UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of:

Enrofloxacin for Poultry:
Withdrawal of Approval of
New Animal Drug Application
NADA 140-828

FDA DOCKET: 00N-1571

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RESPONDENT BAYER'S POST-HEARING BRIEF

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INTRODUCTION[1]

This is a case about whether the use of the approved animal drug enrofloxacin (tradename Baytril®), a FQ antibiotic, for treating chickens and turkeys creates a "selection pressure" that selects for *CP* that are naturally resistant to FQ antibiotics; whether chickens and turkeys are a source of FQ-resistant *CP* infections in humans in the U.S.; and, if so, whether FQ-resistant *CP* presents a potential risk to human health in the U.S. The issue as presented is oversimplified, however, because CVM knew at the time of the prior approval that the use of enrofloxacin in chickens and turkeys can, and does, select for naturally-occurring resistant *CP*, that chickens and turkeys can be a source of resistant *CP* in people, and that there existed a potential risk of treatment failure when people with resistant *CP* infections are treated with a FQ.

Notwithstanding that all of these facts were known, in October 1996 the FDA approved the use of enrofloxacin for use in treating certain specified life-threatening bacterial infections in chickens and turkeys. The FDA's approval shows that as of October 1996 enrofloxacin was deemed safe for the approved uses. The D.C. Circuit's cases interpreting the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 201 *et seq.*, require that, if CVM desires to withdraw approval for the use of enrofloxacin, it must produce some *new* evidence—something that was not known or was not available when enrofloxacin was approved—and that the new evidence must "show" that there are "sufficiently serious questions" about the safety of enrofloxacin use in chickens (and separately in turkeys) in the U.S. to necessitate the drug's withdrawal. Bayer maintains, and will show in this brief, that CVM has failed to carry its burden of production. Bayer also maintains that, even assuming that CVM has carried its initial burden, the evidence taken as a whole shows that enrofloxacin is "safe" within the meaning of the FFDCA because the human health benefits of its use outweigh any human health risks.[2]

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[1] Bayer also hereby incorporates by reference the Post-Hearing Brief of the Animal Health Institute being filed concurrent with this submission.

[2] Bayer does not waive their argument that the risk/benefit analysis of "safety" extends to economic, environmental, and indirect human health as well as direct human health considerations. This tribunal, however, has previously ruled that the risk/benefit analysis for "safety" is limited to human health considerations. *See* ALJ Davidson's March 3, 2003, Order (OR31) (ruling on the parties' motions to strike and stating that "[e]conomic and

OVERVIEW[3]

Enrofloxacin is a FQ antimicrobial used for the treatment of serious infections in many animal species. It is not used to treat human infections. However, other FQs, such as ciprofloxacin, are used in people. Baytril for poultry is a unique formulation of enrofloxacin designed specifically for administration in the drinking water of chickens and turkeys for the treatment of life-threatening respiratory disease known as air sacculitis. It is not administered to treat *CP*; *CP* do not cause disease in poultry. Enrofloxacin is used in not more than about 1–2% of the annual U.S. broiler chicken flock and about 4% of the annual U.S. turkey flock. It is used prudently, ordinarily as a last resort, based on professional diagnosis, and as a prescription drug. Enrofloxacin is not used for growth promotion or to prevent disease, and extra-label use is prohibited by law. It is administered via water to treat a house of birds, all of which are considered exposed to the disease agent and are in need of treatment.

As with other antimicrobials, use of enrofloxacin exerts a selection pressure by killing susceptible bacteria in the intestinal tract. Thus, it selects for FQ-resistant bacteria in treated flocks during the few days that it is being administered. How long the resistant strains persist in the gut ecology after treatment stops is variable. Since *CP* are a normal inhabitant of the intestinal tract of many animals, including poultry, resistance emerges with treatment. Resistant strains, however, are naturally present in the gut as a result of spontaneous genetic mutation or they may have been ingested. Data largely not considered by CVM show that selection pressures from sources other than enrofloxacin usage and bias in techniques used to isolate *CP*, contribute to the isolation of FQ-resistant *CP* from poultry. The reported rates of FQ-resistant *CP* isolated from people in the U.S. can be explained by these other sources and techniques. They include but are not limited to FQ use in humans, contamination of the water sources with runoff from human use, foreign acquired infections and exposure to non-poultry food, animal, and environmental sources. These sources are consistent with the minimal contribution of the selection pressure exerted by use of enrofloxacin in poultry to resulting domestically acquired incidence of FQ-resistant *CP* infection in people. This is important to this hearing because, in calculating the number of people at risk of an adverse impact, CVM's RA only excludes people who have recently traveled outside the U.S. and/or have recently been on FQ medication. They attribute all other resistant human infections to the use of enrofloxacin in chicken, despite the existence of other significant sources.

CP are ubiquitous, inhabiting the intestinal tract of many animals, such as wild and domestic birds, pets, livestock, and insects. *CP* is also found in the environment, mostly in drinking, recreational and wastewaters that have been contaminated by the feces from humans, animals and birds. While most strains of *CP* do not cause disease in their animal hosts, some strains cause infections in people who ingest a sufficient dose by eating undercooked foods, drinking or swimming in water containing *CP*, or by exposure to pets, or sometimes other people. People acquire *CP*, and FQ-resistant *CP* regardless of whether enrofloxacin is used in poultry.

Campylobacteriosis, the disease caused by *CP*, is generally a mild to moderate gastroenteritis, most often characterized by diarrhea, fever, cramps and nausea. Complications from campylobacteriosis are very rare. Though sometimes the symptoms may be more severe, campylobacteriosis is largely self-limiting. Most people recover in about 3–10 days without

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environmental evidence is not relevant to the issues in this proceeding."). For purposes of this submission, therefore, Bayer assumes that the risk/benefit analysis for "safety" is confined to direct human health issues.

[3] This overview does not have citations; the matters are further discussed in detail with citations in the brief.

visiting a physician. Only a small percentage of campylobacteriosis cases are ever treated with antibiotics, including people with more severe symptoms, people at higher risk of more severe illness (generally those who are immune-compromised) and people who are treated empirically (i.e., without waiting for results of stool cultures). Antibiotic treatment includes macrolides, FQs (except for children less than 18 years old) and combinations of more than one antibiotic. Regardless of whether the *CP* causing the infection is classified as susceptible or resistant to FQs, the available epidemiological and clinical data indicate the clinical outcome is essentially the same. In other words, the data do not support an increased human health harm resulting from a "resistant" infection compared to a susceptible one.

It is important to understand that CVM does not claim that the use of enrofloxacin in poultry results in a net increase in incidence, frequency, or rise of human illness, e.g. *CP* infection in people. The issue is whether the illness caused by a resistant infection is any different from illness caused by a susceptible infection. However, Bayer provides data, largely uncontested, that demonstrates that overall resistance illnesses are not worse than susceptible ones and that illness due to *CP* and other foodborne bacteria will increase if enrofloxacin is removed from the market.

In 1994, prior to the approval of enrofloxacin, CVM convened a Joint Advisory Committee to examine the risks to public health from approval of FQs for use in food animals, including specifically the risk of FQ-resistant campylobacteriosis. In consideration thereof, and other evidence, CVM concluded at the time it approved enrofloxacin (1996) that use of enrofloxacin was safe. When the NOOH was issued and in preparation for the hearing, Bayer examined all available information relevant to this matter, including when available raw data underlying most critical studies. Based on this evaluation, Bayer concluded that the studies and data relied on by CVM are either not new, are not reliable, and/or otherwise do not provide a reasonable basis from which serious questions about the safety of enrofloxacin may be inferred. In fact, the new, most relevant data in this matter, do not support CVM's position. Such data, as reanalyzed by Bayer together with other data establish, if anything, that there is even less risk to human health from the use of enrofloxacin now than at the time of approval in 1996, affirming the conclusions of the joint advisory committee and CVM's decision to approve enrofloxacin for use in poultry.

Bayer's conclusions are summarized as follows:

- There is nothing new in the understanding about the emergence of resistance due to selection pressure from use of enrofloxacin. To the extent there are any new data, it confirms that prudent use of FQs in poultry contributes minimally, if at all, to the prevalence of resistant *CP* isolated from humans.

- There is nothing new in the understanding about whether chicken and/or turkey are a potential source of human infections with susceptible or resistant *CP*. To the extent there are any new data, the data confirm that, during the seven years since FDA found enrofloxacin safe, interventional strategies (or other factors) as adopted by producers (such as prudent use), processors (HACCP, more birds commercially processed, different cuts), and consumers (safe handling and cooking practices) have worked. These measures have led to dramatic reductions in the incidence of campylobacteriosis and FQ-resistant campylobacteriosis, not withstanding a rise in per capita poultry consumption.

- There is nothing new in the understanding about whether FQ-resistant campylobacteriosis presents a differential adverse health risk to people compared to susceptible campylobacteriosis. To the extent there are any new data, the data demonstrate that the duration of illness, including duration of diarrhea, extent of hospitalization, and rate and severity of complications are no greater for resistant than for susceptible infections. Most so-called FQ-resistant *CP* remain treatable with FQs, and if not, with other antibiotics.

- The CVM Risk Assessment ("CVM RA") does not determine any clinical harm or demonstrate any other adverse health risk. It simply provides an estimation of the number of people potentially treated, assuming without support that there is additional harm associated with a FQ-resistant infection compared to a susceptible infection treated with a FQ.

- The CVM RA significantly overestimates the number of persons potentially affected by use of enrofloxacin in chicken because of methodological flaws, use of outdated data and other factors. Any appropriately conducted risk assessment would show that the risk to human health from use of enrofloxacin in chickens and turkeys in the U.S. is minimal, and certainly less than what was known at the time of approval.

- CVM has failed to consider the benefits to human health from the use of enrofloxacin in chickens and that the benefits greatly outweigh any risk. These human health benefits accrue because enrofloxacin is the only practical alternative for treatment of air sacculitis in poultry, and in the absence of effective treatment, more underweight birds, with weaker intestines, are processed. Such birds contribute to greater fecal contamination of meat during processing and thereby present an increased risk of foodborne illness from not just *CP*, but other pathogens as well.

- CVM has provided no evidence to support the withdrawal of enrofloxacin for use in turkeys. They mostly rely on studies conducted in chickens, notwithstanding that turkeys are a different species from chickens, contract different diseases, are raised and processed differently, are to a large extent further processed (cooked) prior to retail sale and, therefore, present a much lower risk of bacterial contamination.

- CVM has not sustained its burden to show by new evidence that there is a reasonable basis to raise a serious question about enrofloxacin use in poultry. When the evidence is taken as a whole, including the uncontroverted benefits, it clearly leads to the conclusion that enrofloxacin is safe. Rather than raise a question about the safety of enrofloxacin, new evidence only reaffirms that enrofloxacin is safe.

SUMMARY OF ARGUMENT

Under the FFDCA as construed by the D.C. Circuit, as well as the FDA's regulations interpreting the statute, CVM has the initial burden of proof when it seeks to withdraw approval for a new animal drug. CVM must come forward with "new evidence" that, by itself or analyzed together with the evidence available when the drug's usage was approved, "shows" that there are "sufficiently serious" questions about the drug's safety to necessitate its withdrawal. Only if and

after CVM carries this burden is Bayer charged with proving that enrofloxacin usage, as approved, remains "safe." The D.C. Circuit has defined "safe" in this context to mean that Bayer must show that the benefits of enrofloxacin usage as approved outweigh the risks of such usage.

CVM does not dispute that, prior to the approval of enrofloxacin usage in chickens and turkeys, the FDA was concerned about the possibilities (1) that usage of the drug could exert a selection pressure resulting in the emergence and dissemination of naturally-occurring mutations of *CP* which are FQ-resistant, (2) that chickens and turkeys could be a vehicle for transmission of FQ-resistant *CP* to people, and (3) that there might be a resulting adverse impact on human health. Nonetheless, the FDA approved the usage of enrofloxacin in chickens and turkeys, finding that the drug was "shown to be safe" despite these concerns—i.e., the benefits to human health from the use of the drug outweighed these potential risks. It is also undisputed that, in the time since enrofloxacin usage in poultry was approved, knowledge about, and efforts to prevent, campylobacteriosis and other foodborne illnesses has improved and the incidence of the occurrence of these risks—risks that were found *acceptable* by the FDA—has decreased. As demonstrated below in detail, CVM's purported "new evidence" at best shows what was already known by the FDA when the drug was initially approved, and at worst shows nothing because the evidence is largely unreliable. Indeed, scientific data since enrofloxacin's approval show that there is less risk now than at the time of the original approval in 1996.

Finally, even if CVM has otherwise carried its initial burden, the evidence adduced by Bayer in this proceeding (evidence that CVM was not aware of, and did not even consider when the Notice of Hearing was published, and which CVM has not contested through direct or rebuttal testimony or via cross-examination) shows that the human health benefits of use of enrofloxacin outweigh any potential human health risks, and that the drug is therefore "safe" within the meaning of the FFDCA. Indeed, the evidence demonstrates that if enrofloxacin is withdrawn, human lives will be lost as a result of increased microbial contamination of food that enrofloxacin now acts to prevent.

LEGAL STANDARDS AND APPLICABLE BURDENS

Bayer adopts and incorporates the Legal Standards and Applicable Burdens set forth in Animal Health Institute's Post-Hearing Brief ("AHI Brief") pp. 3–8.

EVIDENTIARY STANDARDS

Bayer adopts and incorporates the Evidentiary Standards set forth in the AHI Brief pp. 8–17.

ARGUMENT

I. CVM HAS NOT MET ITS BURDEN OF SHOWING THROUGH NEW EVIDENCE THAT ENROFLOXACIN USE IN CHICKENS RAISES SERIOUS QUESTIONS ABOUT SAFETY

A. SELECTION PRESSURE, EMERGENCE, AND DISSEMINATION OF FQ-RESISTANT *CAMPYLOBACTER*

CVM sets the bar low by characterizing the selection pressure issue in this proceeding as simply "[w]hether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of FQ-resistant *Campylobacter* spp. in poultry?" [Notice of Hearing 67 FR 7700, 7701] The issue, and CVM's burden related to this issue, is broader than set forth. Under the legal standards governing this proceeding (*see* Section I, *supra*), CVM must come forward with *new* evidence that *demonstrates* ("shows") that enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of FQ-resistant *CP* spp. in poultry that constitutes a *reasonable* basis to raise *serious* questions about enrofloxacin's safety. As is demonstrated below, CVM has not presented *new* evidence on the selection, emergence, and dissemination issue beyond what was known and accepted by CVM prior to enrofloxacin's approval. Taken as a whole, the available evidence does not provide a reasonable basis to raise serious questions about enrofloxacin's safety, and, therefore, CVM has not met its initial burden.

1. CVM Has Presented No New Evidence on Selection Pressure, Emergence, or Dissemination

Bayer does not dispute that enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of FQ-resistant *CP* spp. in poultry. To do so would be folly, as Bayer would be denying a basic principle of evolutionary biology: that organisms that have adapted to survive in an environment will flourish while organisms that have not adapted will not. FQ resistance develops in *CP* as a natural, spontaneous genetic point mutation in the *gyr*A gene within a *CP* population and is not as a result of exposure to FQs. FQ exposure then can select for resistant *CP*. [Joint Stipulation 1 ("JS"); Newell (B-1908) P.12 L.21–22] In any environment in which quinolones are present, bacteria that are resistant to those drugs will have a very large selective advantage over quinolone-susceptible bacteria. [Barrett (G-1453) P.2 L.16–18] Selection and dissemination of resistance is an inevitable result of any antibiotic use. [van den Bogaard (B-1916) P.3 L.5–6] FQ use in poultry can act as a selection pressure for FQ-resistant bacteria in the poultry digestive tract, just as FQ use in humans can act as a selection pressure for FQ-resistant bacteria in the human digestive tract. [JS 6 & 7]

These facts do not constitute "*new* evidence," however, as all of these scientific facts were known by CVM before enrofloxacin was approved for poultry in October 1996 and were considered by CVM in reaching its approval decision.

In late 1993 or early 1994, before FQs were approved for use in chickens and turkeys, CVM management understood and accepted that FQ use in chickens and in turkeys could act as a selection pressure resulting in the emergence and dissemination of FQ-resistant *CP* spp. in chickens and in turkeys. [JS 2] This is not surprising given the published pre-approval scientific literature. For example, in the late 1980s and early 1990s several *in vitro* studies were published which demonstrated the rapid selection of FQ-resistant *Campylobacters*. [van den Bogaard (B-1916) P.3 L.18–21, citing B-1123 and B-367] The scientific literature reported in 1991 that only a single genetic mutation would result in high-level FQ resistance in *CP*. [McDermott (G-1465)

P.5 L.8–10; G-253] Similarly, in 1993 the scientific literature reported that mutations in the *gyr*A gene were linked to FQ resistance in *CP* and that only a single *gyr*A mutation was necessary to confer FQ resistance in *CP*. [McDermott (G-1465) P.2 L.18–19, P.4. L.8–9; B-826]

CVM's pre-approval knowledge specifically included an awareness in late 1993 or 1994 of "foreign studies demonstrating that fluoroquinolone use in chickens or in turkeys can act as a selection pressure and result in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*." [Tollefson (G-1478) P.13 L.22–26] CVM also knew pre-approval that FQ use in poultry *in vivo* leads to the rapid emergence of FQ-resistant *CP* in poultry. That finding was reported in the scientific literature by Jacobs-Reitsma[4] in 1994. [van den Bogaard (B-1916) P.6 L.4–9; G-315] As part of its enrofloxacin New Animal Drug Application, Bayer submitted the 1994 Jacobs-Reitsma paper to CVM on or about June 21, 1996, four months before enrofloxacin's October 1996 approval. [van den Bogaard (B-1916) P.6 L.21–P.7 L.1] But even without Bayer's submission of the Jacobs-Reitsma article, prior to enrofloxacin's approval CVM was well aware of it and other literature demonstrating the selection for, emergence of, and dissemination of FQ-resistant *CP* arising from enrofloxacin use in poultry. In fact, in April 1996 CVM Director Sundlof sent a letter [G-1003] to the American Veterinary Medical Association's Dr. Joe Gloyd that discussed the Jacobs-Reitsma findings and other related literature in detail. The letter noted that Jacobs-Reitsma had demonstrated "that *Campylobacter*-colonized broilers exposed to quinolones all harbored FQ-resistant *Campylobacters*" and that such finding was "consistent with other reports from Europe and England of increasing quinolone[5] resistance in *Campylobacter* . . . isolates from animals during the early and mid-1990's." [G-1003 P.4] More importantly, Sundlof specifically cited articles by Endtz [G-190], Piddock [G-505], Reina [G-529, G-530], and Velazquez [G-671] describing the selection for, emergence of, and

[4] Although most of the scientific articles have multiple authors, articles are cited herein by the first-named author for the sake of brevity.

[5] In the case of *Campylobacter* because of cross-resistance, "quinolone resistance" is essentially equivalent to "fluoroquinolone resistance". [Weber (G-1482) P.8 L.5-13; Smith (G-1473) P.3 L.29-33]

dissemination of FQ-resistant *CP* arising from enrofloxacin use in poultry in other countries. One 1992 Reina article cited by Sundlof reports FQ resistance in human *Campylobacter jejuni* isolated in Spain increasing from 2–3% in 1988 to 32% in 1991. [G-529 P.1] Reina "agree[s] with Endtz, et al. that the introduction of enrofloxacin for the treatment and prophylaxis of animal infections is the principal factor responsible for the increase in resistance to the fluoroquinolones in human strains." [G-529 P.2]Sundlof's letter notes that "FQ resistance has been demonstrated in both *Campylobacter* and *Salmonella* species in animals treated with FQs." [G-1003 P.3] and acknowledges the "potential for widespread and rapid dissemination of resistance." [G-1003 P.4]

CVM's decision to approve FQs for use in chickens and turkeys was made after extensive deliberation and debate due to the controversy surrounding the use of FQs in food-producing animals. [Tollefson (G-1478) P.4 L.18–20] In light of the controversy, the FDA held a Joint Advisory Committee (JAC) meeting of the Veterinary Medicine and Anti-Infective Drugs Advisory Committees in May 1994 to address the specific issue of approval of FQs for use in food-producing animals. [Tollefson (G-1478) P.4 L.18–23] The JAC widely acknowledged that use of any antibiotics, including FQs, would necessarily result in pressure that would select for resistant organisms. [van den Bogaard (B-1916) P.6 L.15–19] Moreover, the JAC specifically discussed the potential selection for, emergence of, and dissemination of FQ-resistant *CP* arising from FQ use in poultry. For example, the JAC discussed the Endtz article [G-190], noting that it "evaluates human isolates in the various time periods and poultry isolates in the various time periods and identifies in both populations a progressive increase in the level of resistance of *CP*" [B-1819 P.95], as well as Endtz' conclusion that "the increasing use of enrofloxacin in poultry in the Netherlands and the almost exclusive transmission route of *CP* from chicken to man in the Netherlands suggest that the resistance observed is mainly due to the use of enrofloxacin in the poultry industry" [G-219 P.135]

CVM claims that its pre-approval knowledge differs from its current knowledge "in the degree to which the selection pressure occurs and the inadequacy of approved labeling conditions to prevent such fluoroquinolone-induced resistance." [CVM Interrog. Ans. 3]

No new studies suggest that the degree to which selection pressure occurs is any different than was demonstrated by Jacobs-Reitsma in 1994. More recent studies, such as that by McDermott [B-868], only duplicate Jacobs-Reitsma's findings. McDermott's results "show that the use of FQs in broiler chickens generates a rapid increase in the fluoroquinolone MICs of resident *C. jejuni*, ... which appears within the treatment time frame and persists long after treatment is stopped." [B-868 P.3] McDermott acknowledges that "[s]imilar results from enrofloxacin-treated birds were reported by Jacobs-Reitsma et al." and that McDermott's results "support the finding of Jacobs-Reitsma et al. that fluoroquinolones do not eliminate *Campylobacter* species from the intestinal tract of chickens, but rapidly select for fluoroquinolone-resistant isolates." [B-868 P.3] While CVM may point to minor methodological differences between Jacobs-Reitsma and McDermott (such as McDermott using both sarafloxacin[6] and enrofloxacin or McDermott continuing to test resistance for a longer period of time), CVM cannot dispute that the key implications of the studies are the same. As CVM itself concedes, "the implications of both studies [Jacobs-Reitsma and McDermott] are mutually supporting—that is that the use of FQs according to lable indications does not eliminate *Campylobacter* from the intestinal tract of chickens, but, rather, rapidly selects for fluoroquinolone-resistant isolates." [CVM critique of BPFOF 64]

There is no new evidence demonstrating any difference in the adequacy of approved labeling conditions to prevent FQ-induced resistance. CVM approved enrofloxacin use under strict labeling conditions, including use only for therapy, only by prescription, only under

[6] Sarafloxacin is a fluoroquinolone antibiotic that was marketed by Abbott Laboratories. SaraFlox WSP was approved in the U.S. on August 18, 1995, for the control of mortality in growing turkeys and broiler chickens associated with *Escherichia coli* organisms susceptible to sarafloxacin. SaraFlox Injection was approved in the U.S. on October 12, 1995, for the control of early mortality in day-old broiler chickens associated with *E. coli* organisms susceptible to sarafloxacin. [JS 47 & 48]

veterinary supervision and never as a growth promoter. Extra-label use was prohibited. [JS 15, 16, 17, and 46] The resistance increases reported by Endtz in the Netherlands [G-190], about which CVM was aware prior to approval of enrofloxacin, occurred even though the use conditions in the Netherlands included use only by prescription, only under veterinary supervision for specific life-threatening diseases, and never for growth promotion. [van den Bogaard (B-1916) P.12 L.18–P.13 L.5] CVM's claim that the inadequacy of approved labeling conditions to prevent resistance is "new evidence" is unavailing, because the labeling conditions in the U.S. are virtually the same conditions of use under which enrofloxacin was approved in the Netherlands. CVM could not have been surprised if it saw post-approval increases in FQ-resistant *CP* in human and poultry isolates in the U.S. of the same magnitude seen in the Netherlands. In light of this, CVM's evidence of such increases in the U.S. is not unexpected and certainly is not "new evidence." However, as demonstrated below, there has not been a rapid rise in *CP* resistance that can be attributed to use of enrofloxacin in chickens and turkeys.

There is no *new* evidence to support any finding that the issue of the selection for, emergence of, and dissemination of FQ-resistant *CP* arising from FQ use in poultry raises concerns that were not anticipated, understood, and accepted by CVM before enrofloxacin was approved in 1996.

2. CVM's Evidence on Selection Pressure, Dissemination, and Emergence Does Not Raise Serious Questions About Enrofloxacin's Safety

CVM contends that "selective pressure exerted by FQ use is the driving force for the development and spread of FQ resistance in large numbers of animals through water or feed, and facilitates the spread of resistant pathogens. Despite restrictions placed by FDA on the use of the approved poultry (chicken and turkey) FQ products, FQ resistance among *CP* organisms isolated from chickens, turkeys and humans developed and increased after the 1995 and 1996 approvals." [CVM Interrog. Ans. 1] CVM's narrow view of selection pressure ignores the fact that there are *other* sources of FQ resistance in *CP*, besides use of enrofloxacin in poultry, that influence the

level of resistance seen in both poultry and humans. This fact must be considered in determining whether CVM has a reasonable basis seriously to question enrofloxacin's safety. If enrofloxacin use in poultry is not responsible for the levels of FQ resistance observed in humans (levels about which CVM is concerned enough to propose withdrawing the NADA for enrofloxacin), how can there be a reasonable basis seriously to question the safety of enrofloxacin use in poultry?

