Peripheral and Central Nervous System Drugs Advisory Committee	June 4, 2002
Psychopharmacologic Drugs Advisory Committee	June 4, 2002
Transmissible Spongiform Encephalopathies Advisory Committee	June 9, 2002
Science Board to the Food and Drug Administration	June 26, 2002
Allergenic Products Advisory Committee	July 9, 2002
Cardiovascular and Renal Drugs Advisory Committee	August 27, 2002
Endocrinologic and Metabolic Drugs Advisory Committee	August 27, 2002
Oncologic Drugs Advisory Committee	September 1, 2002