Enrofloxacin is not the only selection pressure that acts upon *CP* to select for populations of FQ-resistant populations. First of all, it is important to realize that *CP* are ubiquitous in the environment, including in the water environment. Water gets contaminated with *CP* via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. [Patterson (B-1910) P.4 L.12–13; Newell (B-1908) P.8 L.1–3]*CP* spp., including FQ-resistant *CP*, have been widely documented in human, agricultural, and industrial wastewater and in the treated wastewater effluents discharged to the environment. [Patterson (B-1910) P.6 L.20–22] Also, *CP* colonize numerous non-poultry animals; nearly all wild and domesticated animals, including domesticated pets, harbor *CP* as a normal inhabitant of the gastrointestinal tract. [Wegener (G-1483) P.4 L.14–15; JS 32] Flies and other insects can be carriers of *CP*. [G-1612 P.6; G-1719 P.3; G-572] FQ use in chickens and turkeys is not the only cause of the development of FQ-resistant *CP* species in chickens and turkeys. [CVM Interrog.Ans. 4] FQ-resistant *Campylobacters* may be isolated from poultry as a direct result of either the FQ treatment of *CP*-infected poultry or the acquisition by poultry of already FQ-resistant organisms. [Newell (B-1908) P.13 L.13–16]

FQ-resistant *CP* are naturally present in the environment and are found in poultry even where flocks have not been treated with FQs. Quinolone and FQ-resistant *CP* have been found in poultry at places and times for which it is impossible for enrofloxacin use in poultry to be the cause. For example, in Sweden in 1981, at a time and place that FQs had *never* been used in poultry, published scientific literature shows 39% quinolone (nalidixic acid) resistance (61% susceptibility) in *CP* isolated from chicken. [Gonder (A-201) P.14 L.8–13; B-1851 P.3] Also in

Sweden, the scientific literature shows that in 1992–1993 there was 4.5% enrofloxacin resistance in *CP* from chicken flocks that had not been treated with any antimicrobials (including FQs). [G-62 P.2]

Similarly, for humans, quinolone-resistant *CP* has been found in people at places and times for which it is impossible for enrofloxacin use in poultry to be the cause. This could be because human use of FQs, including use for treatment of campylobacteriosis, can lead to the emergence of FQ-resistant *CP* in the treated individual [JS 8]; in other words, FQ-resistant *CP* isolated from humans can merely reflect use of FQs to treat a variety of infections in humans. Some of the scientific literature showing quinolone resistance in *CP* from humans in 1981 and 1983 even predates the use of FQs in human medicine. In Sweden in 1981, for example, the literature reports 11% quinolone resistance in *CP* from humans. [B-1851 P.3] Similarly, the literature reports 15% quinolone resistance in *CP* in Germany in 1983. [B-1936]

Importantly, this phenomenon of pre-approval resistance also occurred in the U.S. Quinolone and FQ-resistant *CP* were identified in humans in the U.S. before 1995, before FQs were approved and actively marketed for use in poultry. In 1988 Barrett found 5% quinolone resistance in *Campylobacter jejuni* isolated from humans.[7] [Barrett (G-1453) P.3 L.3–10; G-1609] Kiehlbach found 88% susceptibility to ciprofloxacin (12% FQ resistance) in *CP* isolated from humans from August 1992 to April 1995. [B-39] Smith found 1.3% FQ resistance in *CP* isolated from humans in 1992, and 6% resistance in isolates from 1995. [G-589 P.1] Williams found 3.3% quinolone resistance in *CP* isolated from humans in 1993. [B-67] Finally, Nachamkin found over 20 % FQ resistance in *CP* isolated from humans in the U.S. in 1995. [G-1517 P.11]

Selection pressure varies based on a variety of factors. These include the type of antimicrobial used, the number of individuals treated, the dosage regimen, the duration of

[7] CVM witness Barrett testified that resistance levels likely were underestimated in surveillance studies in this timeframe. [Barrett (G-1453) P.3 L.29-44]

treatment, and the overall extent of use in the population at risk. In the U.S., enrofloxacin is subject to strict usage requirements. [*See, e.g.,* JS 15, 16, 17] For chickens and turkeys in the U.S., the selection pressure is low and controlled, because FQs are used sparingly, in only a small percentage of total annual poultry output. Only about 1–2% of broiler chickens are treated in a given year and only about 4% of turkeys are treated in a given year. [Bayer Interrog. Ans. 2; Gonder (A-201) P.20 L.9; A-192 P.3]

In light of the fact that there are causes of FQ resistance in poultry and human *CP* isolates other than enrofloxacin use in poultry (factors not controlled for or considered by CVM), CVM does not have a reasonable basis seriously to raise questions about the safety of enrofloxacin use in poultry.

3. CVM Overstates the Impact of Enrofloxacin Use in the Broiler Industry on Selection Pressure, Emergence and Dissemination of FQ-Resistant *Campylobacter*

CVM presumes that there is a simple and predictable relationship between the use of enrofloxacin in chickens and the transfer of selected resistant organisms to retail chicken products. For exam1`ple, McDermott testifies that his laboratory studies showing rapid development of resistant *CP* organisms that persist until slaughter in treated chickens "are consistent with, and support, the findings of the retail meat studies" showing that "*Campylobacter*-contaminated retail chicken meat products carry a fluoroquinolone-resistant strain." [McDermott (G-1465) P.7 L.13–23] McDermott's studies, however, used high enrofloxacin dosages and long treatment durations not typically used by the broiler industry in treating broilers. McDermott's laboratory study administered 50 ppm of enrofloxacin for 5 consecutive days. [McDermott (G-1465) P.2. L.33–34] Typical dose and duration in the commercial broiler industry, however, is 25 ppm for 3 days. [*See, e.g.*, Glisson (B-1903) P.5 L.10–12][8]

[8] Although 25 ppm for 3 days is typical, some broiler companies administer a 50 ppm "loading dose" for 12-24 hours before reducing to 25 ppm for the rest of the treatment regimen. [Smith (B-1914) P.27 L.4-7] This is still far different than the 5 day, 50 ppm experimental regimen administered by McDermott. The McDermott and Luo

The significance of the difference between McDermott's *experimental* regimen and the broiler industry's *actual* regimen is demonstrated by Luo [A-190] Luo treated two groups each of *CP*-colonized broilers with 25 ppm and 50 ppm enrofloxacin for 5 days. [A-190 P.1] Monitoring resistance over time, Luo found that the resistant populations persisted in the groups treated with high-dose enrofloxacin, while FQ-sensitive *CP jejuni* recovered gradually in chicken treated with the 25 ppm. [A-190 P.2 Fig.2] This happened even though Luo's 25 ppm experimental regimen was 2 days longer than typical in the industry. Luo's paper shows that after administering a dose of 25 ppm for 5 days, susceptible *CP* begin to displace resistant *CP* about 8 days after treatment (50% susceptible colonization), and that 67% of isolates recovered from treated chickens 12 days after treatment are susceptible, not resistant. [A-190 P.2 Fig.2] Moreover, Luo's results call into question McDermott's testimony claiming that "when a mixture containing equal numbers of FQ-resistant and FQ-sensitive strains are introduced into a chicken, the fluoroquinolone-resistant strains consistently out-compete their susceptible counterparts, even when the susceptible strains outnumber the resistant the resistant ones." [McDermott (G-1465) P.6 L.23–26] This phenomenon appears to be operative only when the resistant and susceptible organisms are pre-grown in laboratory media and later introduced into the chickens, not when the resistant population emerges *in vivo*, as would occur in field treatment conditions.

Finally, McDermott used pooled feces samples in his experiment; his results are therefore misleading and may overstate resistance levels. In his study, 1 out of 5 resistant samples, pooled together, would be reported the same as 5 out of 5 resistant samples pooled together. [B-868 P.2]

The net result is that CVM overstates the impact of enrofloxacin use in the broiler industry on selection pressure, emergence and dissemination of FQ-resistant *CP*.

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papers relate to broiler chickens; evidence in the record indicates dosage for turkeys is also 25 ppm [Gonder (A-201) P.27 L.6], although it is also administered to turkeys at 50 ppm [Gonder (A-201) P.27 L.6; Wages (B-1917 P.18 L.12]

B. TRANSFER OF FQ-RESISTANT *CAMPYLOBACTER* FROM POULTRY AND CONTRIBUTION TO FQ-RESISTANT *CAMPYLOBACTER* INFECTIONS IN HUMANS

The Notice of Hearing sets forth the second issue in this hearing as "[w]hether fluoroquinolone-resistant *CP* spp. in poultry are transferred to humans and whether they contribute to fluoroquinolone-resistant *Campylobacter* infections in humans?" CVM contends that fluoroquinolone-resistant *CP* in poultry *are* transferred to humans and are a significant cause of FQ-resistant *CP* infections in humans. [CVM's Narrative Statement P.1,3]

Bayer does not dispute that FQ-resistant *CP* in poultry *can be* transferred to humans and *can* contribute to FQ-resistant *CP* infections in humans. That stops short of the relevant issues, however, because the evidence shows that CVM understood and accepted this as a possibility in the U.S. prior to approval of enrofloxacin for poultry. The relevant issues for this hearing are (i) whether evidence shows that transfer of resistant *CP* from poultry to people *is* happening and *is* contributing to FQ-resistant *CP* infections in humans; (ii) if so, whether the transfer and/or contribution to resistant infections in humans is at a level greater than CVM understood and accepted prior to approval such that there is *new* evidence; and (iii) whether CVM's evidence shows that transfer and contribution to resistant infections is occurring at a level that constitutes a reasonable basis to raise serious questions about enrofloxacin's safety.

The evidence shows that prior to approving enrofloxacin for poultry, CVM understood and accepted that FQ-resistant *CP* in poultry could be transferred to humans and could contribute to FQ-resistant *CP* infections in humans. [G-1003 P.3–5] In addition, contrary to CVM's assertions, the most recent, relevant, and robust data demonstrate that poultry is *less* of a cause of campylobacteriosis than previously believed at the time CVM concluded enrofloxacin use is safe. The recent data show that poultry is not a cause of *CP* infections or FQ-resistant *CP* infections in humans sufficient to raise serious questions about the safety of enrofloxacin.

1. CVM Has Presented No *New* Evidence on Transfer of FQ-Resistant *Campylobacter* from Poultry to Humans or Its Contribution to FQ-Resistant *Campylobacter* Infections in Humans

The risk of FQ-resistant *CP* infections in humans was known to, and considered by, CVM prior to the 1996 approval of enrofloxacin for use in chickens and turkeys. There is no evidence that the risk of FQ-resistant *CP* infections in humans in the U.S. poses a greater hazard to public health now than was anticipated by CVM when enrofloxacin was approved in 1996. In fact, taken as a whole, the data demonstrate that things have only gotten better since 1996—there is now less risk of acquiring a *CP* infection, and estimates of the incidence of FQ-resistant *CP* infections has declined since enrofloxacin's approval.

In late 1993 or early 1994, before FQs were approved for use in chickens and turkeys in the U.S., CVM management understood and accepted that articles by Endtz and others posited a temporal association between the use of FQs in chickens in Europe and an increase in FQ-resistant *CP* isolates from humans in Europe. [JS 4] At the same time, CVM management understood and accepted that FQ-resistant *CP* infections have the potential adversely to affect human health. [JS 5]

The JAC convened by CVM to consider the use of FQs in food animals discussed the Endtz paper at length, including the likelihood that "*Campylobacter*, as proposed by the authors, originated in an animal source and became part of the intestinal flora causing disease in humans." [B-1819 P.96] Some JAC participants expressed no doubt that resistant microbes that are zoonotic organisms "will and can transfer between human and animal populations" [G-219 P.144] and acknowledged Endtz's report of transfer of zoonotic *CP* from poultry to man in the Netherlands [B-1819 P.61] and that "[resistant] bacteria that were selected . . . could move from the poultry to the people." [B-1819 P.105]

CVM director Sundlof's pre-approval letter to AVMA's Gloyd specifically raises concerns about foodborne campylobacteriosis due to consumption of poultry and the risks of "superimposing" bacterial resistance on the already "significant public health problem" of

foodborne disease. [G-1003 P.3–4] More specifically, Sundlof and CVM knew prior to approving enrofloxacin that Endtz had demonstrated "parallel increases in FQ-resistant *Campylobacter* in human isolates from 0% to 11% and poultry isolates from 0% to 14%" [G-1003 P.4, citing Endtz G-190] and that by 1990 the resistance in both poultry and human *CP* strains in the Netherlands had increased to 25%. [G-219 P.135]

The resistance increases in the Netherlands occurred even though enrofloxacin was used in the Netherlands only by prescription, only under veterinary supervision for specific life-threatening diseases, and never for growth promotion. [van den Bogaard (B-1916) P.12 L.18–P.13 L.2] These are virtually the same conditions of use under which enrofloxacin was approved for poultry in the U.S. [van den Bogaard (B-1916) P.13 L.3–5; JS 15, 16, 17, and 46] Therefore, as part of CVM's analysis leading to the approval of enrofloxacin for poultry, CVM understood and accepted that there would be increases in FQ-resistant *CP* in human and poultry isolates of the same magnitude as that seen in the Netherlands.

In light of CVM's prior consideration of Endtz and other articles, FQ resistance in poultry and humans in the ranges shown in the U.S. by NARMS was predictable and expected. Evidence of such resistance in the U.S. is not "new evidence" and does not now support a finding that enrofloxacin not shown to be safe.

2. CVM's Evidence on Transfer of FQ-Resistant *Campylobacter* From Poultry and Contribution to Infections in Humans Does Not Raise Serious Questions About Enrofloxacin's Safety

CVM contends that FQ-resistant *CP* in poultry are transferred to humans and are a significant cause of FQ-resistant *CP* infections in humans, thus raising a reasonable basis from which serious questions about the safety of enrofloxacin may be inferred. [CVM Narrative Statement P.2, 3] CVM's case purportedly relies on: poultry consumption data; epidemiological studies finding a strong association between eating poultry and acquiring human *CP* infections; epidemiological studies finding a strong association between eating poultry and acquiring FQ-resistant human *CP* infections; studies linking the genetic makeup of *CP* isolates from poultry

and humans; the temporal relationship between the approval of FQs for use in poultry in the U.S. and the level of FQ-resistant human *CP* infections in the U.S.; the temporal relationship between the approval of FQs for use in poultry in other countries and the level of FQ-resistant human *CP* infections in those other countries; the "biological implausibility" that the level of FQ-resistant human *CP* infections now seen in the U.S. is entirely due to FQ use in humans or human-to-human spread of resistant *CP* cases; and the CVM RA showing that a portion of FQ-resistant *CP* infections in humans is attributable to consumption of poultry treated with FQs. [CVM Narrative Statement P.4] Additionally, CVM relies on data on FQ-resistant *CP* on retail poultry.

Bayer does not dispute that FQ-resistant *CP* from chickens and turkeys *can* be transferred to humans. The available evidence in each of the categories delineated above, however, does not support that any such transfer is occurring sufficiently to contribute to FQ-resistant *CP* infections at a level to raise a reasonable basis seriously to question enrofloxacin's safety. Careful examination of CVM's supporting evidence shows that it is fraught with (i) *a priori* assumptions about poultry as a source of campylobacteriosis that are not supported by the most recent, relevant, and robust epidemiological data; (ii) outdated studies that conflict with the most recent, relevant, and robust data; (iii) non-causal temporal associations between enrofloxacin use in poultry and FQ-resistant *CP* infection incidence that suffer from the common logical fallacy that too often arises when empirical evidence is used as "proof" of a hypothetical causal relationship—*post hoc, ergo propter hoc* (after the fact, therefore because of the fact) reasoning; and (iv) a selective view of the data which ignores contradictory data.

a. Poultry Consumption Data Do Not Raise a Serious Question

Poultry consumption data, which CVM said would support its claims linking FQ-resistant *CP* in poultry to FQ-resistant *CP* infections in humans, demonstrate the opposite—a disconnect between poultry consumption and campylobacteriosis. It is undisputed that in the U.S. chicken consumption per capita has steadily increased since enrofloxacin was introduced for poultry in 1996. [Cox (B-1901) P.36] Nevertheless, overall campylobacteriosis incidence (the annual

number of cases per year per 100,000) has steadily *decreased* since enrofloxacin was approved for poultry from 25.2 per 100,000 (original 5 FoodNet sites) in 1997 to 13.8 per 100,000 (all FoodNet sites) in 2001. [G-748 P.2 and G-1791 P.5] There was a further decrease to 13.37 per 100,000 from 2001 to 2002. [Tr. P.168 L.4–169 L.15; B-1924] More importantly, the estimated incidence of human FQ-resistant *CP* cases in the U.S. has also decreased markedly *after* enrofloxacin approval. Enrofloxacin was approved in the U.S. on October 4, 1996. [JS 39] From 1997 to 2001 (the post-approval time period for which data is available) the estimated incidence of FQ-resistant *CP* cases in humans has *decreased* from 3.28 per 100,000 in 1997 to 2.62 per 100,000 in 2001. [Tr. P.143 L.15–P.144 L.3][9]

Not only does declining U.S. campylobacteriosis rates in the face of data showing increasing poultry consumption demonstrate a disconnect between campylobacteriosis incidence and poultry consumption, but certain "real world" experiments outside the U.S.[10] show a similar disjunction. Campylobacteriosis rates do not change unusually with sudden decreases or increases in poultry consumption. In 1999, a dioxin scare precipitated a sharp decrease in chicken consumption in Belgium. Despite some claims to the contrary [G-672], the data show no unusual drop in Belgian campylobacteriosis rates in 1999 compared to the same months in other years. [Cox (B-1901) P.37–38] A large change in chicken consumption was followed by no unusual changes in campylobacteriosis rates, suggesting that one is not a detectable cause of the other. [*Id.*] This is consistent with other evidence. For example, Newell notes that in England during the foot and mouth disease outbreak, when public perception of a risk from that disease resulted in a reduction in the consumption of lamb, pork, and beef and increased

[9] Angulo reports slightly different overall campylobacteriosis incidence for 1997—24.7 infections per 100,000 population. [Angulo (G-1452) P.4 L.45-46] This does not materially change the decrease in the estimated incidence of fluoroquinolone-resistant campylobacteriosis since 1996. Using Angulo's testimony, the fluoroquinolone-resistant campylobacteriosis incidence declines from 3.21 per 100,000 in 1997 to 2.62 per 100,000 in 2001.

[10] Bayer does not concede the relevance of non-U.S. data. Nevertheless, CVM relies on the Belgian dioxin crisis to support its contention that chicken is a source of *Campylobacter*. [Endtz (G-1457) P.4 L.27-41; Tauxe (G-1475) P.17 L.42–P.18 L.3] Bayer's broader view of Belgian campylobacteriosis incidence data reveals that CVM's contention does not withstand scrutiny.

consumption of poultry meat, there was no detectable increase in campylobacteriosis. [Newell (B-1908) P.24 L.10–14]

Rather than support that poultry is a source of campylobacteriosis, overall poultry consumption data in the U.S. and anecdotal data from Belgium and the U.K. show the opposite.

b. Epidemiological Studies Do Not Raise A Serious Question

The epidemiological studies evaluating risk factors for campylobacteriosis that CVM relies upon to support its claim that poultry is a primary source of *CP* infections do not support its case. In particular, U.S. epidemiological data from the late 1990s do not show general poultry consumption to be a risk factor for acquiring either FQ-susceptible or resistant *CP* infections sufficient to raise serious questions about the safety of enrofloxacin. CVM ignores this recent, relevant, and robust data in this case and instead relies on outdated and irrelevant studies.

i. There Is Not a Strong Association Between Eating Poultry and Acquiring Human *Campylobacter* Infections

There exist many risk factors associated with acquiring a *CP* infection other than poultry consumption. For example, it is undisputed that foreign travel, contact with pets and other animals or their feces, drinking unpasturized milk, drinking raw water, consumption of non-poultry foods of animal origin, and other causative factors are positively associated with people being infected with *CP*, including potentially FQ-resistant *CP*. [Kassenborg (G-1460) P.9 L.10–11; Endtz (G-1457) P.4 L.17–21; Wegener (G-1483) P. 10 L.27–31, P.15 L. 13–18; Tauxe (G-1475) P.5 L.45–P. 6 L.1; Newell (B-1908) P.21 L.16–19]

Epidemiologists conduct case-control studies to determine which risk factors (or exposures) are associated with getting a disease outcome. In such studies, the frequency of exposures is compared between persons with the disease outcome being studied (a case) and persons without the disease (a control). [Feldman (B-1902) P.13 L.9–11, citing B-1902 Att. 1] For example, for determining the important risk factors for getting a *CP* infection, a typical epidemiological study would involve interviewing patients with *CP* infections about things they

had to eat or drink or other potential exposures they had in the week before they became ill, and then comparing the frequency of those exposures with those of another group of people, who lived in the same area and were otherwise similar, but did not have *CP* infections. [Tauxe (G-1475) P.7 L.25–31]

The case-control studies relied on by CVM to show that chicken is a significant source of campylobacteriosis are outdated, and therefore not new evidence, or are severely limited. For example, CVM relies exclusively in its risk assessment [G-953] on two case-control studies from the 1980s—the 1987 Deming study [G-162] and the 1986 Harris study [G-268]—to show that chicken is a significant source of campylobacteriosis as well as to quantify the fraction of all *CP* infections that are caused by chicken consumption for purposes of the CVM RA. [Cox (B-1901) P.38] CVM's case also relies on other U.S. and non-U.S. studies predating the approval of enrofloxacin. [Angulo (G-1452) P.9 L.16–P.11 L.44; G-10; G-182; G-334; G-1686; G-1718]

There have been vast enhancements in the U.S. in the awareness of the risks of foodborne bacterial illness and government and private action, particularly since 1996, resulting in major improvements in food safety. Improvements include specifically reductions in the risk of campylobacteriosis. Actions include adoption of the Hazard Analysis Critical Control Points, poultry safety labeling, FDA approval of poultry irradiation, improved consumer preparation and handling practices, and changes in poultry marketing and distribution. [(HACCP) Minnich (G-1467) P.10 L.8–P.11 L.10; (poultry safe handling) 21 C.F.R § 381.125, Tompkin (A-204) P.11 L.17–22; (irradiation) 21 C.F.R Part 179, Tompkin (A-204) P.27 L.22–P.28 L.1; (improved consumer preparation and handling and poultry marketing) Tompkin (A-204) P.9 L.29–P.11 L.16, Gonder (A-201) P.14 L.22–P.15 L.11]

The largest case-control study of sporadic *CP* infections, conducted by the CDC in U.S. FoodNet sites in 1998–1999 [Angulo (G-1452) P.9 L.46–47], likely reflects such improvements. Friedman analyzed the data from this study to determine the risk factors for becoming infected with *CP*. [Angulo (G-1452) P.10 L.7–12; Tr. P.397 L.13–P.398 L.3] The data from this study

show that the risk of acquiring a *CP* infection from eating chicken and turkey is less than was commonly believed before enrofloxacin was approved.[11]

The case-control study data from the CDC as analyzed by Friedman do not demonstrate a strong correlation between poultry factors that many historically believed to be associated with risk (including chicken and turkey consumption) and the risk of acquiring *CP* infections. Friedman's analysis shows that many presumed poultry risk factors, such as "eating poultry meat at home," "eating chicken prepared at home," "eating turkey prepared at home," "had raw chicken in home refrigerator," "touched raw chickens," and "chicken that was prepared at home required cutting while raw" were all statistically significantly associated with a *lower* risk of *CP* illness. [Tr. P.61 L.1–P.68 L.5 and G-1452 Att. 3 P.98–99] The matched odds ratio for "eating chicken prepared at home" was 0.5, which means people who did not eat chicken at home were twice as likely to acquire *CP* infections as people who did eat chicken at home. Therefore, CDC's 1998–1999 *CP* Case-Control study data demonstrate that chicken consumption at home has a significant association with *reduced risk* of becoming ill with campylobacteriosis. [Cox (B-1901) P.24] It stands to reason that if all poultry consumption were a major risk factor for acquiring campylobacteriosis, as CVM contends, poultry would be a risk factor no matter where it is consumed. The Friedman analysis of the CDC 1998–1999 *CP* case-control study shows that such is not the case, since poultry consumed at home is not a risk factor. [G-1488]

CVM may well point to Friedman's finding that chicken and turkey eaten in a commercial establishment is a risk factor for *CP* infections. But this ignores several points. First, the Friedman study does not support the 57% poultry attributable risk used in the CVM RA. Second, the population attributable fraction for non-poultry meats (21%) eaten in a commercial establishment is nearly the same as for chicken eaten in a commercial establishment

[11] For example, CVM uses Deming [G-162] and Harris [G-268] to show on average a 57% attributable risk for chicken, whereas Friedman [G-1488] shows that chicken is not a risk factor when consumed in the home and has only a 24% attributable fraction when consumed in a restaurant.

(24%), which begs the question of whether the risk is chicken or some non-chicken source of *CP* present in restaurants. [G-1488 P.23]

ii. CVM Does Not Consider Recent, Relevant, Robust Data That Do Not Fit with Its *A Priori* Assumptions

Historically, the public health community has long believed that poultry is a major source of *CP* in humans, and this *a priori* assumption has been accepted by CVM's witnesses. [Angulo (G-1452) P.9 L.28; Bartholomew (G-1454) P.3 L.9–10; G-1679 P.12–13; G-953 P.6; Tr. P.522 L.3–16; Tr. P.599 L.2–6]

The bias introduced from the *a priori* assumption can also be seen in CVM's use of Deming and Harris rather than Friedman. Data from Friedman's analysis of the 1998–1999 *Campylobacter* case control study were publicly presented as early as July 2000. [Tr. P.55 L.11–19; B-27] Compared to the Harris and Deming studies, the Friedman analysis was more recent [Tr. P.57 L.18–P.58 L.11], more robust [Tr. P.413 L.16–22; P.417 L.7–10], and at least equally relevant [Tr. P.411 L.22–P.412 L.4; P.415 L.20–P.416 L.2] to the issue of the risk factors for acquiring a *CP* infection in the U.S. in the late 1990s. Nevertheless, data from the 1998–1999 *Campylobacter* case control study were not used by CVM in determining what portion of *CP* cases come from chicken. CVM only relied on the Harris and Deming studies in its risk assessment [Bartholomew (G-1454) P.8 L.13–15; Feldman (B-1902) P.17 L.20–23; Tr. P.56 L.11–P.58 L.11] and did not consider the more recent findings of the Friedman study. [Cox (B-1901) P.50, 56; Tr. P.57 L.12–17] This is despite the fact that the CDC's 1998–1999 *CP* Case-Control study provided data that could have been used to estimate chicken-attributable fractions directly for FQ-resistant campylobacteriosis cases from data on chicken consumption and FQ-resistant *CP*. [Cox (B-1901) P.22, 57–64] This has a tremendous impact on the CVM RA model. The model's failure to account for the finding that chicken handled or prepared at home is associated with a statistically significant reduction in risk of campylobacteriosis results in the chicken-attributable fractions and other quantities in the risk assessment model incorrectly

describing the chicken-campylobacteriosis relation in the current general US population. [Cox (B-1901) P.15, P.57–64] Despite the availability of the Friedman data, and despite acknowledging limitations in the Harris and Deming studies,[12] the CVM RA relies solely on Harris and Deming to calculate a poultry attributable fraction of 57%. A more accurate estimate of a univariate population-attributable risk (PAR) for chicken consumption as a whole, based on the CDC 1998–1999 *CP* Case-Control data set, is negative (protective effect) while that for restaurant chicken is 3.1%. A multivariate PAR that removes the effects of confounders would be closer to zero. Thus, an attributable fraction of 0 to 3.1% is more realistic than CVM's 57% as used in its risk assessment. [Cox (B-1901) P.56, P.57–64]

The *a priori* assumption that poultry causes campylobacteriosis can introduce a bias into the study design of the questionnaire used to conduct case-control studies. Effler indicated that, since it is well recognized that poultry is a source of *Campylobacter jejuni*, most of the questions in his questionnaire were related to poultry. Effler suggested that associations with other foods may have been missed, since questions were not asked about those other foods. [G-185 P.4] Burkhart made the same observations relative to CDC's *CP* case-control study. [Burkhart (B-1900) P.25 L.25–41] Therefore, this *a priori* assumption is no longer valid. Newell, after reviewing a number of epidemiological studies, concludes that there is a serious question about the widely held assumption that poultry is the principal or major source of *CP* infections. [Newell (B-1908) P.42 L.6–11] Newell's conclusion is supported by the Friedman study and by other U.S. data.

[12] CVM points to limitations of the Harris and Deming studies in its own critique of the risk assessment model. CVM acknowledges that the demographic characteristics of the population and the frequency and proportion of chicken consumed have all changed since the Harris study. CVM also acknowledges that a major limitation of the Deming study is the lack of representativeness of the study population. These and other differences, such as evaluating alternative exposures and outcomes, limits the generalizations of findings that can be drawn to the U.S. population. [G-953 P.102]

iii. There Is Not A Strong Association Between Eating Poultry And Acquiring FQ-Resistant Human *Campylobacter* Infections

Even though *CP* and FQ-resistant *CP* have been shown to be present on retail poultry, there is not a connection between eating retail poultry and acquiring FQ-resistant *CP* infections. CVM has submitted only two U.S. epidemiology studies examining the link between poultry consumption and FQ-resistant *CP* infections in humans—one by Kirk Smith performed on Minnesota residents [G-589] and one by Heidi Kassenborg analyzing data from the 1998–1999 CDC *CP* Case-Control study [G-337] Importantly, neither study shows a statistically significant association between eating poultry and acquiring FQ-resistant human *CP* infections.

Smith's study set out "to analyze . . . risk factors for infection with resistant organisms, and poultry as a potential source of resistant organisms." [G-589 P.1]

Smith's case-comparison epidemiological analysis, however, does not show an association between poultry consumption and FQ-resistant *CP* infections in humans. Smith performed a univariate analysis to identify risk factors for infection with quinolone-resistant *C. jejuni* among Minnesota residents using 1996–1997 data. No chicken-related potential risk factors were identified by Smith's univariate analysis. [G-589 P.4, Table 1] Upon multivariate analysis (to determine if identified risk factors are independently statistically significant [Kassenborg (G-1460) P.8 L.9–13]), the only variables independently associated with *C. jejuni* infections were foreign travel, foreign travel to specific regions, and the use of a quinolone beginning one or more days before the collection of stool specimen. [G-589 P.4]

Despite CVM's claims, Smith's case-comparison epidemiology (both interim and final analysis) did *not* show poultry as a source of FQ-resistant *CP* infections. [Tr. P.522 L.3–16; P.534 L.13–20] Because of this, Smith relies on genetic typing to try to establish the link. But this is a misuse of genetic typing. Genetic typing (DNA fingerprinting) should not be interpreted independently of an epidemiological analysis. The goal of genetic typing is to provide laboratory confirmation of strain similarities in isolates that have *already been causally linked*

through epidemiology. Genetic typing does not provide proof of causation of disease. [Tr. P.518 L.20–P.521 L.4] A further analysis of Smith's use of genetic typing is presented in section I.B.2.c, *infra*.

The Kassenborg study also does not support CVM's contention that enrofloxacin use in poultry leads to FQ-resistant *CP* infections in humans. Kassenborg performed a comparison of ciprofloxacin-resistant *CP* cases and well community controls to determine the risk factors for becoming infected with ciprofloxacin-resistant *CP*. [G-337; Kassenborg (G-1460)] Kassenborg found that domestically acquired FQ-resistant *CP* infections were associated with the following risk factors: eating chicken or turkey cooked at a commercial establishment during the 7 days before illness onset; eating in a non–fast food restaurant during the 7 days before illness onset; and using an antacid during the 4 weeks before illness onset. [G-337 P.15; Kassenborg (G-1460) P.14, Table 1] Kassenborg also found that foreign travel was a risk factor for FQ-resistant *CP* infection [Kassenborg (G-1460) P.7 L.9–11], but her study did not evaluate whether foreign travel–associated cases may also be a consequence of FQ use in food-producing animals. [Kassenborg (G-1460) P.10 L.3–5]

Kassenborg found that eating *any* meat at home, presumably including chicken and turkey, was not a statistically significant risk factor for acquiring a FQ-resistant *CP* infection. [G-337 P.15; Kassenborg (G-1460) P.14, Table 1] For eating meat at home, the matched odds ratio was 0.1 and the p value was 0.03. [G-337 P.15; Kassenborg (G-1460) P.14, Table 1] Note that the matched odds ratio of less than 1.0 means the exposure is not a risk factor for the outcome and a p-value of less than 0.05 means the finding is statistically significant. [Tr. P.58 L.20–P.60 L.18] Kassenborg did not find that eating *all* poultry under every condition is a risk factor for infection with FQ-resistant *CP*. Kassenborg performed a multivariate analysis (one that determines which identified risk factors are independently statistically significant [Kassenborg (G-1460) P.8 L.9–13]). Kassenborg found that eating chicken or turkey *at a commercial*

establishment was the only risk factor that remained independently associated with FQ-resistant campylobacteriosis. [Tr. P.601 L.20–P.602 L.5]

Even that finding is suspect, however, because of her conclusion-driven analysis and her selective choice of models. Kassenborg acknowledged that her findings depended on the model she used and that using a different model could produce a different result. [Tr. P.604 L.4–9] In fact, while Kassenborg did not try other models [Tr. P.604 L.10–12], she did perform a different type of step-wise conditional logistic regression analysis (backwards versus forwards) to determine if any of the risk factors being studied were statistically significantly associated with FQ-resistant campylobacteriosis, and she found that none of the risk factors (including any related to poultry) were significantly associated with FQ-resistant campylobacteriosis. [Tr. P.602 L.21–P.603 L.14] The results of that analysis were neither published nor mentioned in Kassenborg's paper. [Tr. P.603 L.15–21] Kassenborg revealed her conclusion-driven methods on cross-examination when asked about whether the PAF she found showed that it was the chicken or poultry in the restaurant as a cause as opposed to some other factor. "Chicken has *CP* on it. People eat chicken. There are FQ-resistant bacteria on chickens. People—there's a large body of evidence that chicken is a risk factor." [Tr. P.598 L.9–P.599 L.6]

It stands to reason that if all poultry consumption were a major risk factor for acquiring a FQ-resistant *CP* infection, as CVM contends, poultry would be a risk factor no matter where it is consumed. The Kassenborg analysis of the CDC 1998–1999 *CP* case-control study shows that such is not the case. Kassenborg's univariate analysis confirms that eating chicken or turkey meat at home is not a statistically significant risk factor for acquiring a FQ-resistant *CP* infection. [G-337 P.15; Kassenborg (G-1460) P.14] Kassenborg did not examine chicken or turkey at home as a risk factor in her multivariate analysis, as she only looked at statistically significant univariate factors. [Tr. P.605 L.18–P.606 l.6, P.607 L.17–22]

Accordingly, the Smith and Kassenborg studies relied upon by CVM must be considered scientifically unreliable for purposes of proving CVM's case, because they do not support the proposition in support of which CVM has offered them. *See supra* Evidentiary Standards, ¶ A.

c. Genetic Typing Studies of *Campylobacter* Isolates from Poultry and Humans Do Not Raise a Serious Question

Among the evidence CVM relies on to support its position that poultry is a significant source of *CP* and of FQ-resistant *CP* infections in people is "studies linking the genetic make-up of *Campylobacter* isolates from poultry and people." [CVM Narrative Statement at 4] However, genetic typing studies alone cannot at this time provide a reasonable basis seriously to question whether poultry is a source of FQ-resistant *CP* infections in humans.

Various molecular or genetic typing techniques are used to determine whether *CP* isolates are clonally related to one another by comparing variations at the DNA level of the isolates, either at a single site or in the whole genome. [Nachamkin (G-1470) P.7 L.21–32; Newell (B-1908) P.28 L.6–13; Tr. P.517, L.3–11; Barrett (G-1453) P.4 L.16–23] Such genetic typing techniques have limitations, particularly when used to link possible exposures to illness. As CVM's witness Besser points out, genetic typing or DNA fingerprinting "works by facilitating recognition of 'clusters' of disease, not by proving the cause of illness." [Besser (G-1455) P.7 L.1–3] Genetic typing "cannot be interpreted independently of an epidemiologic analysis." [Besser (G-1455) P.6 L.27–28] "It is [the epidemiological] analyses, not the DNA fingerprinting, that provide the 'proof'" of a relationship between ill individuals in a population and specific exposures. [Besser (G-1455) P.6 L.46–P.7 L.1] Other CVM witnesses similarly support these various points. [Barrett (G-1453) P.4 L.30–34, 37–40, P.7 L.25–28; Tr. P.518 L.3–P.521, L.4; Tr. P.716 L.11–22; Tenover (G-1476) P.4 L.32–36 (for PFGE)]

CVM's and Bayer's witnesses recognize that genetic typing techniques have been successfully used in outbreak investigations generally, including outbreaks of *CP*. [Nachamkin (G-1470) P.7 L.37–40, P.8 L.1–8; Newell (B-1908) P.28 L.13–18; Tenover (G-1476) P.10 L.4–6

(for PFGE)] However, the use of such techniques for comparison for outbreak investigations "does not mean such approaches are acceptable for comparisons of disparate strain subpopulations from humans and animals/birds." [Newell (B-1908) P.30 L.16–19] Because of the weakly clonal nature of *CP* and its genetic instability, Newell concludes that "most routinely-used typing techniques should not be applied to the comparison of isolate subpopulations, i.e., from veterinary, environmental and human disease." [Newell (B-1908) P.31 L.23–P.32 L.1] As all strain-typing studies have utilized strains from non-representative and potentially biased populations, the usefulness of such studies is further undermined. [*Id.* P.33 L.10–16] Newell concludes further that from "the studies to date, with the typing techniques developed and strain collections used" one cannot determine the source of the organism, i.e., whether a human *CP* isolate was from a food or environmental source, or if the source was animal whether it was from poultry meat, pork, beef, or other foods. [*Id.* P.34 L.14–18] CVM's witness Tenover agrees that at least one technique (PFGE) should not be used for "studies of large populations of organisms [e.g., *CP*] collected over extended periods of a 1 year or longer." [Tenover (G-1476) P.8 L.15–19]

i. Genetic Typing Studies Do Not Support That Poultry Is the Significant Source of Human *Campylobacter* Infections Represented by CVM

Other than Smith [G-589], Dickins [G-1785] is the only genetic typing study in evidence that compares retail poultry *CP* isolates with those of human campylobacteriosis isolates that is based solely on U.S. data and conducted and reported since approval of Baytril. This 2001 Arkansas study reports a clonal overlap of only 4 chicken isolates out of 54 human isolates (7.4%). [G-1785 P.5; *see also*, Newell (B-1908) P.35 L.7–12]

Several studies from other countries report genetic relatedness between *CP* isolates from humans and poultry supporting that poultry is a possible source of campylobacteriosis. [B-250; B-553; G-265, s*ee also* Nachamkin (G-1470) P.8 L.38–42] However, at least one of these studies was pre-approval of enrofloxacin and does not constitute new evidence. [Nachamkin (G-1470)

P.8 L.38–42] If anything, the more recent studies support that there are *multiple* possible sources of human *CP* infections and that chicken is now *less* of a source of campylobacteriosis than previously believed. For example, in his 1998 article Clow states that his study "provide[s] epidemiological evidence for the *first time* that not all poultry strains are potentially pathogenic to man." [B-250 P.5, emphasis supplied] Newell concludes, after a review of several studies,

> [a]lthough the results of epidemiological and molecular studies have been used to implicate poultry as the major source of human disease, more realistically, these results indicate that poultry is one of several sources. It remains impossible to determine the contribution of poultry as a source of human campylobacteriosis because representative populations from structured surveys have not yet been undertaken. However, it seems likely that the role of poultry has been overestimated, on the basis of these studies, as contributing disproportionally to human campylobacteriosis. The importance of other potential sources, such as sheep, cattle and pets, and environmental contamination is now increasingly recognized at least in Europe (Tam *et al.*, 2002).

[Newell (B-1908) P.36 L.16–24]

ii. Genetic Typing Studies Do Not Support That Poultry Is the Source of Human FQ-Resistant *Campylobacter* Infections in the U.S.

Smith [G-589], a Minnesota study published in 1999, is the only study in evidence relying on U.S.-generated molecular typing, conducted and published since approval of Baytril, comparing FQ-resistant retail poultry and human *CP* isolates. Smith reported that molecular subtyping (using the RFLP-PCR technique of the *fla* gene) showed "an association between molecular subtypes of C. *jejuni* strains that were acquired domestically in humans and those found in chicken products." [G-589 P.6.] However, Smith's univariate analysis of the epidemiological data (questionnaire replies) did not identify chicken as a potential risk factor for FQ-resistant campylobacteriosis. [G-589 P.4, Table 1] Smith's univariate analysis found the overwhelming potential risk factor for FQ-resistant campylobacteriosis was foreign travel (75%) along with potential risk factors for swimming, contact with pets, drinking untreated water, and prior use of a quinolone before stool collection, in ranges from 41 to 20 percent. [*Id.*] Foreign

travel generally and to specific regions and prior use were the only variables independently associated with C. *jejuni* infections in Smith's multivariate analysis. [*Id.*]

In light of the failure to identify chicken as a risk factor in the epidemiology part of the study, Smith's use of RFLP typing and his conclusion must be closely scrutinized. Smith's conclusion regarding poultry as a source of FQ-resistant *CP* does not withstand such scrutiny. CVM witness Nachamkin, who developed the PCR-RFLP method for typing the *fla* gene in *CP* [Besser (G-1455) P.9 L.23–27], states with respect to that method that "strains with similar RFLP types may or may not be similar, and often need to undergo additional 'subtyping' testing." [Nachamkin (G-1470) P.8 L.27–29] It is well accepted that unrelated *CP* may have the same RFLP types [G-444 P.51–52, 382–383, G-483] and that one must be cautious interpreting RFLP typing due to frequent genetic arrangements in the fla-A and B region. [G-444 P.51–52, 382–383] Nachamkin is also in agreement with other CVM witnesses that genetic typing methods "are best used in combination, or interpreted in light of the information taken from epidemiologic investigations." [Nachamkin (G-1470) P.8 L.17–18] There is no evidence in the record that Smith conducted any additional subtyping to support his conclusion, a conclusion that was not in accordance with the epidemiology findings. This absence of conformance between the epidemiology and genetic typing is particularly problematic for Smith in the light of the genetic typing limitations discussed above, particularly those concerning temporal and geographic distances. For example, while Smith collected human isolates statewide over a two-year period, the collection of the retail chicken isolates was limited to the Minneapolis/St. Paul area during a two-month period commencing 18 months or more after the study was begun. [G-589 P.2; Tr. P.525 L.15–19] Newell concludes that Smith's *fla* typing analysis cannot support his conclusion based on the temporal disassociation, comparison of a non-representative chicken population, level of discrimination of the fla-typing technique, the occurrence of genetic instability, and sample size. [Newell (B-1908) P.41 L.16–20]

There are additional reasons to question the reliability of the conclusions drawn from Smith's use of genetic RFLP-typing. First, although the Minnesota Department to Health provided the questionnaire, replies for the study, and other raw data to Bayer pursuant to a request under the Minnesota Data Practices Act, duplicates of the isolates used by Smith were not. Smith testified that the isolates could have been provided but they were not. [Tr. P.556 L.1, P.501 L.14–17] The duplicate isolates were specifically requested in order to permit Bayer's experts the opportunity to type the isolates by RFLP and various newer molecular typing techniques. Duplicate isolates would have afforded Bayer's experts the opportunity to use multiple genetic typing techniques that could have confirmed or challenged Smith's conclusions and his reliance on RFLP-typing. Second, Smith compared the chicken isolate types with the human isolates. He did not, however, compare the chicken isolates or human isolates with any *other* potential known sources of campylobacteriosis, including the significant risk factors he identified in the epidemiological part of his study. [Tr. P.533 L.18–P.534 L.3] Therefore, Smith cannot eliminate the possibility of a common third source for both chickens and people. [Tr. P.533 L.8–17] There is substantial evidence that there may be sources of *CP* common to both chicken and man. [Cox (B-1901) P.20–21, 45]

Even if Smith's genetic typing conclusions are valid, Newell can only conclude from Smith that the overlap is greater than 13%. [Newell (B-1908) P.35 L.13–15] This overlap is far below what CVM, based on various pre-approval epidemiology studies, believed to be the contribution of chicken to campylobacteriosis. [G-162; G-268] Smith himself recognizes that the genetic typing used in his study does not establish causation but is "one piece of evidence that has to be considered with everything else." [Tr. P.538 L.10–11] Smith also acknowledges that he does not know whether Minnesota's population is representative of the U.S. [Tr. P.551 L.5–13] In light of the many deficiencies noted above, Smith's genetic typing analysis is unreliable and does not provide a reasonable basis to raise a serious question by supporting a

conclusion that use of enrofloxacin in poultry is a cause of FQ-resistant campylobacteriosis in Minnesota residents.

d. The Temporal Evidence Does Not Raise a Serious Question

CVM claims that temporal evidence from Europe and the U.S. supports its contention that FQ use in poultry leads to FQ-resistant infections in humans. CVM's citation to temporal examples is selective at best. There are numerous examples of countries that do not fit CVM's temporal model. Similarly, in the U.S. there is no clear temporal trend of increasing FQ-resistant infections in humans after enrofloxacin approval.

i. U.S. Data Do Not Show a Temporal Relationship Between the Approval of FQs for Use in Poultry in the U.S. and an Increase in FQ-Resistant Human *Campylobacter* Infections in the U.S. and Disprove any Causal Relationship

CVM's position on U.S. FQ-resistant *CP* trends in humans is that there was little to no pre-approval resistance in humans and that resistance emerged and increased steadily after enrofloxacin approval. This position, however, is contradicted by available pre-approval data and unsupportable by the post-approval monitoring from Poultry NARMS and Human NARMS.

(a) Pre-Approval Resistance Disproves Temporal Relationship in the U.S.

In the U.S., any purported temporal, much less causal, association between enrofloxacin approval and FQ-resistant *CP* infections in humans is belied by data demonstrating appreciable quinolone and FQ resistance in human *CP* isolates prior to 1996.

Although there is no evidence in the record of any systematic sampling for FQ-resistant *CP* to establish a U.S. pre-approval baseline of resistance, it is clear that the baseline was not zero. Barrett, Kiehlbach, Williams, Smith, and Nachamkin all reported quinolone or FQ resistance in human *CP* isolates sampled *before* FQs were approved or actively marketed for use in poultry in the U.S. Specifically, in 1988 Barrett found 5% quinolone resistance in *Campylobacter jejuni* isolated from humans. [Barrett (G-1453) P.3 L.3–10; G-1609] In *CP*

isolated from humans from August 1992 to April 1995 Kiehlbach [B-39] found 88% susceptibility to ciprofloxacin (12% FQ resistance). Smith [G-589 P.1] found 1.3% FQ resistance in *CP* isolated from humans in 1992, and 6% resistance in *CP* isolated from humans in 1995. Williams [B-67] found 3.3% quinolone resistance in *CP* isolated from humans in 1993. Finally, Nachamkin [G-1517 P.11] found over 20% FQ resistance in *CP* isolated from humans in 1995. All of these findings were from a period before enrofloxacin was approved and before sarafloxacin was actively marketed for use. What this shows is that even before CVM approved FQs for use in poultry, there was already a significant level and increasing trend of FQ-resistance in human *CP* isolates.

While it is true that some or all of this reported pre-approval resistance may be attributable to infections acquired through foreign travel or from the use of FQs in human medicine, these possibilities do not diminish the significance of this evidence to this case. The fact is that resistance levels as high as 20% existed in the U.S. prior to approval regardless of the cause. Such results are directly comparable to the post-approval resistance rates reported by NARMS, because the Human NARMS results include resistant infections acquired through foreign travel and from the use of FQs in human medicine. NARMS only captures limited demographic data. [Tr. P.113 L.12–18] What limited data are collected do not include information about whether the person took a FQ antibiotic prior to submitting his sample [Tr. P.113 L.19–P.114 L.10], or whether the person undertook foreign travel prior to his infection [Tr. P.114 L.11–P.115 L.22], or the source of the infection. [Tr. P.116 L.3–6] The higher pre-approval resistance levels (12% to 20%) are virtually no different than the post-approval rates reported by NARMS (ranging from 13% in 1997 and 19% in 2001). [Angulo (G-1452) P.8 L.9–11]

(b) Post-Approval Monitoring in Poultry and Humans (NARMS) Does Not Show a Temporal Increase in the U.S.

Notwithstanding the above discussion of NARMS data, neither the Poultry NARMS data nor the Human NARMS data are of any value in demonstrating temporal trends in the U.S.

Despite sarafloxacin's late 1995 approval and enrofloxacin's poultry approval in 1996, susceptibility testing of *CP* isolates from poultry was not added to the animal arm of NARMS until 1998. [Tollefson (G-1478) P.9 L.4–5] That alone makes questionable any use of Poultry NARMS data for temporal trend purposes. On top of that, there is no established baseline for pre-approval resistance levels of *CP* in the U.S. Although CVM presumes that the levels are near zero, or at least low, there is no evidence to support this. Non-U.S. evidence tends to support that there is some measurable level of natural background resistance in poultry. For example, as previously noted, Svedhem [B-1851 P.3] found 39% quinolone (nalidixic acid) resistance in *CP* isolated from poultry in Sweden in 1981, at a time and place where FQs had never been used in poultry. Similarly, Berndtson [G-62] found 4.5% enrofloxacin resistance in *CP* from chicken flocks that had not been treated with any antimicrobials (including FQs) in Sweden in 1992–1993.

Additionally, because 2001 Poultry NARMS data have not been released in a final report [Tr. P.105 L.19–P.106 L.10], there are essentially only 3 years of Poultry NARMS data—1998, 1999, and 2000—on which to base any trend. For those years, assuming the reported data to be valid, the reported resistance results of 9.4%, 9.3%, and 10.4% [Tollefson (G-1478) P.12 L.6–7] do not constitute an upward trend.

More importantly, however, there have been so many changes in the Poultry NARMS program over the years that any year-to-year comparisons are meaningless. From the initiation of *CP* testing in 1998 through 2001, the sampling sources for *CP* isolates used in the animal NARMS program were very different. [Carnevale (A-199) P.6 L.17–18] The source of isolates provided by FSIS has not been consistent from year to year. [Tollefson (G-1478) P.9 L.15–P.11

L.8; DeGroot (A-200) P.6 L.13–15, L.22–23] Because no defined, statistically sound, designed sampling source has been used for NARMS poultry, the FQ susceptibility patterns determined by the analysis of the NARMS *CP* isolates neither represent the prevalence of FQ-resistant *CP* present on chicken carcasses at the time of slaughter in the U.S. nor such prevalence in live chickens. [Carnevale (A-199) P.6 L.21–26] The culture techniques utilized to isolate *CP* in the animal NARMS program also have not been consistent. [Carnevale (A-199) P.7 L.2–3] For example, the methodology used to culture and isolate *CP* from HACCP samples by FSIS in 1998 and forwarded to ARS for susceptibility testing was significantly different than the methodology used by ARS in 2001 and 2002 to isolate *CP* from the rinsates received from FSIS after FSIS's use of the rinsates to isolate *Salmonella*. [Carnevale (A-199) P.7 L.3–8] The *CP* susceptibility patterns determined from analysis of the HACCP samples, initially collected by FSIS for *Salmonella* isolation and used for *CP* as an add-on, do not represent a national prevalence, and cannot be used for year-to-year comparison for trends. [Carnevale (A-199) P.8 L.16–19]

Reliance on Human NARMS data to establish year-to-year trends is also unavailing, because Human NARMS data are not reliable.

In order reliably to establish national resistance trends, the data generated by Human NARMS must be generalizable to the U.S. and the *CP* sampling scheme must be representative of the national burden of FQ-resistant *CP* infections. *See supra* Evidentiary Standards, ¶ C. The Human NARMS program meets neither of these criteria.

CVM has not provided a reasonable basis to establish the generalizability of Human NARMS data to the U.S. population. CVM witness Angulo of CDC testified that certain "data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness" [Angulo (G-1452) P.4 L.24–26], but it is clear that the study cited, G-769, relates only to a comparison of the FoodNet population as it existed in 1996 to the U.S. population of 1996 and not for any other year. [Tr. P.307 L.11–P.308 L.21]

Although Angulo claims the existence of other comparative analyses for other years [Tr. P.311 L.13–17; P.313 L.15–21; P.317 L.19–P.318 L.2], such analyses were neither published [Tr. P.317 L.12–17; P.319 L.1–7] nor included in CDC's annual FoodNet reports [Tr. P.318 L.3–11; P.319 L.10–P.320 L.6; P.321 L.4–P.326 L.13] nor adequately explained in his testimony. While there was testimony about the existence of these supposed annual analyses, there is no evidence that CDC actually compared the 1997, 1998, 1999, 2000, or 2001 FoodNet populations to the U.S. populations for those years to verify the generalizability of the FoodNet *CP* data to the U.S. population.

More importantly, the Human NARMS sampling scheme for *CP* does not produce a sample that is representative of the burden of FQ-resistant *CP* in the U.S. population. One only needs to contrast the year 2000 Minnesota statewide *CP* sampling program with the year 2000 Minnesota NARMS submissions to observe the lack of representativeness of the effect on Human NARMS resistance reporting.

CP infections in Minnesota must be reported to the Minnesota Department of Health (MDH) and clinical laboratories are required to forward *CP* isolates to MDH. [Tr. P.391 L.6–22]

In the year 2000, MDH received 1028 *CP* isolates and tested all for ciprofloxacin susceptibility. [B-1934, n.1] MDH reported 11% ciprofloxacin resistance (89% susceptibility) among the 1028 *CP* isolates tested. [B-1934]

Simultaneously, Minnesota participated in Human NARMS [Tr. P.383 L.18–20] and, in compliance with the NARMS sampling protocol, sent 4 or 5 isolates per month (one per week—every Monday of the month). [Tr. P.385 L.12–18] No matter how many monthly cases of *CP* were reported—whether 20 in January or 155 in August—MDH would forward only 4 or 5 isolates to CDC for susceptibility testing. [Tr. P.385 L.19–P.388 L.8] Consistent with this, 49 *CP* isolates were tested and included in the NARMS 2000 final report [Tr. P.389 L.16–P.390

L.7; B-1009 P.54 Table 21b] Of those 49 submitted samples, 12 (24.5%) were resistant to ciprofloxacin. [*Id.*]

While CDC (and CVM) claim that the Human NARMS samples are representative of the larger pool from which they are taken, clearly they are not. In Minnesota in 2000, the 49 isolates were clearly not representative of the pool of 1028 isolates from which they were selected.

This problem stems from the fact that the NARMS sampling program for *CP* only requires one sample per week regardless of the number of incoming samples. NARMS sampling for *E. coli* requires every 5th isolate to be submitted for susceptibility testing and sampling for *Salmonella* requires every 10th isolate to be submitted for susceptibility testing. [Tr. P.355 L.16–P.356 L.10]Angulo acknowledged in November 2002, at the 2002 Annual NARMS public scientific meeting, that "for all pathogens *except Campylobacter*, we [CDC NARMS] have a representative sample of the culture-confirmed cases at the state level." [A-199, Att. 3, P.88 (emphasis supplied)]

Non-representative sampling for *CP* skews the *CP* FQ resistance results towards higher resistance. This makes sense, because FQ resistance in *CP* peaks in the winter and declines in the summer, but overall incidence of *CP* infections peaks in the summer and declines in the winter. [Tr. P.124 L.6–P.128 L.1] Thus, looking at Minnesota in 2000, for example, the 4 or 5 out of 20 January isolates (during high resistance/low incidence) are given the same weight as the 4 or 5 out of 155 August isolates (when resistance is low but incidence is high). [Tr. P.128 L.2–P.129 L.15]

Because the Human NARMS samples are not statistically relevant to the U.S. population as a whole, they cannot be considered scientifically reliable and should not be accorded any significant weight. *Cf. supra* Evidentiary Standards, ¶ C.

ii. Taken as a Whole, Data from Other Countries Do Not Support a Temporal Relationship or to Raise a Serious Question

CVM attempts to bolster its claim that enrofloxacin use in poultry causes resistant *CP* infections in humans by citing to the "temporal association" between enrofloxacin approvals in certain countries and increasing FQ resistance in *CP* isolated from both poultry and humans in those countries.

In general, CVM's temporal association argument is that before enrofloxacin approval in a given country FQ-resistant *CP* is low in both poultry and humans, but after enrofloxacin is approved for poultry in the country FQ-resistant *CP* increases in poultry and then increases in humans. [Tr. P.649 L.21–P.651 L.14]

CVM concedes that such a temporal relationship is not the same as a causal relationship. [Tr. P.649 L.10–13] Moreover, the numerous examples of countries where this chronology does not play out as CVM claims disproves CVM's "temporal association" argument.

In some instances, resistance existed in poultry or people before enrofloxacin was approved. In other words, the temporal associations between enrofloxacin use in poultry and increases in FQ-resistant *CP* infections in other countries go both ways.

(a) Countries with Elevated Poultry or Human Resistance Before FQs Were Ever Used in Poultry Disprove CVM's "Temporal Relationship"

Perhaps the best examples that disprove CVM's so-called "temporal relationship" are those that show measurable levels of quinolone or FQ resistance in poultry or people *before* any FQs were used in poultry or people. For example, Rautelin [G-524 P.3–4] reported "some natural resistance" in *CP* isolated from humans in 1978–1980 "even before the introduction of fluoroquinolones onto the Finnish market." Rautelin defined resistance as an MIC of 8 μg/ml [G-524 P.4] and reported 4% resistance, but if the more typically used MIC of 4 μg/ml were used to define resistance, this "natural resistance" found in human *Campylobacters* would have been

5.8%, even though FQs were not used in human or poultry medicine in Finland in 1978–1980. [Tr. P.681 L.6–P.683 L.9] As previously cited, Svedhem [B-1851 P.3] found 39% quinolone resistance in poultry *CP* and 11% quinolone resistance in human *CP* in Sweden in 1981. FQs were not used in chickens in Sweden in 1981 and were not even approved for poultry until 1989. [Gonder (A-201) P.14 L.11–12; JS 64]

CVM's analysis of "temporal associations" ignores these very important data that are inconsistent with CVM's theory. Accordingly, the analysis should not be considered credible.

(b) Instances with High Poultry Resistance but No Enrofloxacin Use Disprove CVM's "Temporal Relationship"

Other good examples that disprove CVM's "temporal relationship" are instances in which enrofloxacin was not used to treat poultry but the poultry nonetheless had FQ-resistant *CP*.

Berndtson [G-62 P.2] found 4.5% FQ resistance in *CP* isolates from chickens collected in 1992–1993, yet none of those chicken flocks had been treated.

This shows that some driving force other than selection pressure from enrofloxacin use in poultry can cause chickens to be colonized with FQ-resistant *CP*.

(c) Countries with High or Increasing Human Resistance but No Enrofloxacin Use Disprove CVM's "Temporal Relationship"

Similarly, countries with increasing human *CP* resistance despite no use or approval of enrofloxacin in that country also disprove the "temporal relationship" between enrofloxacin use in poultry and increasing resistance in *CP* from humans. Such examples prove that some driving force other than enrofloxacin use in poultry can cause human resistance to increase.

In Finland, where FQs were *never* commercially marketed for poultry use, resistance in humans has increased dramatically. The percentage of ciprofloxacin-resistant *CP* strains nearly doubled from 9% in 1990 to 17% in 1993 without enrofloxacin use in poultry in Finland. [B-881 P.2] By 1997, resistance had doubled again, to over 35% [B-44 P.9], *still without enrofloxacin*

use in poultry in Finland. CVM's testimony discounts the resistance in Finland as being from foreign travel. [Tr. P.686 L.17–19; P.688 L.18–P.689 L.6]This point supports the fact that large percentages of human resistance can come from foreign travel. This is a crucial point, because NARMS has no way of distinguishing whether the resistance it reports in the U.S. is from foreign travel or is domestically acquired, because NARMS does not collect data on source of infection. [Tr. P.116 L.3–6]

(d) Countries with Low Poultry Resistance and High Human Resistance Disprove CVM's "Temporal Relationship"

Finally, countries where poultry resistance is low and human resistance is high also disprove CVM's "temporal relationship" concerns.

Perhaps the most telling evidence comes from Canada, where six related studies are reported. A study of 309 *C. jejuni* isolates taken from humans in Ontario from 1992 to 1994 [B-32] found that 13.6% of the isolates were resistant to nalidixic acid and 11.4% to ciprofloxacin. The study also analyzed 69 *C. coli* isolates gathered during the same time period, of which 29.0% and 24.6% were resistant to nalidixic acid and ciprofloxacin, respectively. The considerable annual fluctuation in resistance rates is also demonstrated by a second study in Ontario [Bayer NOOH Response (B-1(A)) P.8] which reports a nalidixic acid resistance rate of 25.6% in 1992. A third study compared resistance levels in human *C. jejuni* isolates in Quebec from 1985–1986, 1992–1993, and 1995–1997, respectively. [B-29] Resistance to both nalidixic acid and ciprofloxacin rose from 0% in 1985–1986 to 4.7% and 3.5%, respectively, in 1992–1993, and finally to 13.9% and 12.7% in 1995–1997. [*Id.* P.3 Table 1] In 1999 a fourth study showed that ciprofloxacin resistance in 60 *C. jejuni* strains amounted to 25%. [B-28] A fifth and sixth study also report results from poultry isolates. In 1999, one study found 32% resistance in 83 human isolates, but found no FQ resistance in 124 poultry isolates from retail stores. [B-63] This is in line with an earlier study, which also reported an absence of FQ resistance in poultry *C. jejuni* from meat processing plants. [Bayer NOOH Response (B-1(A)) P.8]

These rates of quinolone resistance in human *CP* isolates are similar to those reported in the U.S., yet FQ use in Canadian food animals, including poultry, is limited to experimental use.[13] Moreover, since Baytril's introduction in the U.S. in 1996, only a negligible amount of poultry consumed in Canada could have been Baytril-treated U.S. imports. [Bayer NOOH Response (B-1(A)) P.8] Thus, FQ use in poultry cannot be causing the resistance in human isolates in Canada.

(e) If the Data from Foreign Countries Show Anything, It Is That FQ Resistance Can Be Controlled Through Prudent Use

The foreign country data on emerging resistance prove nothing about temporal associations, because a fair analysis of the published literature shows that the trends go both ways. Nevertheless, foreign country data are useful in this case to demonstrate that both the rate and extent of emerging FQ resistance can be controlled through prudent, regulated use in veterinary and human medicine.

Unrestricted use of FQs in veterinary and human medicine results in rampant resistance. In Spain, for example, where FQ use has been characterized as "indiscriminate" [B-655 P.5; G-530 P.2] and not strictly regulated [Tr. P.675 L.22–P.676 L.1] resistance increased rapidly in both poultry *CP* isolates between 1987 and 1997 from 0% to 99%. [G-549 P.2] Resistance also increased in human *CP* isolates between 1987 and 1993 from 0% to 48.8%. [G-532 P.2]

In contrast, Denmark has strongly regulated antimicrobial use in both veterinary and human medicine from the very beginning of market introduction. Even as late as 2000, Denmark was reporting only 8 and 10% FQ resistance in broiler chicken *C. jejuni* and *C. coli* respectively. [G-151 P.25] In humans, FQ resistance in domestically-acquired cases in Denmark was 22%. [G-151 P.27]

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[13] The only exception is the approval of Baytril for a turkey egg dip in late 1988 and its use as such through October 1997; despite this use, as indicated, Canadian studies on poultry isolates show no resistant *Campylobacter* isolates. [B-63; Bayer's NOOH Response (B-1(A)) P.8]

Taken as a whole, data from foreign countries comparing dates of poultry FQ approval, and use, with rates of FQ resistance in human isolates do not support claims of a causal relationship (nor even a temporal relationship) between FQ approval for use in poultry and an increase in human isolate *CP* FQ resistance. If anything, the data show that prudent use restrictions, like those put in place when enrofloxacin was approved in the U.S., have successfully controlled resistance levels. Accordingly, CVM's "temporal association" evidence should be given no credibility because it is unreliable in that it does not support the proposition in support of which CVM has offered it. *See supra* Evidentiary Standards, ¶ A.

e. It Is Not "Biologically Implausible" That the Level of FQ-Resistant Human *Campylobacter* Infections Now Seen in the U.S. Is Unrelated to Use of Enrofloxacin in Poultry

CVM contends that it is biologically implausible that the level of FQ-resistant human *CP* infections now seen in the U.S. is unrelated to use of enrofloxacin in poultry.

CVM's contention ignores the fact that the levels of FQ-resistant *CP* reported by Human NARMS are similar to resistance levels reported in the scientific literature in instances where enrofloxacin use in poultry could not possibly be the source.

Examples from the U.S. and abroad show the biological plausibility of having significant quinolone and FQ resistance unrelated to enrofloxacin use in poultry. Rautelin's 5.8% "natural resistance" in Finland in 1978–1980 [Tr. P.681 L.6–P.683 L.9, citing G-524 P.2], Svedhem's 11% resistance in Sweden in 1981 [B-1851 P.3], and Hollander's 15% resistance in Germany in 1983 all demonstrate this biological plausibility.

In the U.S., Barrett's 5% resistance in 1988 [Barrett (G-1453) P.3 L.3-10; G-1609], Kiehlbach's 12% resistance in 1992–1995 [B-39 P.3], Smith's 6% resistance in 1995 [G-589 P.3], and Nachamkin's 20% resistance in 1995 [G-1517 P.11, Graph] indeed demonstrate the biological plausibility of resistance in humans in the absence of poultry use in the U.S. These resistance rates can be explained only by human use and other non-poultry uses. Also consider that enrofloxacin is used prudently in poultry, under stringent controls, [*see, e.g.*, JS 15, 16, 17]

and in limited amounts, *e.g.*, 1–2% of the chicken flock and 4% of the turkey flock. [Bayer Interrog. Ans. 2; Gonder (A-201) P. 20 L.9; A-192 P.3] On the other hand, since approval of enrofloxacin, both foreign travel and use of various FQs in humans to treat some *CP* infections, but primarily many other types of bacterial infections, have shown a marked increase. [Burkhart (B-1900) P.9 L.1–2, P.44 L.45–P.45 L.11]

f. Retail Studies Do Not Raise a Serious Question

CVM claims that "most retail chicken and some retail turkey is contaminated with *C. jejuni*" and that "Fluoroquinolone-resistant *Campylobacter* often can be recovered from retail chicken and turkey meats." [*See* White (G-1484) P.2 L.17–19] However, the retail studies upon which CVM relies for these statements suffer from inherent flaws and therefore do not provide a reasonable basis for raising serious questions about the safety of enrofloxacin. In addition, the retail study evidence is not "new evidence"; retail studies showing the prevalence of *CP* on poultry were available prior to the approval of enrofloxacin [*see, e.g.*, B-387, A-169] and CVM knew prior to approval that use of enrofloxacin in poultry-harboring *CP* could lead to FQ-resistant *CP* being present on poultry. [JS 2]

i. The Retail Studies Are Not Representative of the U.S. Poultry Market

CVM cites numerous retail studies purporting to show prevalence of *CP* on chicken ranging from 44% [G-541; G-1528] to 88% [G-652, G-589] and on turkeys from 8% [White (G-1484) P.4 L.13] to 90% [G-652] [*See generally* White (G-1482) P.3 L.7–P.8 L.2] None of these studies, however, purports to be representative of the entire U.S. market for poultry products, and as such cannot be relied on for this purpose. The U.S. retail market consists of approximately 8.6 billion broilers and 270 million turkeys annually. [JS 43, 44] For comparison, the Zhao study [G-727] on which CVM relies tested only 184 chicken samples and 172 turkey samples for prevalence of *CP*. Such a small sample cannot possibly be considered statistically representative

of the immensely larger U.S. retail market as a whole, and as such this evidence is unreliable and should be accorded no credibility in the final analysis. *Cf. supra* Evidentiary Standards, ¶ C.

ii. Isolation Methods Used in Retail Samples Can Introduce Bias

Isolation methods for *CP* result in the isolation of strains that are not the disease-causing strain. Unlike many other bacteria, *CP* will not multiply outside the host gut and do not tolerate exposure to atmospheric oxygen or to drying. [Angulo (G-1452) P.9 L.29–31; Wegener (G-1483) P.4 L.18–20, P.5 L.4–5] Therefore, food samples often contain only small numbers of *CP*, and the bacterial cells may also be seriously injured during processing such as freezing, cooling, heating, and sanitizing. [Meng (G-1466) P.2 L.2–4] Thus, food samples are typically enriched and cultured for *CP* so that detection of small numbers of sub-lethally damaged cells is promoted. [Meng (G-1466) P.2 L.4–7] Sub-lethally damaged cells, which can be cultured, do not cause disease [Silley (B-1913) P.8 L.16–18, P.18 L.21–22], though when recovered from samples they are shown as part of the total load of potentially disease-causing *CP*. [Meng (G-1466) P.2 L.2–9; Silley (B-1913) P.18 L.19–21, P.19 L.1–3]

The culture method for isolating *CP* from retail food products is different from that used to culture human stool samples (i.e., Human NARMS) [Meng (G-1466) P.1 L.44–P.2 L.9] and can introduce different types of biases. First, the pre-enrichment step in carcass washes and retail product sampling can allow revived *CP* cells to multiply. Rapidly growing cells will have the opportunity to overgrow slow-growing cells, with resulting sample biasing. [Silley (B-1913) P.36, Att. 1, ¶ 3; B-1062] Second, the choice of isolation medium will influence the relative distribution of *CP* spp. and phenotypes recovered. [Silley (B-1913) P.7 L.1–2] Antimicrobials in selective media developed for *Campylobacters* are chosen on the basis of those to which test strains are resistant and those most effective in inhibiting competitive flora. [Silley (B-1913) P.6 L.8–14] Incorporation of antimicrobials into selective media has the greatest significance with regard to introducing bias into the isolation procedure. [Silley (B-1913) P.6 L.15–17]

This is not merely a theoretical bias, since incorporation of antimicrobials into selective media is a common isolation method. For example, Zhao used double strength Bolton's Broth to enrich for *Campylobacters* in the retail meat samples in his study. [G-727] Bolton's Broth contains antibiotics. Specifically, Bolton's Broth contains cefoperazone, vancomycin, trimethoprim, sulfamethoxazole, and cyclohexamide. [Silley (B-1913) P.35, Att. 1, ¶ 3] The retail study resistance results are therefore unreliable because they fail to correct for confounding factors—indeed, they *introduce* confounding factors, or at the very least the methodology used itself confounds the data. *See supra* Evidentiary Standards, ¶ B.

iii. The Retail Studies Provide No Information About the Crucial Issue of Dose

Critically important in determining whether exposure will lead to infection is the amount of *Campylobacter* present and ingested. This reflects the fundamental principle that "the dose makes the poison." [Haas (B-1904) P.21 L.21–22; Cox (B-1901) P.16] CVM acknowledges that the risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *CP* ingested. [JS 27] The retail studies on which CVM relies provide no quantitative information about the amount of *CP* present on the meat; instead, they report merely the presence of *CP* or FQ-resistant *CP*. Nothing in the retail studies CVM put into evidence demonstrates that the reported FQ-resistant *CP* are present in sufficient quantity to render an infective dose. In fact, one study put into evidence by CVM "found no epidemiological association with consumption of chicken" and campylobacteriosis even though "large numbers of chicken carcasses at retail stores were contaminated with *C. jejuni*." [G-564 P.4] Bayer has provided evidence of a dramatic decrease in *CP* contamination levels on slaughter carcasses from 1994–1995 to 1999–2000. [A-102 P.3] As discussed below, and based on the finding of Friedman [G-1488] and Effler [G-185], these increases have not translated into risk of campylobacteriosis from home cooked chicken. Accordingly, CVM's retail studies are not reliable to establish an actual causal link between retail poultry and FQ-resistant or susceptible

campylobacteriosis. *Cf. supra* Evidentiary Standards, ¶ A. Accordingly, the retail studies should be given no credibility in the final analysis.

iv. Epidemiological Studies Demonstrate That Retail Chicken and Turkey Cooked In the Home Are Not A Risk Factor For Acquiring Campylobacteriosis

The most significant reason why the retail studies do not provide any basis for raising serious questions about the safety of enrofloxacin is the fact that the best epidemiological evidence demonstrates that *CP* on retail poultry meat (i.e., meat purchased from a grocer to be consumed at home) is not a risk factor for acquiring campylobacteriosis or FQ-resistant campylobacteriosis. Retail poultry sales comprise sales directly to consumers for home consumption. However, epidemiological data shows that chicken and turkey eaten in the home (meaning retail chicken and turkey purchased at the supermarket by consumers and brought home) is associated with a *reduced* risk of campylobacteriosis. [Angulo (G-1452) P.10 L.22–32; G-1488 P.23, Table 4; G-945 P.5] This is not altogether surprising, given the vast improvements in consumer awareness of microbiological food safety issues compared to before enrofloxacin was approved for use in poultry. [Tompkin (A-204) P.9 L.29–P.13 L.8] Therefore, irrespective of what retail studies show in terms of prevalence, epidemiological evidence shows that consumers do not face any risk from retail chicken. Accordingly, even if the retail studies are credible, they do not support CVM's case because they show the *opposite* of the proposition in support of which CVM offers them. *Cf. supra* Evidentiary Standards, ¶ A.

It is also important to note that not all *CP* strains present on retail chickens or turkeys are capable of colonizing humans and causing disease. Several studies suggest that the population of C. *jejuni* isolates from humans with campylobacteriosis only partially overlaps with the population of isolates from poultry. [G-589; G-1785 P.5; Newell (B-1908) P.35 L.7–12] Therefore, the mere presence of *CP* on retail chicken or turkey does not necessarily present a risk to human health. This lack of overlap is supported by comparing the results of the retail meat study reported by Meng in which *CP* on chickens had a resistance rate of 54% to erythromycin.

[Meng (G-1466) P.3 L.24–29] At the same time, the NARMS has never reported an erythromycin resistance rate in humans of more than 3% [Angulo (G-1452) P.74 Att. 2, L.74], suggesting that the majority of the *CP* isolates found on chickens are not causing disease in people.

v. The Poultry Retail Studies Do Not Constitute "New Evidence"

The fact that *CP* may be present on retail meats, including chicken and turkey, is not new evidence. Retail studies showing the prevalence of *CP* on poultry were available prior to the approval of enrofloxacin. [*See, e.g.*, B-387, A-169] Furthermore, prior to approval CVM knew that use of enrofloxacin in poultry harboring *CP* could lead to FQ-resistant *CP* being present on poultry. [JS 2] CVM has also acknowledged that it does not have any facts or data demonstrating any increase in FQ-resistant *CP* loads in retail chicken products or in retail turkey products after FQs were approved for use in chickens and turkeys [CVM Interrog. Ans. 24], so the retail studies do not demonstrate any increase in prevalence.

In sum, retail study evidence does not raise serious questions about the safety of enrofloxacin. CVM therefore has not carried its burden of proof.

g. CVM's Risk Assessment Does Not Raise a Serious Question

As discussed above, CVM has the initial burden of providing a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred. Moreover, the evidence that provides this basis must be new, i.e., not available at the time CVM approved Baytril as being safe for such use in 1996.

According to CVM, at the time it approved Baytril for use in poultry, it was not aware of the impact that such use would have on human health, but that impact was subsequently revealed by the CVM *CP* risk assessment. [G-953; the "CVM RA"] According to CVM, the CVM RA provided CVM with evidence of the magnitude of the impact of FQ use in chicken by

establishing that such use has a negative impact on human health. [CVM Interrog. Ans. 8; Tollefson (G-1478) P.16 L.30–34; Cox (B-1901) P.24]

This argument fails for several reasons. First, although the parties appear to agree that risk assessments must comport with certain accepted guidelines and standards, such as demonstrating factual evidence of a causal relation between exposure and harm, the CVM RA does not do so. Second, the CVM RA suffers from conceptual problems that make it unable to provide evidence of the objective nature and extent of the human health impact from use of Baytril in chickens. Third, the CVM RA is not supported by, and indeed is contradicted by, relevant data. Fourth, the CVM RA miscalculates the impact it was intended to quantify.

i. The CVM Risk Assessment Has Significant Conceptual Problems Such That It Cannot Objectively and Adequately Provide Evidence of the Magnitude of the Human Health Impact of the Use of Baytril in Chickens

In constructing the CVM RA and in departing from the standard NAS Paradigm, CVM made a multiple string of *a priori* assumptions [Tr. P.769 L.20–P.770 L.12] that led it to apply incorrect, problematical, distorting, and limiting concepts to its interpretation of data and its estimates of risk. This section discusses these conceptual problems. The following section will discuss how these problems led CVM to overlook, discount, ignore, or distort crucial, actual data and studies.

(a) The CVM RA Assumes That Resistant Infections Equate With Adverse Human Health Impact and Fails to Consider Data to the Contrary

To begin, the CVM RA conceived that it could quantify a human health impact merely by quantifying the number of persons in the U.S. who were infected with FQ-resistant *CP* (to at least some extent, though with no number or proportion of resistant CFUs specified) from eating domestically-produced chicken and who were treated with a FQ. This assumes that (a) such treatment will be ineffective or less effective in some way, or to some extent, than if the resistant CFUs were susceptible and (b) some (unspecified) adverse health consequence(s) will follow.

[Cox (B-1901) P.25] Because the CVM RA made these assumptions, it did not test or refine the fundamental concept by examining actual data to see what conditions might be affected by treatment, whether and to what extent treatment of FQ-resistant *CP* infections might be ineffective (or effective), or whether and to what extent such treatment might be less (or more) effective than the treatment of FQ-susceptible *CP* infections. [Tr. P.744 L.21–P.745 L.8, P.826 L.7–12]

Thus, the CVM RA did not objectively examine the data to assess whether the criterion on which it relied for distinguishing "resistant" from "susceptible" *CP* infections was clinically probative. [*Id.*] It did not do so, despite the fact that the criterion the CVM RA used has not been clinically validated. [JS 14] Nor did it consider data showing that FQ-resistant campylobacteriosis responds at least as well to therapeutic doses of ciprofloxacin as FQ-susceptible campylobacteriosis, such as the data from Smith [G-589] and from McClellan/Nelson [G-1679, G-1489] and from Marano [G-394] controlled for foreign travel and prior FQ use as analyzed by Burkhart and Feldman. [Burkhart (B-1900) P.20 L.20–23; P.33–40; Feldman (B-1902) P.36 L.12–P.39 L.7]

As explained below, because of this conceptual model (regarding resistance and treatment success or failure) CVM overlooked or disregarded relevant data from the 1998–1999 CDC case control study, even though it utilized other data collected in that study. As also noted below, the CVM RA also failed to consider other studies which bear on the question of clinical resistance and treatment success and failure for "resistant" and "susceptible" isolates. (*See* section I.C.2.b., *infra*).

The CVM RA conceived that it could estimate the mean (annual) number of domestically acquired, non-treatment-related FQ-resistant *CP* infections caused by enrofloxacin use in the United States by multiplying the number of cases of domestically acquired, non-treatment-related *CP* infections (all of which are assumed to be "chicken-associated") by an estimated "proportion of resistance among domestically acquired cases." [Bartholomew (G-1454) P.9

L.29–31 and Tr. P.798 L.7–P.799 L.22, P.804 L.5–P.805 L.17, P.811 L.9–17] In other words, it conceived of estimating the FQ-resistant cases of interest by the following multiplication:

> Mean domestically acquired resistant cases attributed to resistance from chickens = (total domestic non-treatment chicken-associated cases) x (proportion of resistance among domestically acquired cases)

Yet "chicken-associated" does not mean "caused by ingestion of chicken," as CVM assumes, nor does it preclude the possibility that "chicken-associated cases" are caused by non-chicken sources associated with chicken consumption (for example, because eating in a restaurant, income, Medicare coverage, etc. influence or confound detected associations with *CP* or mask non-chicken sources of *CP*). [Tr. P.592 L.8–11, P.595 L.9–22, P.598 L.9–P.599 L.20, P.608 L.6–8; Tr. P.537 L.21–P.538 L.22; Cox (B-1901) P.15, 21, 38–39, 47, 49] Moreover, the formula is offered by CVM without citations or authority. It is mathematically incorrect, as can be seen by applying it to simple hypothetical examples where the correct answer is known. For example, if all resistant cases come from non-chicken sources (e.g., via drinking water), and if these cases account for half of all domestically acquired cases (with the rest coming from chicken), then the mean number of resistant cases attributed to FQ resistance from chickens by CVM's above formula would be:

> (total domestic non-treatment chicken-associated cases) x (proportion of resistance among domestically acquired cases)
>
> = (total domestic non-treatment chicken-associated cases) x (0.5)

In other words, in this simple hypothetical example where it is known (by construction of the example) that the correct answer is that 0% of resistant cases are caused by chicken, CVM's formula implies that half (50%) of all domestic non-treatment chicken-associated cases are attributed to FQ resistance from chickens. This and similar examples in the other direction show that CVM's multiplication formula, which is provided without references or justification, is not mathematically valid—the answers that it gives have no necessary relation to the correct answer. [Cox (B-1901) P.21–22, 39, 57–60, 64]

(b) Failure to Utilize Recent Data on Risk Factors Leads CVM to Overestimate the Chicken Attributable Risk, and Thus Human Health Impact

The CVM RA conceived that it could estimate the total number of *CP* infections in the U.S. by extrapolating from the number of such infections tabulated in the FoodNet catchment areas in 1998 and 1999. It recognized that "ideal extrapolation of FoodNet incidence rates to the U.S. population would require knowledge of the distribution of risk factors that affect the rates of disease." [G-953 P.32] Nevertheless, it assumed that actual conditions did not allow it to make such an "ideal extrapolation," so it assessed the representativeness of the FoodNet sample by utilizing straightforward demographic data. [*Id.*] Yet, inspection of the data shows that there is a great deal of unexplained variability in campylobacteriosis rates across FoodNet sites that is not related to differences in reported chicken consumption. [Cox (B-1901) P.37; Tr. P.1076 L.3–P.1080 L.11] The FoodNet data on the relation between chicken consumption and campylobacteriosis rates are so variable that different sites do not even reliably represent one another, let alone the rest of the U.S.

The concept and assumption that total *CP* infections in the U.S. can be straightforwardly extrapolated from FoodNet data led CVM to pay insufficient attention to data that were readily at hand and pertinent to judging whether or not its extrapolation of total infections was too large. CVM acknowledged toward the very end of its Risk Assessment that there was an "analysis of [the 1998–1999 CDC case control study] . . . currently underway . . . [that] will provide updated risk factor information from which etiologic fractions associated with identified risk factors may be determined." [G-953 P.103] In fact, this analysis was published in draft form by Friedman in 2000 [B-27 and G-228], well before the CVM RA was completed in January 2001. [Tr. P.738 L.2–20] A similar analysis of the CDC case control date analyzing risk factors for domestically-acquired FQ-resistant *CP* infections was also conducted and published in draft form in 2000 by Kassenborg [B-38 and G-337], also before the CVM RA was completed in January 2001.

Friedman found that eating chicken prepared at a restaurant had the largest etiologic fraction. [G-1488 P.23] Kassenborg found that eating chicken or turkey cooked at a commercial establishment was the *only* risk factor for FQ-resistant campylobacteriosis. [Kassenborg (G-1460) P.8 L.16–18] Bartholomew agreed that this risk factor would have been a proper factor to consider in evaluating the representativeness of the FoodNet sample [Tr. P.757 L.12–P.759 L.9], but it was not so evaluated. Moreover, it is clear that chicken consumption habits differ greatly among FoodNet areas and that the ratio of *CP* case rates to chicken consumption varies widely from area to area, making extrapolation to other areas unreliable unless other relevant factors (e.g., income, Medicare coverage, restaurant dining habits, etc.) are considered [Cox (B-1901) P.37, 39; Tr. P.1076 L.3–P.1080 L.11] These factors were omitted from CVM's modeling.

More importantly, the CVM RA conceived that chicken accounted for a significant etiologic fraction (57%), or population attributable fraction/risk, for *CP* infections. It assumed that the risk factor for chicken was positive (or that the odds ratio was greater than 1). Accordingly, it used a formula for estimating the proportion of total U.S. *CP* infections attributable to or caused by chicken that could not accommodate a negative (protective) risk factor or an odds ratio less than 1. [Cox (B-1901) P.19, 71–73]

When the Friedman analysis showed that eating chicken at home was protective (odds ratio less than 1), it became necessary to use all the various attributable fractions for chicken to come up with a global fraction to apply, but the CVM RA did not do so. [Tr. P.799 L.13–P.800 L.14; P.803 L.8–P.804 L.4] If this fraction is less than one—as it is [*see* Cox (B-1901) P.17, 9; P.20, 22, 27, 35, 37–39, 55–59]—then the formula for separating chicken-associated *CP* infections from total *CP* infections becomes at least problematical [Tr. P.800 L.1–19], and indeed unworkable. [Cox (B-1901) P.19–20, 39, 66, 71–73]

Further to this point, the CVM RA acknowledges that use of epidemiological attributable risks and etiologic fractions entails the limitation "that those cases that were exposed to the risk factor of interest, even though the exposure may not have been the cause of the disease, would be

included in the calculated level of risk, thereby potentially overestimating the level of actual risk." [G-953 P.102] As a result, the CVM RA's use of these concepts to quantify the fraction of *CP* infections attributable to chickens does not mean that those infections were necessarily or probably caused by consumption of contaminated chicken. It may include infections that were not caused by exposure to chickens, in contrast to CVM's interpretation of the resulting numbers as being causally "attributable to" chickens. [Tr. P.768 L.8–P.769 L.7]

Moreover, the Friedman study found that non-poultry meats eaten away from home constitute a risk factor of similar magnitude to chicken eaten away from home [G-1488 P.23] This raises the likely possibility that some commercial food preparation or other "outside the home" meal preparation practices may be unsanitary, regardless of whether chicken or something else is being prepared. It also suggests that a classic "feedback" problem is presented. That is, statistically, where, as in the Friedman study, a multiple regression framework is utilized,

> the expert often assumes that changes in explanatory variables affect the dependent variable, but changes in the dependent variable do not affect the explanatory variables—that is, there is no feedback... In making this assumption, the expert draws the conclusion that a correlation between an explanatory variable and the dependent variable is due to the effect of the former on the latter and not vice versa. Were the assumption not valid, spurious correlation might cause the expert and the trier of fact to reach the wrong conclusion...

[Federal Judicial Center, Reference Manual on Scientific Evidence ("FJCRMSE") (2d ed.) at 195][14]

[14] 21 C.F.R. § 12.95(a) provides that "[o]fficial notice may be taken of such matters as might be judicially noticed by the courts of the United States or of any other matter peculiarly within the general knowledge of FDA as an expert agency." Federal courts have cited to the Federal Judicial Center, Reference Manual on Scientific Evidence (2d ed.), as a reliable authority. *E.g* , *Nguyen v. INS*, 533 U.S. 53, 67 (2001); *Rudebusch v. Hughes*, 313 F.3d 506, 518 n.3 (9th Cir. 2002); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 264 (2d Cir. 2002); *Hollander v Sandoz Pharms. Corp.*, 289 F.3d 1193, 1206 (10th Cir. 2002); *Chavez v. Ill. State Police*, 251 F.3d 612, 642 (7th Cir. 2001). Moreover, the D.C. Circuit has relied upon this reference in the context of an administrative law case. *See Appalachian Power Co. v. Pub. Serv. Elec. & Gas. Co.*, 135 F.3d 791, 804 (D.C. Cir. 1998). Although not in the evidentiary record, this reference is the type of reliable material judicially noticed and, therefore, it should be officially noticed here as well.

In other words, the fact that Friedman finds similar population-attributable fractions for eating poultry at a restaurant (24%) and eating *non*-poultry meat at a restaurant (21%) [G-1488 P.23], while eating both poultry meat and non-poultry meat *at home* are protective (odds ratios of less than 1) [G-1488 P.23], begs the question whether the cause is in the meat or some other source of campylobacteriosis in restaurants. In such cases, although there is no single approach that is entirely suitable, "one possibility is for the expert to drop the questionable variable from the regression to determine whether the variable's exclusion makes a difference. If it does not, the issue becomes moot." [FJCRMSE at 196] Notably, Kassenborg did this in her analysis of risk factors for domestically acquired FQ-resistant infections (i.e., via backward step-wise regression). When she did, she found that chicken was not a risk factor. [Tr. P.603 L.2–14] She did not, however, report this fact, because in her view negative results are not published. [Tr. P.603 L.15–21]

The CVM RA compounds these difficulties by the conceptual approach it takes to calculate the fraction of chicken-attributable cases that are resistant and attributable to the use of Baytril on U.S. chickens. The CVM RA utilizes a further "partitioning" concept to calculate this fraction: it calculates the fraction of resistant cases attributable to foreign travel and prior treatment, subtracts those cases from the universe of all resistant cases, and assumes that all the remaining resistant infections come from the use of Baytril on chickens. In so doing, it must ignore other sources of resistant *CP*, including even one source identified in the CVM RA—water, including water from wastewater treatment plants that do not receive meat processing waste. [G-953 P.49–50; Tr. P.810 L.1–P.815 L.20; *see also* G-1488 P.23 (showing untreated lake, river, and stream water as a risk factor] Indeed, studies have discovered that wastewater treatment plants may preferentially discharge resistant bacteria, including resistant *CP*. [*See* Patterson (B-1910) P.13 L.4–14] *CP* found in water most probably originates from sewage, including that containing hospital and other health care facility discharges. [Patterson (B-1910) P.9 L.20–P.10 L.2; Newell (B-1908) P.8 L.1–3] Such wastewaters thus contain FQ-resistant *CP*

from human patients treated with FQs and introduce them into the environment, where other humans, wild animals, and wild birds may be exposed to them. [Tr. P.806 L.11–P.810 L.10; Patterson (B-1910) P.4 L.8–14, P.6 L.8–11, P.6 L.20–22, P.10 L.7–14, P.13 L.12–14; Burkhart (B-1900) P.4 L.5–8]

In addition to these problems, CVM's partitioning approach is unnecessarily indirect. CVM had available to it the CDC data that Kassenborg used to calculate directly a population-attributable fraction for domestically-acquired resistant *CP* from chicken. Although Kassenborg reported such a fraction, based on one model, as noted above, when she used a different model (the one suggested in the Federal Judicial Center Manual), she found no attributable risk for chicken. Moreover, as further discussed in the following section, Cox also found no, or virtually no, attributable risk for chicken-related, resistant *CP* when analyzing the same data set.

ii. The CVM Risk Assessment Is Not Supported by, and Is Contradicted By, The Relevant Data

It is noted above that the failure of the CVM RA to follow the NAS Paradigm's well-considered four-step process led to conceptual difficulties and factual conflicts. The previous section elucidates some of the key conceptual difficulties. This section focuses on the factual conflicts, beginning with those resulting from the failure of the CVM RA to conform to the NAS Paradigm's hazard identification step.

(a) CVM Fails To Consider That There Is No Actual Human Health Consequence of Resistant Infections

As explained above, the CVM RA attempted to quantify the number of persons suffering from chicken-related resistant *CP* infections who were treated with a FQ, stopping short of identifying specific adverse health impacts that could afflict such persons or quantifying the risk of being so afflicted. Further, the CVM RA made no attempt to compare the rates of any postulated adverse impacts from resistant infections to those occurring with susceptible

infections. Nonetheless, there are studies and data, such as those by Smith [G-589] and Nelson/McClellan [G-1679], that do examine and quantify such risks and rates.

The basic assumption of the CVM RA seems to have been that treatment of FQ-resistant *CP* infections with FQs will result in increased rates of undesirable outcomes and/or "treatment failures." The concept of a "treatment failure," however, is meaningless except in relation to some disease or condition. Although it is certainly true that there are a number of complications related to *CP* infections, CVM has presented no facts or data demonstrating any statistically significant increase in the rate or extent of such complications from infections caused by FQ-resistant *CP* compared to infections caused by FQ-susceptible *CP* infections. [CVM Interrog. Ans. 60; Molbak (G-1468) P.21 L.11–15, P.22 L.1–2] There are no studies or data in evidence which directly address the potential for FQ treatment failure or success with regard to such complications, except for a few case reports regarding the treatment of patients with AIDS and extra-intestinal infections such as bacteremia, and in such cases the recommended treatment is either with other antibiotics or with FQs in combination with other antibiotics. [B-742 P.5; B-273 P.7; Iannini (B-1905) P.5 L.6–8, L.18–20; Pasternack (B-1909) P.8 L.21–22, P.9 L.1–3]

The disease condition most focused on by CVM in this proceeding with respect to FQ treatment, and the condition most studied in the CDC case control study and in other studies regarding the potential for FQ treatment success or failure, is diarrhea. The CDC case control study, however, showed that, on average, persons with FQ-resistant *CP* respond to FQ treatment. Marano's analysis of the CDC data set showed that patients with a so-called FQ-resistant *CP* infection who were treated with a FQ had fewer days of illness than those who had resistant infections and were not treated (8 days versus 12 days). [G-394] These findings have been confirmed by McClellan/Nelson. [G-1679; G-1489 P.11] Moreover, the CDC data indicate that persons with FQ-susceptible *CP* infections on average did not respond to treatment with FQs—i.e., the mean duration of diarrhea in such patients was not significantly less than the mean

duration of diarrhea in patients with susceptible infections who were not treated with FQs. [G-394; G-1489 P.11; G-1679]

Overall, the days of diarrhea in FQ-treated patients did not differ significantly between FQ-resistant and FQ-susceptible infections. [*Id.*] This shows that patients with FQ-resistant *CP* treated with a FQ did not have any evidence of increased morbidity compared to FQ-susceptible infections treated with a FQ. [Burkhart (B-1900) P.40 L.4–7]

The findings of Marano and McClellan/Nelson are further supported by the analyses of the Smith data by Burkhart and by Feldman. When the Smith data are properly adjusted for foreign travel and prior FQ use, there is no difference in duration of illness. [Burkhart (B-1900) P.21, Table 1; Feldman (B-1902) P.38 L.1–P.39 L.1] Smith acknowledged on cross-examination that when considering only domestically acquired cases, there is no statistically significant association between FQ resistance and longer duration of diarrhea. [Tr. P.545 L.1–5]

These findings are consistent with other studies that report that most persons with FQ-resistant *CP* infections who are treated with FQs do respond to treatment with FQs. Piddock reported that only 1 of 39 patients with resistant infections failed to respond to treatment. [B-50 P.2] In a more extensively-reported study, Sanders reported that between 58% and 75% of resistant cases responded to treatment. [B-1920 P.4] In another study, among 37 patients with *CP* infections who were treated with FQs, there were only two failures—one of which was a susceptible infection, and one of which was a resistant case. [G-354 P.3]

While these studies do not demonstrate that there will never be a diarrhea-related treatment failure in the subgroup of patients treated with FQs with which the CVM RA terminated its quantitative analysis, they do show that it is by no means clear that such failures will be common or will occur at a significantly greater rate than treatment failures among persons with susceptible infections. On the contrary, as a quantitative matter, in the CDC study on which the CVM RA relied for much of its data, FQ treatment of resistant cases was effective, and more effective in reducing duration of illness, than was treatment of susceptible cases. Thus,

by stopping short of identifying the specific adverse health impacts that might be caused by treatment failures, the CVM RA overlooked data that at a minimum would reduce the number of persons at risk for the only well-studied impact, diarrhea, and overlooked studies (particularly Marano G-394 and McClellan G-1679) which indicate that treatment of resistant cases is generally effective and may be as or more effective than treatment of susceptible cases.

(b) CVM Fails to Consider All Available Relevant Studies

The CVM RA disregards available studies that showed chicken was not a risk factor. For example, it dropped the Hopkins study, one of the three studies it originally used to estimate the risk factor for chicken, [G-953 P.52 n.1; Tr. P.738 L.21–P.739 L.8, P.782 L.2–16] because of purported inconsistencies in the reported results.[15] [G-953 P.52 n.1] Hopkins found that there was no overall correlation between chicken consumption and campylobacteriosis. [G-299 P.2] In this study, conducted in Colorado in 1981, ill persons were less likely than either set of controls to have eaten chicken. [G-299 P.2] Ill persons were more likely to have eaten undercooked chicken (a marker for tendency to eat other undercooked foods and for restaurant dining habits in the CDC case-control data), but illness was not associated with eating chicken skin or with specific methods of cooking or preparing chicken. [*Id.*] Hopkins's findings regarding a lack of association or negative association between eating chicken and campylobacteriosis is repeated among many U.S. studies available in the general literature at the time of the CVM RA. For example, in a year-long study conducted in Dubuque, Iowa, between April 1982 and March 1983, no epidemiological association was found with consumption of chicken, even though large numbers of chicken carcasses at retail stores were contaminated with *Campylobacter jejuni*. [G-564 P.4]

Studies from other countries available at the time of the risk assessment support the same lack of association between chicken and campylobacteriosis. A study, conducted in the U.K. in

[15] Hopkins does not mention any inconsistencies, nor does CVM elaborate on what the inconsistencies were.

1990 and 1991, found no positive associations between consumption of chicken in various settings and campylobacteriosis—including consumption of chicken at barbecues. [G-10 P.1, 5, 6] The study also found that consumption of chicken in the home was significantly associated with a decrease in risk. [*Id.*] Also, a study conducted in the summer of 1992–1993 in Christchurch, New Zealand, found that consuming chicken was insignificantly negatively associated with campylobacteriosis (odds ratio = 0.89; confidence interval = 0.44–1.82; p value = 0.73). [G-307 at 2, Table 1] Ill patients ("cases") were significantly less likely to have eaten poultry at home, although knowingly eating undercooked poultry (including duck, as well as chicken and turkey) carried an increased risk of infection, as did consumption of barbecued chicken, although the reason was not defined. [*Id.* P.2, 3]

Although not available at the time the CVM RA was finalized, additional studies from both the U.S. and abroad continue to demonstrate the lack of association between chicken consumption and *CP* infections. A study conducted in Hawaii in 1998, published in 2001, found that exposures that were not significantly associated with campylobacteriosis included "consumption of any chicken." [G-185 at 3, Table 1 Note] It also found that eating chicken prepared by a commercial food establishment and consuming antibiotics during the 28 days before illness onset were significant independent predictors of such illness [*Id.* P.1,3] while consumption of chicken prepared in the home was inversely proportional to illness. [*Id.* P.2] A large study conducted in England and reported in 2001 found no statistically significant risk associated with consumption of chicken other than in restaurants nor with reported domestic kitchen hygiene practices. [G-1711 at 1, 2–5]

In summary, as illustrated by these examples, the *a priori* assumption that there is a directly proportional, positive relation between chicken consumption and campylobacteriosis rates, as in CVM's risk model, is contradicted by multiple independent studies and data sets. The CVM model assumes that cases increase in proportion to contaminated chicken consumed, and hence in proportion to total chicken consumed. The estimated constant of proportionality

between chicken consumed (a positive variable) and cases of campylobacteriosis (another positive variable) is their ratio, and hence is necessarily positive (i.e., ratios of positive quantities are positive). This *a priori* assumption does not reflect or correct for the repeated, widespread findings of a negative relation between chicken eaten at home and risk of campylobacteriosis. It simply ignores the available data that contradict it.

(c) Failure to Account for Dose/Response Leads to an Overestimate of Risk

The CVM RA's exposure assessment does not adequately consider *CP* dose/response. CVM agrees that whether or not a person gets sick from ingesting *CP* depends in part on the number of organisms ingested. [JS 27] Nevertheless, the CVM RA ignores this fact and instead assumes that the risks are equal. For example, CVM uses a prevalence-based approach that assumes the risk of consuming a portion of chicken with 1 *CP* to be equal to the risk of consuming a portion with 1000 organisms. [Haas (B-1904) P.10 L.6–7] However, other noted risk assessors have used a dose-response model and acknowledge that such models are "currently the standard method used to model probability of infection or illness for most bacterial pathogens" and in particular use *CP* as an example. [B-147 P.5, citing to B-517] Although the studies regarding dose-response for campylobacteriosis are limited, the more robust of these studies showed that many of the participants did not get sick even when exposed. [B-517 P.4; B-748 P.3; G-67 P.4; Cox (B-1901) P.23, 63] The probability that an infection would lead to illness was calculated to be in the range of 20%. [B-517 P.4; B-748 P.3; G-67 P.4]

Similarly, the data concerning exposure concentrations—microbial loads—on chicken reflect a wide range, including concentrations in the range of doses that typically did not produce disease in the dose response study. Studies from 1987 and 1992 reported contamination levels on fresh chicken products ranging between 100 and 100,000 cells per carcass. [Newell (B1908) P.23 L.11–13; G-444 P.472]

Thus, while the data indicate that there is some level of *CP* on chicken meat, the exposure concentrations due to chicken consumption may not necessarily be relevantly elevated with respect to the human dose-response curve. In other words, consistent with the studies on attributable risk discussed above, while some retail studies show some prevalence of chicken contaminated with a small amount of *CP*, the actual microbial load which determines exposure concentration and dose is not necessarily high enough on chickens in the U.S. and some developed countries to produce any statistically significant increase in illness rates. This is consistent with the fact that, statistically, the dose-response data show that concentrations of *CP* in ingested food that are relatively high compared to average concentrations are disproportionately likely to cause illness in humans. [Cox (B-1901) P.22]

A first indication that the CVM approach might be problematical is revealed by Cox's analysis showing that consumption of chicken in the FoodNet sites is negatively associated with *CP* incidence. That is, statistically, the more chicken consumed, the less disease. [Cox (B-1901) P.17, 37] This initial analysis is more extensively borne out by Cox's finding of a statistically significant negative association between chicken consumption at home and risk of campylobacteriosis in more thorough (nonparametric, multivariate) analyses of the raw data reported on by Effler [G-185] and the CDC case-control raw data reported on by Friedman [G-1488], Kassenborg [G-337], Nelson/McClellan [G-1679, G-1489], and Marano [G-394] CVM's consumption-disease approach is further called into question by Kassenborg's finding that only chicken consumed in commercial establishments is a risk factor, as well as by Friedman's findings that eating chicken away from home is a risk factor, but one of approximately the same magnitude as eating non-poultry meats away from home, while eating chicken, and other meats, at home is protective. Thus, at a minimum, CVM's dose-response/exposure assessment surrogate calculations would have to be corrected to remove chicken consumed at home.

This, it turns out, leads to even more difficulties. When Cox performed the "global" risk factor analysis Bartholomew agreed should be done [Tr. P.799 L.18–P.800 L.7], but which the

CVM RA did not do, he discovered that the "global" risk factor for eating chicken was either protective or not significantly different from zero. [Cox (B-1901) P.17, 19, 37, 49, 56–57] Furthermore, when Cox focused on resistant infections and eating away from home, he found virtually the same result—either a zero association or a slightly negative (or protective) one. [Cox (B-1901) P.22, 35, 39, 49, 57–58, 72, 78] When Kassenborg did her calculations using a backward stepwise regression analysis, she also found no association between consuming chicken and resistant campylobacteriosis. [Tr. P.603 L.2–14]

(d) Unreliability Of The CVM Risk Assessment

The above difficulties individually and collectively undermine the reliability and usefulness of the CVM RA as a tool for characterizing risk. It is hard to see how one might credibly rely on or effectively use a risk assessment that does not identify or quantify specific health impacts; that does not analyze or take into account dose response or exposure concentrations; that attempts to substitute an alternative method that produces results that conflict with the actual data; and that disregards or overlooks quantitative studies in the general literature, as well as findings of studies of the same data set that it uses for other purposes, that conflict with its basic *a priori* assumptions regarding causation and association between the practice being assessed and the disease outcome of interest. These points are especially relevant to the appropriate interpretation and use of statistical analysis in regard to causation.

Although statistical evidence alone can never prove a substantive theory, it can assist in assessing the likelihood that the causal theory is correct by assessing whether data is consistent with a postulated causal relationship or theory. [*See* Federal Judicial Center Reference Manual on Scientific Evidence (2d) at 193] Statisticians have developed a number of tests and standard software programs to do just this. [Cox (B-1901) P.27, 29] The CVM RA, however, did not use them.

CVM did not perform any formal statistical tests of the causal hypothesis that FQ use in chickens causes increases or decreases in FQ-resistant *CP* infections in humans. [CVM Interrog.

Ans. 13] Yet, CVM's own witnesses describe data showing that relatively high levels of FQ resistance in humans can occur without significant resistance in chickens [Hanninen (G-1458) P.3–4 ¶ 4, P.4 ¶ 5] and that, conversely, changes in enrofloxacin use in chickens may be followed by opposite changes in human FQ resistance [Hanninen (G-1458) P.4–5 ¶ 6] CVM did not perform any conditional independence tests for possible causality in any sets of data that involve FQ use in chickens and FQ-resistant *CP* infections in humans, including data sets from the CDC 1998–1999 *Campylobacter* Case-Control study [G-1488, G-1452, Att. 3, P.79–107], Smith [G-589], and Effler [G-185] [CVM Interrog. Ans. 16] CVM did not perform any formal statistical tests for omitted explanatory variables and/or confounders in analyzing possible statistical associations between FQ use in chickens and FQ-resistant *CP* infections in humans [(e.g., to determine whether enrofloxacin use in chickens protects human health by reducing the total prevalence of airsacculitis-positive flocks and the total microbial loads of resistant as well as susceptible CFUs reaching humans). [CVM Interrog. Ans. 18]]

Bayer's expert did perform such tests. The hypothesis that human campylobacteriosis and resistant campylobacteriosis are caused by chicken consumption consistently failed. [Cox (B-1901) P.27, 33] Cox's causal analysis was based primarily on conditional independence tests for causality based on analysis of the actual data underlying the Friedman, Smith, and Effler studies. That analysis indicated that there is no detectable causal relation between chicken consumption and FQ-resistant rates in humans, which is contrary to the theory of a causal link between use of Baytril in chickens and increased FQ-resistant *CP* infection rates in humans. [Cox (B-1901) P.45]

Conditional independence tests examine whether an observed statistical association between two variables can be fully explained away by their associations with other variables. When Cox applied readily available, objective statistical tests of conditional independence to the actual data underlying the studies referenced above, he found that overall consumption of chicken is not a risk factor for campylobacteriosis. On the contrary, he found that preparation

and consumption of chicken at home, buying or handling raw chicken, etc., are statistically significantly protective against campylobacteriosis, that restaurant dining, rather than chicken consumption *per se*, appears to be the major human health threat for campylobacteriosis in the CDC data set, and that, after correcting for foreign travel, there is no significant association between FQ-resistant *CP* and duration of diarrhea in the CDC or Smith data sets. [Cox (B-1901) P.29–37; Burkhart (B-1900) P.19 L.37–41; Feldman (B-1902) P.37 L.1–P.39 L.7] Thus, in keeping with the application of statistical analysis endorsed in the Federal Judicial Center's manual quoted above, Cox found that

> *the epidemiological data from the CDC case-control study and other sources generally refutes the assumption that there is such a hazard* [i.e., a human health hazard associated with chicken-borne *Campylobacter* or FQ-resistant *Campylobacter*] *and provide weak evidence of a possible negative association* (protective effect) between chicken consumption and FQ-r CP [i.e., FQ-resistant *Campylobacter*] illness risk in the US.

[Cox (B-1901) P.33 (italics in original)]

Cox also performed causal graph modeling to model the effects of confounders and to isolate the direct causal contribution of chicken consumption to *CP* risk. When he did so, he found that removing the effects of other variables removed the entire association between chicken consumption and human *CP* risk. This result indicates that CVM's estimation of a non-zero risk is based entirely on a failure properly to correct for other variables. [*Id.* at 49]

Finally, in this regard, Cox carried out formal statistical tests of the causal hypothesis that FQ use in chickens reduces FQ-resistant infections in humans, using the raw data provided to him. If CVM had performed the required formal statistical tests of the causal hypothesis that FQ use in chickens causes increases in FQ-resistant campylobacteriosis in humans, the limited data available would have shown that causation by a common third source or causation from humans to chickens was better supported than CVM's hypothesis that FQ-resistant *CP* in chickens causes FQ-resistant *CP* in people. [*Id.* at 45]

Accordingly, for all of the reasons stated above, the CVM RA fails to satisfy *any* of the requisite elements for scientific reliability, and it therefore fails to satisfy the statutory and regulatory standards to allow it to be given any weight in this proceeding. *See generally supra* Evidentiary Standards and AHI Brief P.17-35. Accordingly, CVM has failed to carry its burden of producing evidence from which "serious questions" about the safety of enrofloxacin usage "may be inferred."

iii. The CVM Risk Assessment Overestimates the Impact It Was Intended to Quantify

As might be inferred from the previous discussion, the CVM RA miscalculates even the impact it was intended to quantify, i.e., the number of persons having FQ-resistant campylobacteriosis related to use of Baytril in chickens in the U.S. who are treated with a FQ. First, the extrapolation of the universe of campylobacteriosis cases in the U.S. in 1998 and 1999 is uninformed or calibrated by readily available data on the principal chicken-related risk factor reported by Friedman and Kassenborg, i.e., eating away from home or at a commercial establishment.

Second, the etiologic fraction of such cases associated with chicken consumption also is not based on those readily available data from the CDC case control study, but rather on old, limited studies which are used to calculate an attributable risk many times higher than what the CDC data will support. These studies were conducted entirely before enrofloxacin was introduced into food animals, making their potential relevance to these proceedings questionable at best. In addition, the CVM RA made no attempt to calculate or apply an overall risk factor for chicken consumption by analyzing the CDC data or considering the 6 other studies between 1981 and 2001 that showed no general association between chicken consumption, a reduced risk/protective effect of eating chicken at home, and/or only an association with restaurant dining.

Third, the attempt by the CVM RA to "partition" out the fraction of resistant cases attributable to chicken by subtracting only foreign travel and prior FQ use in treated individuals overstates that fraction by ignoring other known and unknown sources of resistant *CP*. In addition to water and other known sources, it must be noted that the Friedman study attributed almost half of the cases to unknown sources. [Tr. P.810 L.1–P.815 L.13; Angulo (G-1452) Att. 3, P.101, Table 4] It is not credible simply to conjecture that these sources either are not sources of resistant *CP* or that they come entirely from foreign travel, prior treatment, or use of Baytril on chickens. In addition to skepticism founded on common sense, it should be noted that before Baytril was licensed for use on chickens in the U.S., Barrett found 5% resistance in 1988 [Barrett (G-1453) P.3 L.3–10; G-1609], Kiehlbach found 12% resistance in 1992–1995 [B-39 P.3], Smith found 6% resistance in 1995 [G-589 P.3], and Nachamkin found 20% resistance in 1995 [G-1517 P.11] These percentages are in line with the 11% FQ-resistant fraction found by McClellan/Nelson [Angulo (G-1452) Att. 4, P.110], Marano [G-394 P.1], and Kassenborg [G-337 P.3, 7, 11] in the CDC case control study in 1998–1999. These examples reveal the arbitrary and counter-factual nature of CVM's assumption that all domestic, non-treatment-related resistance to FQs is due to enrofloxacin use in chickens. In fact, it is not clear from any objective facts or data in evidence that any detectable proportion of human resistance is actually caused by enrofloxacin use in chickens, while there is abundant evidence that non-chicken sources made a substantial contribution to human resistance long before the approval of enrofloxacin.

Fourth, despite the available findings of Friedman and others that eating chicken at home is protective, the CVM RA made no attempt to remove chicken consumed at home from the universe of chicken consumed used to provide the exposure term in the calculation. Nor did it correct its chicken-attributable risk estimates for the negative association between chicken eaten at home and campylobacteriosis rates. Finally, and also related to exposure, the CVM RA made no attempt to quantify the distribution of microbial load on chickens. This gap opens the door to

an over-estimation by failing to account for the chicken that is contaminated but not sufficiently to cause infection.

In summary, the CVM RA arbitrarily attributes a number of campylobacteriosis cases to chickens, and a number of FQ-resistant campylobacteriosis cases to enrofloxacin use in chickens, without presenting any justification for not considering other (non-poultry) sources of resistance, or any justification for assuming, contrary to long-standing and widely available facts and data, that all domestic resistant cases (not related to foreign travel or prior treatment with FQs) are due to FQ use in chickens. The result is a risk assessment that, in effect, assumes its major conclusions without any critical testing of its assumptions or validating that they provide a useful description of the real world.

Accordingly, the CVM RA fails to satisfy the statutory and regulatory standards for evidence in an FDA proceeding because it compounds the use of inadmissible material. First, it relies on outdated evidence that has been shown to be unreliable by other more recent evidence. Second, even setting aside this fact, it is inherently unreliable in and of itself because it is scientifically unreliable in that it fails to correct for confounders and cannot prove a causal link between the cause studied and the effect sought. *Cf. supra* Evidentiary Standards, ¶¶ A, B. All of these problems result in a vast overstatement of risk.

C. WHETHER FQ-RESISTANT *CAMPYLOBACTER* INFECTIONS IN HUMANS HAVE THE POTENTIAL ADVERSELY TO AFFECT HUMAN HEALTH

1. CVM Has Presented No *New* Evidence That FQ-Resistant *Campylobacter* Illnesses in Humans Have the Potential to Affect Human Health Any Differently from FQ-Susceptible *Campylobacter* Illnesses

CVM understood and accepted that use of enrofloxacin in chickens and turkeys could lead to FQ-resistant *CP* infections in humans before it approved Baytril for such use in 1996. [JS 3] CVM also understood and accepted before it approved Baytril for such use that FQ-resistant *CP* infections have the potential adversely to affect human health. [JS 5; CVM Interrog. Ans.

52; van den Bogaard (B-1916) P.5 L.10–11, P.10 L.10–P.12 L.11] In particular, CVM considered, prior to approving enrofloxacin for use in chickens and turkeys that treatment failure or other public health risk was possible if diarrhea from resistant *CP* were treated with FQs. [van den Bogaard (B-1916) P.10 L.23–25; B-1819 P.186 L.22–P.187 L.5; B-22 P.1, 7, 8; G-1003 P.3] Thus, these conclusions and evidence supporting them cannot serve as the basis for withdrawing approval of Baytril for use in chickens and turkeys, because they do not constitute *new* evidence as required by the FFDCA. *See supra*, Summary of Argument.

CVM contends that its current understanding that FQ-resistant *CP* infections have the potential adversely to affect human health differs from its pre-approval understanding in that it now knows that use of FQs in poultry is a significant cause of FQ-resistant *CP* infections in humans. [CVM Interrog. Ans. 53] CVM further contends that the CVM RA and new surveillance data give a better understanding of the potential for FQ-resistant *CP* adversely to affect human health. [*Id.*] Since the CVM RA was addressed above, it remains here to consider the other reasons and evidence that CVM contends support its current, different understanding of the potential adverse health effects of FQ-resistant *CP* infections and whether it raises serious questions about the safety of enrofloxacin.

2. CVM's Evidence on FQ-Resistant *Campylobacter* Infections in Humans and the Potential Adversely to Affect Human Health Does Not Raise Sufficiently Serious Questions About Enrofloxacin's Safety

a. There Is No Credible Evidence That the Duration of Campylobacteriosis Generally, or Associated Diarrhea or Complications in Particular, Depends on Whether the *Campylobacter* Is or Is Not Resistant to FQs

CVM contends that individuals infected with FQ-resistant *CP* are more likely to suffer greater adverse effects than those infected with FQ-susceptible *CP*. [CVM Interrog. Ans. 54] By this, CVM means that studies have shown that FQ resistance in *CP* leads to increased duration of diarrheal illness, increased rates of hospitalization, and increased mortality and other complications. [CVM Interrog. Ans. 55, 56, 57, 58, 59; Molbak (G-1468) P.19 L.13–P.22 L.6,

P.22 L.21–25] The studies on which CVM bases its contention are the Marano and McClellan/Nelson studies [G-394, G-780, G-1367, G-1489] examining the CDC case control data, the Smith study [G-589] and the Neimann study [B-561; G-455] These assertions have not survived the scrutiny given them in this proceeding, however.

If chicken or turkey is the source of a sufficient dose of *CP* infection, one will get campylobacteriosis, regardless of whether or not the organism is FQ-susceptible or resistant.

The key question therefore in assessing these assertions is whether there is a difference between the human health effects of FQ-resistant and FQ-susceptible *CP* infections. The evidence on which CVM relies to show such differences is based on statistical analyses in the studies referenced above. Thus, as explained by the author of one of those studies, Smith, unless any difference is statistically significant, it should not be said that there is a difference—"different" means "statistically significantly different." [Tr. P.544 L.15–21] With this in mind, consider the uncontested evidence that has been adduced concerning the particular adverse human health effects cited by CVM as supporting its contention that it now knows that use of Baytril in poultry causes adverse human health effects:

The CDC case control study data showed no statistically significant relation between ciprofloxacin resistance and duration of diarrhea overall, even without adjusting directly for international travel. [Cox (B-1901) P.31; G-1679 P.57] Nor was there any statistically significant difference in duration between resistant and susceptible cases treated with FQs. [G-1679 P.52; G-1489 P.10-12, P.21–22 Table 1, P.23 Table 2]

Similarly, in his analysis of the data from the Smith study [G-589], Burkhart found no evidence of increased morbidity from treatment failure for domestic cases of FQ-resistant *CP* infections without prior FQ use. [Burkhart (B-1900) P.20 L.13–21]Smith himself has confirmed that there was no statistically significant association between FQ resistance and longer duration of diarrhea in domestically acquired cases in the data set used in his study. [Tr. P.545 L.1–5] As explained in detail by the CVM RA, it is domestically acquired cases that are of interest, since

cases acquired through foreign travel are subject to uncontrolled confounding by other risk factors. [G-953 P.25, 55–57, 103] CVM's own evidence thus illustrates why the Smith study is unreliable. *Cf. supra* Evidentiary Standards, ¶ B.

With regard to CVM's assertion regarding increased risk of hospitalization, the CDC case control data on the contrary show fewer days of hospitalization for FQ-resistant cases compared to susceptible. [Angulo (G-1452) Att. 4, P.117, 118, 128; Burkhart (B-1900) P.38 L.7, Table 10]

Neimann and coworkers analyzed a Danish data set for duration of illness in relation to human quinolone susceptibility of the isolated *CP*. More than 75% of the cases with a ciprofloxacin-resistant isolate also had a history of foreign travel, for which Neimann did not control. In patients who did not receive antibiotics, the duration was similar for all *CP*, independently of susceptibility to FQs. For patients treated with antibiotics, there was also no statistically significant difference in the duration for susceptible versus resistant infections. [B-561 P.200 Table 3; G-455 P.1; Burkhart (B-1900) P.49 L.37–40]

Moreover, in a large, recent U.K. study not referenced by CVM, there was no statistically significant difference in illness length between resistant and non-resistant *CP* when controlling for foreign travel (as recommended by, *inter alia*, the CVM RA). [Burkhart (B-1900) P.49 L.33–37; Newell (B-1908) P.46 L.13–18] In addition, resistant cases were significantly less likely to be admitted to the hospital compared to cases with a fully sensitive isolate. [Newell (B-1908) P.46 L.18–22]

Further, regarding complications, Professor Kist concludes after a review of available data that there has been no increase in complications reported since the introduction of FQs in human and veterinary medicine and that there is no evidence for increased risk of complications due to FQ-resistant *CP*. [Kist (B-1906) P.16 L.6–7, P.18 L.6–7]

Thus, the reasons given by CVM as supporting its contention that its understanding of the potential of FQ-resistant infections to cause adverse human health effects differs from its pre-approval understanding do not survive the uncontested facts.

b. The Clinical and Laboratory Evidence Supports That So Called Resistant Infections Are Largely Treatable with Macrolides or FQs and Other Antibiotics

As discussed previously in this document, FQ-resistant *CP* infections seem to be treatable with FQs at least as effectively as susceptible infections, perhaps even more so. They are also treatable with macrolides [Pasternack (B-1909) P.8 L.5–7] such as erythromycin and azithromycin. Resistance to macrolides among human *C. jejuni* isolates in the U.S. is lower compared to the rate of FQ resistance [Pasternack (B-1909) P.8 L.11–13] Azithromycin is generally well tolerated, including in individuals intolerant to erythromycin. [Pasternack (B-1909) P.13 L.20–21]

Empiric antimicrobial treatment is generally not recommended for diarrheal disease, including campylobacteriosis. [Iannini (B-1905) P.3 L.15–18; B-816 P.4] In fact, only a small minority of individuals will require antibiotic therapy as part of their treatment [Pasternack (B-1909) P.7 L.18–19] In the U.S. macrolides are recommended for suspected cases of campylobacteriosis before FQs due to the narrow spectrum and the more favorable resistance situation. [Pasternack (B-1909) P.8 L.7–16] Among patients with underlying immunodeficiency status, parenteral therapy is often preferred (intramuscular or intravenous, not oral) for extraintestinal infections, and combination treatment with imipenem and gentamycin has been recommended. [Iannini (B-1905) P.5 L.6–8; Pasternack (B-1909) P.8 L.21–P.9 L.3; B-273 P.7]

The fact that there were no statistically significant observable differences in morbidity between FQ-treated resistant and non-resistant cases in the Smith and CDC case control study data sets calls into question whether *in vitro* definitions of resistance equate to clinical resistance. [Burkhart (B-1900) P.49 L.16–18] At present, CVM and many investigators use a "breakpoint" value for defining *CP* resistance based on *in vitro* testing and analogizing to another class of enteric bacteria. [Kassenborg (G-1460) P.4 L.3–6; Walker (G-1481) P.7 L.8–10; Pasternack (B-1909) P.14 L.19–22] A "breakpoint" refers to a MIC, or "minimum inhibitory concentration," used to indicate susceptible, intermediately susceptible, or resistant bacteria, and a "minimum

inhibitory concentration" is the minimum concentration of an antimicrobial agent required to inhibit the growth of a susceptible organism. [Besser (G-1455) P.4 L.36–P.5 L.2; Tr. P.208 L.14–19, P.209 L.14–21]

At present, however, there is no NCCLS breakpoint for establishing clinical resistance for FQ use in *CP* infections in humans. [JS 14; Kassenborg (G-1460) P.4 L.3–4] There is no evidence that FDA has established such a breakpoint. Further, the breakpoint that CVM and many investigators use is based on serum, or blood-level concentrations of the antimicrobial. [Tr. P.244 L.3–7, P.251 L.4–22, P.257 L.16–P.258 L.6] Yet, FQ antibacterial activity is based on dose-dependent pharmacokinetics, i.e., the peak concentration of the drug at the infected site, and the site of infection for campylobacteriosis is the epithelial cells lining the gastrointestinal tract. [See McDermott (G-1465) P.6 L.38–41; Tr. P.243 L.5–P.244 L.2]

There are indications that actual concentrations of FQs in the human gastrointestinal tract are high compared to MICs of human *CP* isolates. [Pasternack (B-1909) P.15 L.14–16] These findings suggest that the observed effectiveness of FQs in treating "resistant" *CP* infections may mean that the currently utilized MIC for FQs is clinically too low. [Pasternack (B-1909) P.14 L.17–P.17 L.6, P.20 L.8–10; Silley (B-1913) P.18 L.13–15] If true, this would mean that the public health importance of this issue has been overestimated. [Burkhart (B-1900) P.4 L.22–24, P.49 L.16–21] Whether true or not, the fact remains that the data show that the treatment of human *CP* infections by FQs and other approved antibiotics does not appear to have been significantly impaired by FQ "resistance" as currently defined by CVM.

II. ENROFLOXACIN IS SAFE FOR USE IN CHICKENS BECAUSE THE BENEFITS TO HUMAN HEALTH FROM ENROFLOXACIN USE IN CHICKENS OUTWEIGH ANY POTENTIAL RISKS

A. Inserting Corrected Data into the CVM Risk Assessment Shows that the Risk of Adverse Health Impacts From Enrofloxacin Use is Minimal

As pointed out, Bayer and AHI contend that the CVM RA model is conceptually flawed in drawing its conclusion that 9,261 people had FQ-resistant *CP* illness from chickens and received a FQ in 1999. [G-953 P.64] In addition, Bayer and AHI have shown that two major variables in the CVM RA are not supported by the evidence: the 57% chicken-associated cases and the presumed 100% treatment failure rate. Assuming for the sake of argument that the CVM RA is useful for predicting risk, inputting corrected data for these parameters in the CVM RA model shows that the risk is much lower than CVM claims.

The CVM RA uses Deming [G-162] and Harris [G-268] to show on average a 57% attributable risk for chicken, whereas Friedman [G-1488] shows that chicken is not a risk factor when consumed in the home and has only a 24% attributable fraction when consumed in a restaurant. Simply inputting Friedman's 24% for the fraction of all *CP* cases attributable to chicken (and setting aside that the 24% finding was for *restaurant* consumption, that the fraction for home consumption would be near zero and that Bayer's evidence shows that a more realistic attributable fraction is between 0 to 3.1%. [Cox (B-1901) P.56, 57–64] would reduce CVM's 9,261 figure to only 3,900 people impacted.

The CVM RA merely estimates the number of people having a FQ-resistant *CP* illness from chicken and receiving a FQ in 1998 and 1999, presuming some adverse health affect for 100% of people in that group. [G-953 P.64] The CVM RA does not include any factor to correct its estimate to account for people who have a so-called resistant case, receive a FQ, and have an effective treatment. Yet Bayer has submitted evidence that the treatment failure rate of resistant cases is at most between 25% and 42% [B-1920, P.4 reporting that between 58% and 75% of resistant cases responded to treatment] and may be as low as 2.56% [B-50, P.2 reporting only one of 39 patients with resistant infections failing to respond to treatment] Simply correcting the

CVM RA to account for between a 42%–25% failure rate reduces CVM's 9,261 figure to between 3890 and 2315 people impacted.

Simply accounting for *both* of these straight forward corrections would reduce CVM's estimate from 9,261 people to 1638 people (3900 people * 0.42) or perhaps as low as 975 people (3900 people * 0.25), or to about 10% of the risk estimate in CVM's RA. However, this number still does not take into account the other shortcomings in CVM's model. E.g., proper consideration of a dose-response relationship or probability of illness would further substantially lead to even lower numbers.

B. The Bayer Risk Assessment Demonstrates That the Risks from Enrofloxacin Use Are Minimal

Since the late 1990s, almost all risk assessments of campylobacteriosis have applied a fairly standardized farm-to-fork methodology (www.dsr.kvl.dk/forening/MF/files/show3.ppt) that follows the microbial loads of campylobacter from live birds through transportation, processing, storage, and preparation, using various available data sources to estimate how microbial loads change at each stage, and then passing the resulting microbial load distributions through a dose-response model (usually based on the human data of Black et al. 1988 and the Beta-Poisson dose-response model) to estimate resulting illnesses. This approach has been taken by investigators for Health Canada in 1999 (http://www.who.int/fsf/Micro/studycourse/annac/annac1.html), WHO/FAO in 2000 and subsequently (www.who.int/fsf/Documents/reportcv.pdf, www.dsr.kvl.dk/forening/MF/files/show3.ppt) and independent investigators in the UK (VLA), Denmark (Rosenquist et al., 2002) and the US (Cox, 2001, RIsk Analysis: Foundations, Models and Methods, pages 92-129).

When this standard farm-to-fork approach is applied to US data using most of CVM's assumptions, but assuming that 21% of all campyobacteriosis cases are attributed to chicken (based on upper-bounding estimates from CDC epidemiological data), the estimated number of

cases of chicken-associated fluoroquinolone-resistant campylobacteriosis cases prescribed fluoroquinolones is 985 cases in the whole US population per year (Cox, 2001, p. 113.)

The same model assumes, following CVM, that the number of chicken-associated fluoroquinolone-susceptible cases is much larger (210,206). If enrofloxacin is withdrawn, the increase in susceptible microbial loads and cases far exceeds the hypothesized reduction in resistant microbial loads and cases.

C. Any Examination of the Safety of Enrofloxacin Requires a Consideration of Benefits and Risks

As described above, the D.C. Circuit has recognized that a proper determination of the safety of a drug product must include consideration of the risks versus the benefits of the drug. *See Hess & Clark, supra* 495 F.2d 975. A risk/benefit analysis on the withdrawal of the NADA for enrofloxacin therefore must include an analysis of the total effect on human health risks from the withdrawal of the NADA for enrofloxacin, including whether the human health benefits of using the drug outweigh the human health risks from use of the drug. [Bayer PFOF 1012; Cox (B-1901) P.12; ALJ Davidson's March 3, 2003, Order (OR31), P.1] As noted above, Bayer believes that in the first instance, CVM has not met its required burden of proof, and therefore Bayer is not required to demonstrate the safety of enrofloxacin. However, for the sake of argument, Bayer nevertheless believes that a full examination of the risks and benefits of enrofloxacin demonstrates that the continued benefits of enrofloxacin use clearly outweigh any minimal risks of use, therefore demonstrating that enrofloxacin is safe.

Because at the time of approval CVM did not consider any potential benefits to human health nor did they consider such benefits at the time of the Notice of Opportunity for Hearing [*see e.g.*, NOOH, NOH], a review of these benefits tracks a common theme in this hearing: new evidence, including evidence on the benefits of enrofloxacin, shows that the number of human cases of campylobacteriosis and FQ-resistant campylobacteriosis has decreased since the approval of enrofloxacin [G-748 P.2 and G-1791 P.5; Tr. P.143 L.15–P.144 L.7] while poultry

consumption has increased [Cox (B-1901) P.36], that the measures originally put in place to protect against antibiotic resistance are working, and that continued use of enrofloxacin produces demonstrable benefits to human health.

Significantly, the record demonstrates that Bayer's evidence on the human health benefits of enrofloxacin use is uncontroverted. CVM did not provide any evidence of its own with respect to the benefits, even though it had the opportunity to present rebuttal testimony, and it did not seek to controvert Bayer's evidence during the cross-examination process.

D. Enrofloxacin Is the Only Effective Treatment for Air Sacculitis

1. Air Sacculitis Is a Recurring Secondary Infection Common in Chickens

Although this case is primarily about *CP* infections in humans, chickens and turkeys do not get sick from *CP* [Wegener (G-1483) P.2 L.43–46; White (G-1484) P.2 L.42–43] and, in fact, enrofloxacin is not used to treat *CP* in chickens and turkeys. *E. coli*, on the other hand, is pathogenic to both chickens and turkeys and is the target pathogen for enrofloxacin. [Smith (B-1914) P.18 L.8–9; A-54] *E. coli* is a normal inhabitant of all poultry intestines and therefore will always be found in all broiler and turkey farms. [Hofacre (A-202) P.7 L.20–21] There is currently no vaccine for *E. coli* in either chickens or turkeys, and no effective means to eliminate it from the chicken or turkey breeding environment.

Air sacculitis is an infection of the air sacs by organisms such as *E. coli.* [Russell (B-1912) P.18 L.5] Respiratory *E. coli* is rarely a primary infection in chickens; rather, some other insult, typically a viral agent, damages either the non-specific and/or the specific defense mechanisms, allowing *E. coli* to penetrate beyond those barriers and set up infection. [B-1412; Smith (B-1914) P.18 L.9–11; Hofacre (A-202) P.8 L.12–17] *E. coli* is by far the most common secondary invader in respiratory disease in chickens. [B-1412; Smith (B-1914) P.24 L.15–16] A sufficient primary insult almost guarantees a secondary *E. coli* infection. [Smith (B-1914) P.18 L.15]

2. Enrofloxacin Is Efficacious for the Treatment of Air Sacculitis

It is undisputed that enrofloxacin is effective in treating air sacculitis. Enrofloxacin is approved for control of chicken mortality associated with *E. coli* susceptible to enrofloxacin. [JS 39] In fact, enrofloxacin is the most efficacious antibiotic available in the U.S. for treatment of *E. coli* infections in broiler chickens and *E. coli* and *Pasteurella multocida* infections in turkeys. [Glisson (B-1903) P.5 L.21–22] Therefore, it is also undisputed that all other alternatives to enrofloxacin are less effective.

3. There Are No Effective Alternative Treatments for Air Sacculitis Other Than Enrofloxacin

Poultry veterinarians have very few antibiotics available for treatment of *E. coli* infections. [Hofacre (A-202) P.24 L.2–3] The available options are to use those for which there is a specific label indication for *E. coli* and those for which AMDUCA allows the veterinarian to use his discretion for extra-label use.[16] [Hofacre (A-202) P.24 L.3–5] However, the evidence in this record reflects the undisputed testimony of practicing poultry veterinarians (including the current Acting Associate Dean of the University of Georgia School of Veterinary Medicine, John Glisson) who testified that there are no real alternatives to enrofloxacin. [Glisson (B-1903) P.12 L.3–4] This is significant because, while there may be other medications that are labeled for treatment of *E. coli*, as described below, each of these other medications have significant reasons why they are simply either ineffective or not safe as compared to enrofloxacin, and thus not a practical alternative. Tollefson conceded on cross-examination that, while CVM has knowledge of products which are approved for treatment of *E. coli*, CVM has no knowledge of what practicing veterinarians are actually using to treat diseases, and thus no knowledge of the current effectiveness of products in the field used by practicing veterinarians. [Tr. P.157 L.18–P.159 L.16] CVM's only other witness on enrofloxacin alternatives, Aarestrup, is not relevant here, as he is not a U.S. veterinarian and testified only with respect to alternatives available in Denmark.

[16]AMDUCA is the "Animal Medicinal Drug Use Clarification Act of 1994." *See* Pub. L.103-396. AMDUCA permits extra-label usage of animal drug products under certain circumstances. *See* 21 C.F.R. Part 530.

[Aarestrup (G-1451) P.3 L.15–19] Moreover, Aarestrup's testimony nevertheless acknowledged that there is no alternative treatment for *E. coli* in broilers. [Aarestrup (G-1451) P.3 L.23–24]

In general, the alternatives to enrofloxacin for therapeutic use in broilers are the tetracyclines and the sulfa drugs. [Glisson (B-1903) P.7 L.5–10; Hofacre (A-202) P.24 L.5–9; Wages (B-1917) P.19 L.6–9] CVM's interrogatory responses acknowledge this by only listing tetracycline drug products as products which are approved for oral use in chickens for the prevention, control, or treatment of *E. coli* infections in chickens: chlortetracycline, oxytetracycline, and tetracycline. [CVM Interrog. Ans. 87] The remaining products on CVM's list are injectable products for chickens 1 to 3 days old. [*Id.*]

However, tetracycline usage for treatment of *E. coli* infections in poultry is usually ineffective or poorly effective because of widespread resistance to tetracyclines among avian *E. coli* isolates. [B-1376; B-1379; B-1377; Glisson (B-1903) P.7 L.11–17; Wages (B-1917) P.19 L.1–2] Tetracyclines have been used for decades in the U.S. poultry industry, without veterinary prescription requirements, to treat *E. coli* infections. [B-1377; Glisson (B-1903) P.7 L.15–16] Nearly 90% of *E. coli* isolates are resistant to the tetracyclines. [Hofacre (A-202) P.27 L.2–3] High tetracycline resistance is seen in other surveillance systems as well. [Glisson (B-1903) P.7 L.4] Similarly, sulfa drugs are not a viable alternative to enrofloxacin. Sulfa drugs have also been available for decades in the U.S., and usage of sulfas has been very limited in recent years because of serious concerns about sulfa residues in poultry meat and poultry products. [Glisson (B-1903) P.8 L.9–11] Sulfa drugs typically have long withdrawal periods. Since respiratory disease in broilers usually occurs in the late stages of the production cycle, it is difficult to use a sulfa drug for treatment in broilers without risking product residues. [Glisson (B-1903) P.8 L.11–14]

As noted above, other available drugs with labeled indications for *E. coli* are injectable dosage forms only. For commercially grown broiler chickens and turkeys in the U.S., it is neither feasible nor practical to administer antibiotics on an individual bird basis. [JS 36] This

also limits the extra-label alternatives available under AMDUCA. For example, use of the aminoglycosides and cephalosporins are eliminated as an option due to their very poor absorption when administered orally. Although there is a label for streptomycin for water administration for *E. coli* therapy, clinical experience indicates it is not very efficacious. [Hofacre (A-202) P.24 L.9–14]

Glisson conducted a study to compare the efficacy of enrofloxacin, oxytetracycline, and sulfadimethoxine for the treatment of *E. coli* infections in broiler chickens. This study confirms the superior efficacy of enrofloxacin over the alternatives. [Glisson (B-1903) P.10 L.3–4] All parameters measured favored enrofloxacin treatment, but the two important factors, mortality and air sac lesions, provided the most striking evidence of the efficacy of enrofloxacin. Enrofloxacin treatment prevented all further *E. coli*-associated mortality and reduced air sac lesion scores very significantly. Oxytetracycline and sulfadimethoxine provided marginal mortality reductions when compared to the nonmedicated treatment and had essentially no effect on air sac lesion scores. [Glisson (B-1903) P.10 L.4–9]

Glisson's study reproduced very closely the effect seen when:

- enrofloxacin is used in the field to treat *E. coli* infections in broilers—typically a dramatic reduction in mortality and a dramatic reduction in the lesions in the respiratory tract at slaughter;

- oxytetracycline or sulfadimethoxine treatment is used in the field to treat *E. coli* infections in broilers—typically the reduction in mortality was entirely unacceptable in a commercial setting and those treatments had no real effect on internal lesions of the respiratory tract.

[Glisson (B-1903) P.10 L.10–16]

Glisson's study confirms that, while other products may contain label indications for *E. coli*, and AMUDCA permits other products to be used off-label, in fact, there are no suitable alternatives for enrofloxacin use.

E. Cross Contamination of Fecal Matter During Processing Is Responsible for Increased Levels of Human Pathogens on Poultry Products

At the processing level, the gut of live birds is the principal source of *CP* spp. and can be transferred from bird to bird during slaughter and processing. [Logue (G-1464) P.2 L.16–17] In addition, stresses associated with transporting poultry from farms to commercial slaughter facilities prior to slaughter, such as the actual transport, pre-slaughter holding, and feed withdrawal, can increase pathogen populations such as *Salmonella* and *CP* in the intestinal tract, fecal material, and on carcass exteriors and can result in poultry being presented for processing with greater bacterial carcass contamination levels than compared to what was on the birds originally at the farm. [Logue (G-1464) P.2 L.4–10]

As compared to turkeys, the slaughter and processing of broilers is highly automated. [Minnich (G-1467) P.2 L.16–18; Gonder (A-201) P.12 L.4–5] Therefore, size variations are problematic because processing equipment is set for the average size of a uniform flock. [Hofacre (A-202) P.9 L.16–17] During slaughter, intestinal contents of poultry may spread on the carcasses causing contamination of end-products. [Jacobs-Reitsma (G-1459) P.2 L.19–21] This includes the evisceration process, where there is a risk of cross-contamination due to the breakage of intestinal contents by the plant employees or their equipment. The intestinal contents (and pathogens such as *CP* contained within the intestines) can then be spread between animals. [Minnich (G-1467) P.9 L.8–12] Feces can, and will, contaminate the animal carcass during slaughter and, consequently, *CP* is transferred to carcass surfaces during processing of the fresh meat products. [Wegener (G-1483) P.4 L.25–27] Poultry carcasses can then provide a significant source of bacterial cross contamination (including *CP* spp.) of other carcasses and the processing equipment at commercial processing, influencing overall contamination rates at the production level. [Logue (G-1464) P.2 L.11–14] Research has demonstrated that fecal contamination on carcasses as the result of processing errors may increase pathogen loads. [Russell (B-1912) P.38 L.16–17] Renwick (1993) demonstrated that visible fecal contamination

on carcasses had a significant impact on the microbiological profile of roaster chickens. [Russell (B-1912) P.38 L.17–19] Therefore, gut ruptures or other processing cuts or tears by the automated machinery or otherwise will be responsible for increased levels of human pathogens on the birds, including *CP*, *Salmonella*, and other human pathogens.

F. Air Sacculitis Positive Birds Not Treated with Enrofloxacin Have Higher Pathogen Levels of *Campylobacter* and Other Human Pathogens

1. Sick Birds Have More Fragile Intestines Which Are More Likely to Be Ruptured During Processing

A common trait of both broilers and turkeys is that when they get sick, they "go off feed," i.e., stop eating. [Russell (B-1912) P.16 L.13–14; Wages (B-1917) P.11 L.21–22] Chickens respond to illness similarly to people in that an infection results in fever. The fever causes the animal to decrease feed consumption. [Russell (B-1912) P.16 L.14–15] As a result, its intestines become fragile. [Gonder (A-201) P.22 L.18–20; Wages (B-1917) P.11 L.22] This can be due to increased water consumption, actual intestinal disease resulting in edema of the wall of the intestines (coccidiosis, *E. coli*), or changes in the bacterial population of the intestines due to altered eating patterns (necrotic enteritis), leading to diarrhea, gas, and actual damage to the intestinal lining. [Gonder (A-201) P.22 L.20–23] In modern processing facilities, if the intestine of the birds are weak, they are much more likely to be cut, torn, or ruptured during automated viscera removal. [Russell (B-1912) P.16 L.17–19] Ultimately, poultry that becomes ill from systemic *E. coli* infections will at the very least become depressed (increased morbidity) and stop eating (poor growth and poor feed efficiency). [Hofacre (A-202) P.9 L.11–13] If left untreated, many will die (increased mortality). Those that survive will usually be smaller, so the flock will have increased variability in body weight (poor uniformity). [Hofacre (A-202) P.9 L.13–15]

When birds "go off feed," they are also more susceptible to enteric problems, including parasites such as coccidiosis and the overgrowth of pathogenic bacteria such as *Salmonella*. [Russell (B-1912) P.17 L.3–5] The importance of this is that studies indicate that broiler

chickens and turkeys that "go off feed" early are more likely to be populated with both *CP* and *Salmonella*. [Russell (B-1912) P.17 L.16–18] Conversely, healthier poultry generally are more resistant to colonization by *Salmonella* and *CP* and are less likely to be subjected to processing errors due to gut tears or cuts or lack of flock uniformity. [Robach (B-1911) P.16 L.2–4]

2. The Presence of Air Sacculitis in Chickens at Processing Contributes to Reduced Carcass Weight and Uniformity, Increased Fecal Contamination, and Increased Processing Errors and Results In Increases in Microbiological Contamination

In 2002, Russell conducted a study to test the interrelationship of pre-chiller microbial loads and the disease condition of incoming live broilers. As described below, the study demonstrated that broilers that had air sacculitis and were not treated with FQs were underweight and less uniform. The presence of air sacculitis resulted in significantly higher rates of processing errors, leading to significantly higher fecal contamination, and increased microbial contamination, as measured by increased populations of *CP* and *E. coli*. [Russell (B-1912) P.20 L.1–6]

The study compared air sacculitis-positive birds to air sacculitis-negative birds using four criteria: carcass weight and uniformity; fecal contamination; processing errors; and microbiological contamination. [Russell (B-1912) P.21 L.9–P.22 L.22] During the conduct of the study, Russell worked at the initial processing stage, first to determine whether field reports indicated that air sacculitis positive flocks were to be processed. Air sacculitis-positive and air sacculitis-negative flocks were paired into 5 replications chronologically as they presented to the plant. None of the chickens evaluated in this study were treated using FQs, while some flocks, both air sacculitis-positive and air sacculitis-negative, were treated with tetracycline and sulfa drugs. [Russell (B-1912) P.20 L.7–21]

Carcasses were chosen randomly by picking a particular carcass and removing the fifth carcass on the line from the chosen carcass. For each measured criteria, broiler chicken carcasses were collected prior to the inside/outside bird washer (IOBW) in each of 5 replicate

trials over a 5-day sampling period. For carcass weight and uniformity, one hundred carcasses were collected from a flock containing high levels of air sacculitis and 100 were collected from a flock containing low levels of air sacculitis in each trial for a total of 1,000 carcasses. The carcasses were weighed and weights were recorded. [Russell (B-1912) P.21 L.1–14]

This same process was repeated to measure fecal contamination. Thus, also prior to the IOBW, one hundred carcasses were collected from a flock containing high levels of air sacculitis and 100 were collected from a flock containing low levels of air sacculitis in each trial for a total of 1,000 carcasses. [Russell (B-1912) P.21 L.15–20] Each replicate trial was then tested for fecal contamination. [*Id.*] The percentage of carcasses that were positive was recorded. [*Id.*] After evisceration, but prior to USDA inspection, carcasses were also tested for processing errors. [Russell (B-1912) P.22 L.1–9] For each carcass, the entire digestive tract (except for the crop) was removed and examined for processing errors, such as cuts or tears. [*Id.*] The proventriculus, gizzard, duodenal loop, small intestines, ileal junction, and ceca were inspected and cuts or tears were expressed as percent positive for each location in the digestive tract for each group of 100 carcasses. [*Id.*]

Finally, a microbiological evaluation was performed on 40 carcasses, collected before the IOBW in each replicate trial. [Russell (B-1912) P.22 L.10–22] Twenty were collected from air sacculitis-positive flocks and twenty from air sacculitis-negative flocks. [*Id.*] Samples were numerically coded to prevent identification of samples from air sacculitis-positive and air sacculitis-negative flocks by technicians responsible for testing the samples, as a means of eliminating bias. [*Id.*] All rinsates were transported to ABC laboratories in Gainesville, Fla. [*Id.*] *CP spp.* were enumerated using the Cefex method described by Line. *Escherichia coli* were enumerated using Petrifilm *E. coli* count plates (AOAC approval number 991.14). [*Id.*]

The results from Russell's study show that flocks of chickens with air sacculitis infections are significantly more likely to: 1) weigh less than uninfected birds, 2) be contaminated with fecal material during processing; 3) have a processing error or multiple

processing errors during venting, opening, and evisceration; and 4) have higher *CP* counts. [Russell (B-1912) P.26 L.8–11] Specifically, the data showed the following: 1) air sacculitis-positive flocks were consistently lower in weight than the air sacculitis-negative flocks in all 5 Replications [Russell (B-1912) P.23 L.2–3]; 2) the presence of air sacculitis significantly increased fecal contamination in 4 of 5 Replications [Russell (B-1912) P.23 L.21–22]; 3) the presence of air sacculitis significantly increased the number of processing errors observed where, for example, the total combined cuts or tears were much higher on air sacculitis-positive carcasses at 42, 49, 37, 60, and 59 % as compared to 14, 12, 17, 24, and 16 % for air sacculitis-negative carcasses for the 5 Replications [Russell (B-1912) P.24 L.4–5, 11–13]; and 4) finally, in three of five replications, the presence of air sacculitis in the flocks significantly ($P \leq 0.05$) increased the number of *CP* recovered from broiler carcasses, while in two of the replications *E. coli* counts for air sacculitis-positive flocks were significantly higher. [Russell (B-1912) P.25 L.8–9, 17–18]

Russell's study provides evidence, undisputed by CVM, that flocks of chickens showing air sacculitis, untreated with FQs, have lower weights, more fecal contamination, more processing errors, and higher levels of *CP*. This translates into higher levels of pathogens present on food and increased incidences of subsequent foodborne bacterial infection in humans. As described below, Bayer quantifies this level of increased infections were enrofloxacin's approval to be withdrawn.

G. A Withdrawal of Enrofloxacin Would Lead to Human Health Harm

Although CVM's RA does not do so, Bayer has quantified the increase in human health risks that would be caused by a withdrawal of enrofloxacin, or, in other words, the benefits of the use of enrofloxacin on human health. Based on data from Russell's study, Bayer has calculated that the withdrawal of enrofloxacin will greatly increase human health risks from campylobacteriosis and salmonellosis. [Cox (B-1901) P.7 L.15–18, P.25, P.83–87] As noted above, Bayer's submitted testimony on the calculation of benefits is uncontroverted, in that

CVM neither provided its own testimony or data on the benefits of enrofloxacin use (despite being given an opportunity for rebuttal testimony) nor questioned Bayer's calculation of benefits during cross examination.

1. Bayer's Model Provides a Reasonable Estimate of the Benefits of Enrofloxacin Use

To quantify the increase in human health risks that would be caused by the withdrawal of enrofloxacin, Bayer's expert applied a farm-to-fork risk assessment model using the data of Russell's study to estimate the change in the probability distribution of microbial loads due to the withdrawal of enrofloxacin. [Cox (B-1901) P.83–87] The model assumes a 1% value for the fraction of U.S. broilers receiving enrofloxacin, which is higher than recent levels. [*Id.*] In the absence of enrofloxacin, farmers are assumed to use less effective alternatives such that half of chickens now treated with enrofloxacin would remain air sacculitis positive. [*Id.*] Thus, the model assumes that only 0.5% of processed chickens will be subject to the microbial load increase. [*Id.*] Nevertheless, as described below, even an increase in microbial load of only 0.5% of the total number of broilers processed (8.6 billion in 2001) leads to significant additional cases of both campylobacteriosis and salmonellosis.

2. A Withdrawal of Enrofloxacin Would Lead to an Increase in Campylobacteriosis

Bayer calculates the increase in mean days of illness due to higher microbial loads of *CP* in chicken servings if enrofloxacin is withdrawn to be 143,224.5 $\pm$ 45,754.5 days. [Cox (B-1901) P.85] In comparison, the baseline version of the Cox-Popken (2002) model predicts 2,814 treatment failures per year averted by a withdrawal of enrofloxacin, using most of CVM's assumptions, but with a corrected p_{rh} value of 0.064 and a 20% chicken-attributable risk. This corresponds to 5,628 illness-days if, for the purposes of discussion, the Marano estimate of 2 average excess days of illness per case is applied. [*Id.*]

Thus, in the base case, a withdrawal of enrofloxacin is expected to create approximately 143,224.5/5628 = 25 new days of *CP* illness due to increased microbial loads, for each hypothetical excess day of illness prevented. [*Id.*]

However, if a forty-fold correction factor is introduced to reflect that most ciprofloxacin prescriptions may be effective against FQ-resistant *CP*, then the withdrawal would be estimated to cause an excess 1000 days of illness per illness-day prevented. Thus, under CVM's assumptions about days of illness, the human health harm-to-benefit ratio from the proposed withdrawal of enrofloxacin is estimated to be at least one to three orders of magnitude (25 to 1000), depending on how the probability of treatment failure is modeled (effectively 100% according to CVM, or as low as 2.5% suggested by the one data point reported in Piddock, 1999). [*Id.*]

The large ratio of health harm to health benefit arises in part from the undisputed fact that FQ-sensitive *CP* cases vastly outnumber FQ-resistant *CP* ones. [Cox (B-1901) P.85] Thus, a risk management action, such as the proposed enrofloxacin withdrawal, that increases the former in order to decrease the latter leads to a large net loss in health. [*Id.*]

3. A Withdrawal of Enrofloxacin Would Also Lead to an Increase in Other Foodborne Diseases Such As Salmonellosis

Bayer also calculated that a withdrawal of enrofloxacin would lead to an increase in other foodborne illnesses, such as salmonellosis. Applying the CVM approach to risk estimation to the Russell data (i.e., assuming that excess illness-days are directly proportional to prevalence of contaminated carcasses) indicates that about 97 excess illness-days from salmonellosis would be created per hypothetical FQ-resistant campylobacteriosis illness day prevented, as well as an excess of 60 fatalities per year from increased *Salmonella* infections. [Cox (B-1901) P.86–87]

Withdrawal of enrofloxacin is expected to create approximately 97 new days of *Salmonella* illness due to increased microbial loads for each hypothetical excess day of *CP* illness prevented.

Further, invasive cases of *Salmonella* are fatal much more often than with *CP*. The evidence shows 63 additional fatalities from *Salmonella* annually due to a withdrawal of enrofloxacin. [Cox (B-1901) P.86]

Excess illnesses due to other pathogens are even harder to estimate from the scarce available data but certainly will occur.

Thus, added together, a withdrawal of enrofloxacin would result in an estimated 60 fatalities per year from increased *Salmonella* infections, in addition to 97 new days of *Salmonella* illness due to increased microbial loads for each hypothetical excess day of *CP* illness prevented.

H. When Weighed with These Benefits, It Is Clear That Enrofloxacin Is Safe for Use in Chickens Because the Benefits of Continued Use of Enrofloxacin Outweigh Any Potential Risks

Bayer's analysis of these data demonstrates, unrefuted by any evidence in the record, that the benefits of continued use of enrofloxacin outweigh any potential risks raised by CVM. Thus, an evaluation of the safety of the product, as required by the D.C. Circuit to include both risks and benefits, shows that, even assuming the risks alleged by CVM, the product remains safe.

III. CVM HAS NOT MET ITS BURDEN OF SHOWING THROUGH NEW EVIDENCE THAT ENROFLOXACIN USE IN TURKEYS RAISES SUFFICIENTLY SERIOUS QUESTIONS ABOUT SAFETY

Bayer adopts and incorporates the argument that CVM has not met its burden of showing through new evidence that enrofloxacin use in turkeys raises sufficiently serious questions about safety, as set forth in the AHI Brief, pp. 33–46.

IV. ENROFLOXACIN IS SAFE FOR USE IN TURKEYS BECAUSE THE BENEFITS TO HUMAN HEALTH FROM ENROFLOXACIN USE IN TURKEYS OUTWEIGH ANY POTENTIAL RISKS

Bayer adopts and incorporates the argument that enrofloxacin is safe for use in turkeys because the benefits to human health from enrofloxacin use in turkeys outweigh any potential risks, as set forth in the AHI Brief, p. 46

V. CONCLUSION

The credible evidence introduced by CVM, fairly viewed in its totality, does not meet the statutory burden because it is either not new, not reliable, and/or otherwise does not provide a reasonable basis to raise a serious question about the safety of the use of enrofloxacin in chickens or turkey. In fact, Bayer's recent and credible data, most reflective of the conditions of use of enrofloxacin in the U.S., demonstrates a lower potential risk to human health, after enrofloxacin was found safe in 1996, than before. This is true whether the adverse health consequence is viewed as the risk of campylobacteriosis, of FQ-resistant campylobacteriosis, or the risk that FQ-resistant campylobacteriosis will result in additional adverse health consequences beyond that of susceptible campylobacteriosis.

Even assuming arguendo that CVM has raises a serious question about the safety of enrofloxacin use in chickens and turkeys, the credible, reliable evidence fairly viewed in its totality demonstrates that risks are small and that the uncontroveted benefits of use of enrofloxacin far exceed the potential risks. Accordingly, enrofloxacin use is safe and there is no basis to withdraw NADA 140-828 for either the chicken or turkey indication.

BAYER'S PROPOSED FINDINGS OF FACT/CONCLUSIONS OF LAW

1. Enrofloxacin was found to be safe under the conditions of use upon the basis of which the application was approved when FDA approved its use in chickens and turkeys in 1996. [JS 26]

2. CVM was aware of pre-approval studies in the scientific literature, including those by Endtz [G-190], Piddock [G-505], Reina [G-529, G-530], and Velazquez [G-671] describing selection for, emergence of, and dissemination of fluoroquinolone-resistant *Campylobacter* arising from enrofloxacin use in poultry in other countries. [Bayer Brief P.9]

3. CVM's evidence regarding the purported inadequacy of labeling conditions to prevent resistance is not new evidence because the U.S. approval conditions imposed by CVM are virtually identical to those used in the Netherlands prior to U.S. approval of enrofloxacin usage. CVM was aware of the Netherlands conditions of use prior to its approval of enrofloxacin and thus could not have been surprised if it saw post-approval increases in fluoroquinolone-resistant *Campylobacter* in human and poultry isolates in the U.S. of the same magnitude seen in the Netherlands. [Bayer Brief P.11, 18]

4. The McDermott study [B-868] regarding the development of resistant *Campylobacter* is not new evidence because its implications are the same as the 1994 study by Jacobs-Reitsma, namely that the use of fluoroquinolones according to label indications does not eliminate *Campylobacter* from the intestinal tract of chickens, but, rather, rapidly selects for fluoroquinolone-resistant isolates. [Bayer Brief P.10]

5. None of the studies upon which CVM now relies shows that the degree to which selection pressure, emergence, or dissemination of fluoroquinolone-resistant *Campylobacxter* occurs is any different from that which was known prior to 1996. [Bayer Brief P.7-11]

6. CVM's evidence on the selection for, emergence, and dissemination of fluoroquinolone-resistant Campylobacter from use of enrofloxacin in poultry does not constitute new evidence, because it contains no findings or conclusions different from what CVM considered, understood, and accepted during the enrofloxacin application process. [Bayer Brief P.7-11]

7. *Campylobacter* spp., including fluoroquinolone-resistant *Campylobacter*, has been widely documented in human, agricultural, and industrial wastewater and in the treated wastewater effluents discharged to the environment. [Bayer Brief P.12]

8. Fluoroquinolone use in chickens and turkeys is not the only factor resulting in colonization by fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. Fluoroquinolone-resistant Campylobacters may be isolated from poultry as a direct result of either the fluoroquinolone treatment of *Campylobacter*-infected poultry or the acquisition by poultry of already fluoroquinolone-resistant organisms. [Bayer Brief P.13]

9. Fluoroquinolone-resistant *Campylobacter* are naturally present in the environment and are found in poultry even where flocks have not been treated with fluoroquinolones. [Bayer Brief P.13-14]

10. Studies such as Svedhem [B-1851] and Berndtson [G-62] showing quinolone and fluoroquinolone resistant *Campylobacter* in poultry in the absence of fluoroquinolone use in poultry, and studies such as Svedhem [B-1851] and Hollander [B-1936] showing quinolone resistant *Campylobacter* in humans in the absence of fluoroquinolone use in poultry, demonstrate that there are factors contributing to both human and poultry colonization or infection with fluoroquinolone resistant *Campylobacter* other than enrofloxacin use in poultry. [Bayer Brief P.12-14]

11. Studies in the U.S. showing quinolone and fluoroquinolone resistant *Campylobacter* in people before enrofloxacin or any fluoroquinolone was approved for use in poultry, such as Barrett's 5% resistance in 1988 [Barrett (G-1453) P.3 L.3-10; G-1609], William's 3.3% resistance in 1993 [B-67], Kiehlbach's 12% resistance in 1992–1995 [B-39 P.3], Smith's 6% resistance in 1995 [G-589 P.3], and Nachamkin's 20% resistance in 1995 [G-1517 P.11, Graph] demonstrate that there are factors contributing to human infection with fluoroquinolone resistant *Campylobacter* other than enrofloxacin use in poultry. [Bayer Brief P.13-14]

12. The pre-approval percentage of fluoroquinolone-resistant *Campylobacter* in humans shown by the available evidence, 5% [Barrett (G-1453) P.3 L.3-10; G-1609], 3.3% [B-

67], 12% [B-39 P.3], 6% [G-589 P.3], and 20% [G-1517 P.11, Graph] is of the same magnitude as the post-approval resistance demonstrated by NARMS, 13% - 19%.[Bayer Brief P.36]

13. If the pre-approval percentage of fluoroquinolone-resistant *Campylobacter* in humans shown by the available evidence is of the same magnitude as the post-approval resistance demonstrated by NARMS, enrofloxacin use in poultry is not responsible for any increase in the levels of fluoroquinolone resistance observed in humans. [Bayer Brief P.12]

14. If enrofloxacin use in poultry is not responsible for any increase in the levels of fluoroquinolone resistance observed in humans, there cannot be a reasonable basis seriously to question the safety of enrofloxacin use in poultry.

15. The McDermott study [B-868] is not reliable to demonstrate any connection between enrofloxacin use in poultry and findings of fluoroquinolone-resistant *Campylobacter* in retail chicken because it does not realistically simulate enrofloxacin usage in the broiler industry, and instead uses unusually high dosage rates and long treatment duration not seen in actual practice. This study overstates the effect of enrofloxacin usage and its results cannot realistically be related to the actual usage of enrofloxacin. [Bayer Brief P.15]

16. Evidence shows that after treating broiler chickens with the industry standard dosage, susceptible *Campylobacter* begin to displace resistant *Campylobacter* about 8 days after treatment and continue to displace the resistant *Campylobacter*. [Bayer Brief P.15]

17. CVM's evidence on selection for, emergence, and dissemination of fluoroquinolone-resistant *Campylobacter* does not provide a reasonable basis to raise serious questions about enrofloxacin's safety.

18. Before fluoroquinolones were approved for use in chickens and turkeys in the U.S., CVM management understood and accepted that articles by Endtz and others posited a temporal association between the use of fluoroquinolones in chickens in Europe and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans in Europe. Also before approval, CVM management understood and accepted that fluoroquinolone-resistant *Campylobacter* infections have the potential adversely to affect human health. [JS 5; Bayer Brief P.17]

19. The Joint Advisory Committee convened by CVM considered and understood that resistant microbes that are zoonotic organisms "will and can transfer between human and animal populations" [G-219 P.144] and acknowledged Endtz's report of transfer of zoonotic *Campylobacter* from poultry to man in the Netherlands [B-1819 P.61] and that "[resistant] bacteria that were selected . . . could move from the poultry to the people." [B-1819 P.105]. [Bayer Brief P.18]

20. Before enrofloxacin was approved for use in chickens and turkeys, CVM director Sundlof raised concerns about foodborne campylobacteriosis due to consumption of poultry and the risks of "superimposing" bacterial resistance on the already "significant public health problem" of foodborne disease. [Bayer Brief P.18]

21. There is no evidence that the risk of acquiring a fluoroquinolone-resistant *Campylobacter* infection by humans in the U.S. is different than was anticipated by CVM when enrofloxacin was approved in 1996. [Bayer Brief P.17-18]

22. CVM's evidence showing that fluoroquinolone-resistant *Campylobacter* in poultry can be transferred to humans and can contribute to fluoroquinolone-resistant *Campylobacter* infections in humans is not new evidence because CVM considered, understood, and accepted that such transfer could occur prior to its approval of enrofloxacin in 1996. [Bayer Brief P.17-18]

23. There is no evidence that the risk of acquiring a fluoroquinolone-resistant *Campylobacter* infection by humans in the U.S. is greater after the approval of enrofloxacin than before approval, and, in fact the risk has decreased. [Bayer Brief P.20]

24. In the U.S., chicken consumption per capita has steadily increased after enrofloxacin was introduced for poultry in 1996. Nevertheless, overall campylobacteriosis incidence has steadily decreased after enrofloxacin was approved for poultry. Therefore, U.S. chicken consumption data do not reflect that chicken is much of a source of campylobacteriosis. [Bayer Brief P.20]

25. Estimates of the incidence of fluoroquinolone-resistant *Campylobacter* infections in the U.S. show the incidence has declined since enrofloxacin's approval. From 1997 to 2001 (the post-approval time period for which data is available) the estimated incidence of fluoroquinolone-resistant *Campylobacter* cases in humans has decreased from 3.28 per 100,000 in 1997 to 2.62 per 100,000 in 2001. [Bayer Brief P.20]

26. The most recent, relevant, and robust U.S. data demonstrate that poultry is less of a cause of campylobacteriosis than previously believed at the time CVM concluded enrofloxacin use is safe. The data show there is now less risk of acquiring a *Campylobacter* infection than was anticipated when enrofloxacin was approved. [Bayer Brief P.23]

27. CVM's studies intended to show that fluoroquinolone-resistant *Campylobacter* in poultry can be transferred to humans and can contribute to fluoroquinolone-resistant *Campylobacter* infections in humans fail to raise serious questions about enrofloxacin's safety. [Bayer Brief P.19-51]

28. Recent studies support that there are multiple possible sources of human *Campylobacter* infections and that chicken is now less of a source of campylobacteriosis than was believed when enrofloxacin was approved for use. [Bayer Brief P.31]

29. There have been vast enhancements in the awareness of the risks of foodborne bacterial illness in the U.S. since 1996, resulting in major improvements in food safety. Poultry-related improvements include adoption of the Hazard Analysis Critical Control Points, poultry safety labeling, FDA approval of poultry irradiation, improved consumer preparation and handling practices, and changes in poultry marketing and distribution. These improvements result in reductions in the risk of campylobacteriosis. [Bayer Brief P. 23]

30. Bayer obtained the raw data from NARMS, the Smith study [G-589], the Effler study [G-185] and the CDC 1998 - 1999 *Campylobacter* case control study for analysis by its witnesses. [Bayer Brief P.33, 64, 68]

31. The epidemiological studies evaluating risk factors for campylobacteriosis on which CVM relies to support its claim that poultry is a primary source of *Campylobacter* infections in the U.S. are not relevant or probative in light of the more recent and more robust CDC 1998–1999 *Campylobacter* case control study data. Foreign studies from the 1980s and early 1990s such as G-10, G-182, G-334, G-1680, B-561, and G-1718 are not relevant to the risk factors for acquiring a *Campylobacter* infection in the U.S. in the late 1990s. Similarly, the primary U.S. studies on which CVM relies, such as Harris (1986) [G-268] and Deming (1987) [G-162] are outdated and not representative of the current U.S. population. The Harris and Deming findings do not take into account changes in poultry production practices due to HACCP, nor do they take into account consumer behavior changes relating to foodborne disease prevention. [Bayer Brief P.22-23]

32. Analyzing data from the CDC 1998–1999 *Campylobacter* case control study, Friedman found no risk associated with eating chicken or turkey at home. [Bayer Brief P.20]

33. Analyzing data from the CDC 1998–1999 *Campylobacter* case control study, Friedman calculated a population attributable fraction for chicken eaten in a commercial establishment of 24% and a population attributable fraction for non-poultry meats of eaten in a commercial establishment of 21%. This raises the question of whether the risk is chicken or some non-chicken source of *Campylobacter* present in restaurants. [Bayer Brief P.24, 57]

34. Analyzing data from the CDC 1998–1999 *Campylobacter* case control study, Kassenborg found that eating any meat at home, including chicken and turkey, was not a statistically significant risk factor for acquiring a fluoroquinolone-resistant *Campylobacter* infection. [Bayer Brief P.26-28]

35. Analyzing data from the CDC 1998–1999 *Campylobacter* case control study, Kassenborg performed backwards step-wise conditional logistic regression analysis to determine if any of the risk factors being studied were statistically significantly associated with fluoroquinolone-resistant campylobacteriosis, and she found that none of the risk factors (including any related to poultry) were significantly associated with fluoroquinolone-resistant campylobacteriosis, but did not publish those results. [Bayer Brief P.28-29, 57]

36. Data from the CDC 1998–1999 *Campylobacter* case control study as analyzed and reported on by Friedman [G-1488] and Kassenborg [G-338] show that poultry overall is not a cause of *Campylobacter* infections or fluoroquinolone-resistant *Campylobacter* infections in humans. These data therefore are not sufficient to raise serious questions about the safety of enrofloxacin. [Bayer Brief P.23-29]

37. Smith's [G-589] use of genetic typing to establish that poultry is a source of fluoroquinolone-resistant *Campylobacter* infections in humans is unreliable because accepted scientific methods discourage reliance on genetic typing evidence in isolation, without the support of properly-conducted epidemiological studies to establish a link between poultry and infections. [Bayer Brief P.27]

38. The Smith study [G-589] fails to identify chicken as a risk factor in the epidemiological portion of the study but then relies on genetic typing data to reaches an unsupported conclusion that poultry is a source of fluoroquinolone-resistant *Campylobacter*. [Bayer Brief P.27]

39. CVM's temporal evidence is unreliable and does not raise serious questions about the safety of enrofloxacin because there are numerous examples of countries that do not fit CVM's temporal model and because in the U.S. there is no clear temporal trend of increasing fluoroquinolone-resistant infections in humans after enrofloxacin approval. [Bayer Brief P.34-44]

40. A temporal relationship is not the same as a causal relationship. [Bayer Brief P.41]

41. Studies in the U.S. showing quinolone and fluoroquinolone resistant *Campylobacter* in people before enrofloxacin or any fluoroquinolone was approved for use in poultry, such as Barrett's 5% resistance in 1988 [Barrett (G-1453) P.3 L.3-10; G-1609], William's 3.3% resistance in 1993 [B-67], Kiehlbach's 12% resistance in 1992–1995 [B-39 P.3], Smith's 6% resistance in 1995 [G-589 P.3], and Nachamkin's 20% resistance in 1995 [G-1517 P.11, Graph] demonstrate that prior to 1996 there was already a significant level and increasing trend of fluoroquinolone-resistance in human *Campylobacter* isolates in the U.S. at levels shown by NARMS' post-approval monitoring. [Bayer Brief P.36]

42. CVM's retail studies are not representative of the entire U.S. poultry market because the samples are small and not a statistically valid random sample of U.S. poultry production. [Bayer Brief P.46-48]

43. CVM's retail studies introduce confounding factors and render the results unreliable. For example, *Campylobacter* will not multiply outside the host gut and do not tolerate exposure to atmospheric oxygen or to drying, but in the retail studies food samples are typically enriched and cultured for *Campylobacter* so that detection of small numbers of sub-lethally damaged cells is promoted. [Bayer Brief P.46-47]

44. CVM's retail studies provide no information on the issue of dose, even though CVM concedes that the risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *Campylobacter* ingested. [Bayer Brief P.48]

45. Nothing in the retail studies CVM put into evidence demonstrates that the reported fluoroquinolone-resistant *Campylobacter* are present in sufficient quantity to render an infective dose. [Bayer Brief P.48]

46. CVM's retail studies do not raise serious questions about the safety of enrofloxacin in light of the fact that Friedman [G-1488] shows that chicken and turkey purchased at the supermarket and eaten at home is associated with a reduced risk of campylobacteriosis. [Bayer Brief P.48-49]

47. CVM's retail studies do not raise serious questions about the safety of enrofloxacin. [Bayer Brief P.46-50]

48. The CVM RA uses non-representative and outmoded data. [Bayer Brief P.27-29,58-62, 66-68]

49. The CVM RA fails to comport with accepted guidelines and standards for the conduct of quantitative risk assessments. [AHI Brief P.15-27]

50. The CVM RA fails to provide evidence of the objective nature and extent of the human health impact from use of enrofloxacin in chickens. [Bayer Brief P.55-76]

51. The CVM RA is contradicted by relevant data, and overstates the human health impact it was intended to quantify. [Bayer Brief P.63-76]

52. The CVM RA does not provide a reasonable basis to raise a serious question about the safety of enrofloxacin use in chickens. [Bayer Brief P.55-76]

53. The CVM RA does not provide a reasonable basis to raise a serious question about the safety of enrofloxacin use in turkeys. [Bayer Brief P.55-76]

54. The CVM RA is not reliable to assess the risks and adverse human health consequences of the use of enrofloxacin in poultry. [AHI Brief 16-30; Bayer Brief P.55-76]

55. CVM's evidence relating to the transfer of fluoroquinolone-resistant *Campylobacter* from poultry to humans and its contribution to fluoroquinolone-resistant *Campylobacter* infections in humans fails to raise serious questions about the safety of enrofloxacin. [Bayer Brief P.18-55].

56. CVM has presented no new evidence that fluoroquinolone-resistant *Campylobacter* illnesses in humans have the potential to affect human health any differently from fluoroquinolone-susceptible *Campylobacter* illnesses. [Bayer Brief P.76-82]

57. Before approval of enrofloxacin in 1996, CVM understood and accepted that use of enrofloxacin in chickens and turkeys could lead to fluoroquinolone-resistant *Campylobacter* infections in humans. [Bayer Brief P.7-11]

58. Before approval of enrofloxacin in 1996, CVM understood and accepted that fluoroquinolone-resistant *Campylobacter* infections have the potential adversely to affect human health. [Bayer Brief P.76-82]

59. CVM considered, prior to approving enrofloxacin for use in chickens and turkeys, that treatment failure was possible if diarrhea from resistant *Campylobacter* is treated with fluoroquinolones. [Bayer Brief P.76-82]

60. CVM's evidence on adverse human health impacts is not new evidence as required by the FFDCA. [Bayer Brief P.76-82]

61. Foreign travel is a statistically significant risk factor for acquiring fluoroquinolone-resistant *Campylobacter* infections. Foreign travel is a statistically significant risk factor for having a longer duration of diarrhea. Therefore, foreign travel is a confounding variable in case-control studies that are evaluating the risk of acquiring a fluoroquinolone-resistant infection and on the effect of fluoroquinolone-resistance on duration of diarrhea, and therefore must be controlled for in such studies.[Bayer P.27-28, 32]

62. Prior use of a fluoroquinolone is a confounding variable in case-control studies that are evaluating the risk of acquiring a fluoroquinolone-resistant infection and on the effect of fluoroquinolone-resistance on duration of diarrhea, and therefore must be controlled for in such studies. [Bayer P.27]

63. The Smith case comparison study [G-589] and the Nelson/McClellan analysis of the CDC 1998–1999 *Campylobacter* case-control study data [G-1679, G-1489] attempted to evaluated the effect of fluoroquinolone-resistance on duration of diarrhea but did not control for foreign travel or prior fluoroquinolone use. [Bayer P.52, 60]

64. When the Smith data [G-589] are properly adjusted for foreign travel and prior fluoroquinolone use, there is no difference in duration of illness. Smith acknowledged on cross-examination that when considering only domestically acquired cases, there is no statistically significant association between fluoroquinolone resistance and longer duration of diarrhea. [Bayer P.52, 60]

65. When the CDC 1998–1999 *Campylobacter* case-control study data are properly adjusted for foreign travel and prior fluoroquinolone use, there is no difference in duration of illness in domestically acquired cases of resistant and susceptible cases of campylobacteriosis. [Bayer Brief P.60]

66. CVM's studies, when analyzed according to reliable scientific standards show no increase in the duration of illness as a result of fluoroquinolone-resistant *Campylobacter* infections, compared to non-resistant infections. [Bayer Brief P.52, 60]

67. CVM's studies, when analyzed according to reliable scientific standards show no increase in the complications as a result of fluoroquinolone-resistant *Campylobacter* infections, compared to non-resistant infections. [Bayer Brief P.72, 74]

68. CVM's studies, when analyzed according to reliable scientific standards show no increase in hospitalizations as a result of fluoroquinolone-resistant *Campylobacter* infections, compared to non-resistant infections. [Bayer Brief P.72]

69. There is no evidence in the record of increased mortality as a result of fluoroquinolone-resistant *Campylobacter* infections, compared to non-resistant infections. [Bayer Brief P.72]

70. Evidence in the record, such as B-1920, P.4 and B-50, P.2, demonstrates that so-called resistant infections can be successfully treated with fluoroquinolones. [Bayer Brief P.72-74]

71. CVM's evidence on adverse human health impacts does not provide a reasonable basis to raise serious questions about the safety of enrofloxacin. [Bayer Brief P.71-75]

72. In the U.S., enrofloxacin is used sparingly, only by prescription and only under veterinary supervision. Enrofloxacin is used only for therapeutic purposes and never for growth promotion. [Bayer Brief P.14]

73. In the U.S., the number of human cases of campylobacteriosis and fluoroquinolone-resistant campylobacteriosis has decreased since the approval of enrofloxacin. [Bayer Brief P.20]

74. Air sacculitis is a recurring secondary infection common in chickens. Chickens with air sacculitis are more likely to be populated with *Campylobacter* and *Salmonella.* Cross-contamination of fecal matter during processing results in increased loads of human

pathogens on poultry products. Chickens with air sacculitis have weaker intestines, which are much more likely to be cut, torn, or ruptured during automated processing, resulting in the cross-contamination of fecal matter and increased human pathogen loads on the end product. Chickens with air sacculitis untreated by fluoroquinolones have lower weights, are subject to more processing errors and more fecal contamination from processing errors, and have higher levels of *Campylobacter* and *Salmonella*, which results in higher levels of pathogens present on food and increased incidences of subsequent food-borne bacterial infections in humans. [Bayer Brief P.78-79, 82-87]

75. Enrofloxacin is efficacious for the treatment of air sacculitis in chickens, and there are no practical effective alternative treatments. [Bayer Brief P.79-82]

76. The evidence shows that for each hypothetical excess day of illness prevented by the withdrawal of enrofloxacin, it would create an additional 25 to 1,000 new days of *Campylobacter* illness due to increased microbial loads on chickens. [Bayer Brief P.88]

77. The evidence shows that the withdrawal of enrofloxacin would result in approximately 97 new days of *Salmonella* illness due to increased microbial loads, for each hypothetical excess day of *Campylobacter* illness thereby prevented. [Bayer Brief P.88-89]

78. *Salmonella* results in human fatalities much more often than *Campylobacter*. The evidence shows 63 additional fatalities from *Salmonella* annually due to a withdrawal of enrofloxacin. [Bayer Brief P.89]

79. The withdrawal of enrofloxacin would result in a net loss to human health because of the resulting increased microbial loads on chickens and subsequent foodborne infections of humans with *Campylobacter* and *Salmonella*. [Bayer Brief P.87-90]

80. The use of enrofloxacin in poultry results in a net gain to human health by controlling poultry health, resulting in increased control of fecal contamination at processing and increased control of foodborne infections of humans with *Campylobacter* and *Salmonella*. [Bayer Brief P.78-90]

81. The FDA's original approval of enrofloxacin required separate label indications for chickens and turkeys, requiring separate data for each species to support the label indication for that species. [AHI Brief P.36-37]

82. There are substantial differences between chickens and turkeys: they are members of different species; all factors that influence the diagnosis, prevalence, and treatment of disease in chickens are not the same as in turkeys; grow-out differences between turkeys and chickens contribute to reduced bacterial loads on turkeys; turkeys are processed differently than chickens, resulting in substantially less human pathogen loads for turkeys as compared to chickens; the evidence suggests that the prevalence and number of *Campylobacter* in the average colonized chicken is less than the prevalence and number of *Campylobacter* in the average colonized turkey. [AHI Brief P.38-41]

83. There is no evidence in the record that fluoroquinolone usage in turkeys acts as a selection pressure for fluoroquinolone-resistant *Campylobacter*. [AHI Brief P.43]

84. The most recent and robust U.S. data indicate that turkey is at most a source of Campylobacteriosis in cases of turkey eaten at restaurants, which CVM admits at most is a 4% attributable population risk for campylobacteriosis. [AHI Brief P.43-46]

85. Although mere prevalence is not relevant to this matter, retail studies suggest substantially lower prevalence of Campylobacter on turkey meat compared to chicken meat. [AHI Brief P.46]

86. CVM has presented no evidence that enrofloxacin use in turkeys poses any harm to human health. [AHI Brief P.35]

87. The CVM RA provides no evidence of any adverse impact to human health from the use of fluoroquinolones in turkeys. [AHI Brief P.35]

88. CVM's NARMS resistance data does not measure *Campylobacter* resistance from turkey isolates. [AHI Brief P.38]

89. Enrofloxacin is the most effective treatment in turkeys for *E. coli* infections and there are no practical alternative treatments. [AHI Brief P.49-50]

90. To the extent that conclusions with regard to turkeys may be extrapolated from data on chickens, as CVM contends, the available data on the human health benefits from enrofloxacin usage in chickens shows that the human health benefits of enrofloxacin use outweigh any potential human health risks. [Bayer Brief P.78-98; AHI P.49]

91. A determination of whether a new animal drug is safe under 21 U.S.C. § 360b(e)(1)(B) requires a balance of the risks and at least the human health benefits of use and/or withdrawal of the drug.

92. CVM has presented no new evidence on the issue of whether enrofloxacin is safe for the approved usage in chickens. CVM's evidence with respect to chickens is at best cumulative of evidence that was available and known at the time of the original approval. Therefore, CVM has failed to carry its initial burden under 21 U.S.C. § 360b(e)(1)(B) for withdrawing approval of enrofloxacin usage in chickens and such approval may not be withdrawn.

93. CVM has presented no new evidence on the issue of whether enrofloxacin is safe for the approved usage in turkeys. While CVM has attempted to extrapolate as to turkeys from data pertaining to chickens, the many and substantial factual differences between chickens and turkeys and the methods of processing applicable to each preclude such extrapolation. Therefore, CVM has failed to carry its initial burden under 21 U.S.C. § 360b(e)(1)(B) for withdrawing approval of enrofloxacin usage in turkeys and such approval may not be withdrawn.

94. To the extent that any of CVM's evidence on the issue of whether enrofloxacin is safe for the approved usage in chickens can be considered "new," that evidence fails to raise a serious question about the safety of enrofloxacin usage in chickens, CVM has failed to carry its initial burden under 21 U.S.C. § 360b(e)(1)(B) for withdrawing approval of enrofloxacin usage in chickens, and such approval may not be withdrawn.

95. To the extent that any of CVM's evidence on the issue of whether enrofloxacin is safe for the approved usage in turkeys can be considered "new," that evidence fails to raise a serious question about the safety of enrofloxacin usage in turkeys, CVM has failed to carry its initial burden under 21 U.S.C. § 360b(e)(1)(B) for withdrawing approval of enrofloxacin usage in turkeys, and such approval may not be withdrawn.

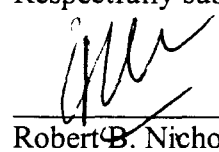
96. To the extent that CVM has succeeded in raising a serious question about the safety of enrofloxacin usage in chickens, Bayer has demonstrated that the human health benefits of enrofloxacin usage in chickens outweigh the human health risks of such usage. Bayer has demonstrated that substantial public health harms would result from the withdrawal of enrofloxacin use in chickens. Therefore, enrofloxacin is safe for use in chickens under the conditions of use upon which the application was approved, and approval may not be withdrawn under 21 U.S.C. § 360b(e)(1)(B).

97. To the extent that CVM has otherwise carried its burden relating to turkeys in whole or in part by the extrapolation of data applicable to chickens, such extrapolation also leads to the conclusion that enrofloxacin usage in turkeys is safe, as Bayer has demonstrated that substantial public health harms would result from the withdrawal of enrofloxacin use in turkeys. Therefore, enrofloxacin is safe for use in turkeys under the conditions of use upon which the application was approved, and approval may not be withdrawn under 21 U.S.C. § 360b(e)(1)(B).

98. Enrofloxacin use in turkeys is safe.

99. Enrofloxacin use in chickens is safe.

Respectfully submitted,



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CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of Respondent Bayer's Post-Hearing Brief was hand-delivered this 18th day of July, 2003 to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

I also certify that a copy of the foregoing Brief was e-mailed this 18th day of July, 2003 to:

The Office of the Administrative Law Judge
Food And Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, MD 20857

I also certify that a copy of the foregoing Brief was e-mailed and mailed via first-class mail, postage pre-paid, 18th day of July, 2003 to:

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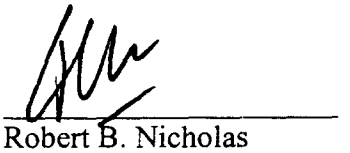

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July 18, 2003

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5:20 p.m. -
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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, Maryland 20852

Re: Enrofloxacin for Poultry: Withdraw of Approval of New Animal Drug Application
FDA Docket: 00N-1571

Dear Sir/Madam:

Enclosed for filing please find an original and copy of Respondent Bayer Animal Health's Post-Hearing Brief.

Please call if you have any questions.

Sincerely,

Robert B. Nicholas

Enclosures

cc: Nadine Steinberg, Esquire (w/o enclosure)
Kent McClure, Esquire (w/o enclosure)

00ON-1571

BRFR