DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. Food and Drug Administration

INITIAL DECISION

Docket No. 00N-1571

PROPOSAL TO WITHDRAW APPROVAL OF THE NEW ANIMAL DRUG APPLICATION FOR ENROFLOXACIN FOR POULTRY

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Enrofloxacin found not shown to be safe under the conditions of use upon the basis of which the application was approved as required under § 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 360 b(e)(1)(B)]. Approval of NADA for enrofloxacin ordered withdrawn.

M. Miller Baker, Jeffrey C. Bates, Gregory A. Krauss, and Robert B. Nicholas for the Respondent Bayer Corporation.

Kent D. McClure for the non-party participant Animal Health Institute.

Candace K. Ambrose, Robert M. Spiller, Jr., Nadine R. Steinberg,, and Claudia Zuckerman for the Center for Veterinary Medicine, Food and Drug Administration.

By DANIEL J. DAVIDSON, Administrative Law Judge

[1] Pursuant to 21 C.F.R. § 12.125(a), exceptions to this initial decision must be received by the Dockets Management Branch not more than 60 days after the date of issue of this initial decision. Pursuant to 21 C.F.R. § 12.125(c), replies to exceptions must be received by the Dockets Management Branch not more than 60 days thereafter.

By Notice of Opportunity for Hearing (NOOH) published in the Federal Register of October 31, 2000 (65 Fed. Reg. 64,954), as revised on January 22, 2001 (66 Fed. Reg. 6,623), the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) proposed to withdraw approval of new animal drug application (NADA) 140-828 for use of enrofloxacin, or Baytril® 3.23% Concentrate Antimicrobial Solution, in poultry under § 512(e)(1)(B) of the Act (21 U.S.C. § 360b(e)(1)(B)). On November 29, 2000, Bayer, the manufacturer of Baytril, requested a hearing on CVM's proposal, and a hearing was granted. The Animal Health Institute (AHI), non-party participant, joined in the administrative hearing process by submitting a Notice of Participation pursuant to 21 C.F.R. § 12.45.[2] The Notice of Hearing (NOH) published in the Federal Register on February 20, 2002 (67 Fed. Reg. 7,700) provided factual and legal information concerning the proposal to withdraw NADA 140-828 and identified the issues that were the subject of the evidentiary hearing in this matter.

I. ISSUES FOR HEARING

The issues in this proceeding as set forth in the NOH of February 20, 2002, are:

A. Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred, such as:

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

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

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

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

[2] AHI made several contributions to Respondent Bayer's arguments contained herein, though credit is at times given to Bayer alone. In its Brief, Bayer incorporated AHI's arguments made in the AHI Brief.

II. HISTORY

Enrofloxacin is a flouroquinolone, a class of antimicrobial drugs used in humans and animals for therapeutic purposes. Fluoroquinolones are used in the treatment of foodborne diseases that have a significant public health impact. The first fluoroquinolones were introduced in human medicine in the U.S. in 1985 and since that time and their usage has increased.

As part of its regulatory process of fluoroquinolone approvals, in May 1994 the FDA convened government and non-government experts in antibiotic use for a joint meeting of CVM's Veterinary Medicine Advisory Committee and FDA's Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee. Following the suggestions of this Joint Advisory Committee, the FDA decided to approve enrofloxacin limited to prescription use in chickens and turkeys subject to restrictions and post-approval monitoring of resistance.

On October 4, 1996, NADA 140-828 for enrofloxacin was approved for use in poultry in accordance with the standards set forth in § 512 of the Act. (61 Fed. Reg. 56,892). In chickens, enrofloxacin is indicated for the control of mortality associated with *Escherichia coli* (*E. coli*), and in turkeys it is indicated for the control of mortality associated with *E. coli* and *Pasteurella multocida (P. multocida)*. In the U.S., an estimated 1-2% of broiler chickens and 4% of turkeys are treated with Baytril.[3] The CDC estimates that foodborne infections cause approximately 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths each year. (Exhibit Nos. G-1452, P. 2, L. 41-43, and G-410).

CVM proposed to withdraw approval of NADA 140-828 for enrofloxacin and issued a NOOH on October 31, 2000 to that effect. The proposed withdrawal was based on its examination of data from surveillance programs, published literature, and other sources

[3] These percentages are an estimate and may not include poultry indirectly exposed to Baytril. CVM estimates that at least between 93,500,000 and 136,000,000 broilers and 10,800,000 turkeys are treated with Baytril each year.

suggesting that the use of fluoroquinolones in poultry results in selection of fluoroquinolone-resistant *Campylobacter* (a significant cause of fluoroquinolone-resistant campylobacteriosis in humans). Although campylobacteriosis is caused by both susceptible and resistant *Campylobacter*, CVM maintains that fluoroquinolone therapy is less effective in campylobacteriosis caused by fluoroquinolone-resistant *Campylobacter* bacteria.

Bayer responded to CVM's NOOH by filing a request for a hearing on November 29, 2000. The FDA's then Acting Principal Deputy Commissioner granted Bayer's request in the NOH, where the issues for hearing are found. (67 Fed. Reg. 7,700). On April 15, 2002, Bayer moved to modify the issues for hearing set forth in the NOH, and contended that the issues formulated by the FDA do not accurately reflect the parties' burdens of proof and legal standards governing this proceeding. After review of Bayer's Motion to Reformulate Issues for Hearing and the response thereto, it was concluded that there was no compelling reason to modify the issues in this proceeding. The issues designated in the NOH adequately reflect the statutory requirements and therefore Bayer's motion was denied.

Joint stipulations were submitted by the parties on September 20, 2002 and revised joint stipulations on December 24, 2002. Documentary evidence and written direct testimony was submitted by CVM on December 9, 2002, and by Bayer and AHI on December 13, 2002. The written direct testimony was received in evidence subject to motions to strike. Oral hearing for purposes of cross-examination of witnesses was held between April 28, 2003 and May 7, 2003. Pursuant to 21 C.F.R. § 12.96(a) initial briefs were filed on July 18, 2003 and reply briefs were filed on August 15, 2003. The briefs contained over 275 numbered proposed findings of fact and conclusions of law. To the extent these are adopted, they may be included in this initial decision in narrative form.

III. PRELIMINARY MATTERS

A. Burdens of Proof

Pursuant to § 512(e)(1)(B) of the Act, CVM proposed to withdraw approval of NADA 140-828 for use in poultry. The relevant portions of § 512 state:

> (e)(1) The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) with respect to any new animal drug if the Secretary finds—
>
> (A) that experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;
>
> (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved...

CVM has the initial burden of producing new evidence that raises serious questions about the ultimate safety of enrofloxacin's use in poultry. If this threshold burden is met, Respondent Bayer is required to demonstrate the safety and efficacy of enrofloxacin's use in poultry.

1. CVM's Burden to Raise Serious Questions Concerning Enrofloxacin's Safety

In this NADA withdrawal proceeding, CVM bears the initial burden of showing that it has serious reasons to vacate the prior approval of enrofloxacin. To meet its burden, CVM must provide a reasonable basis from which serious questions about the ultimate safety of enrofloxacin may be inferred. *See Rhone-Poulenc, Inc., Hess & Clark Div. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980); Commissioner's DES Decision, 44 Fed. Reg. 54,851 (1979). "'Serious questions' can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect." (44 Fed. Reg. 54,851, 54,861). CVM has applied a "reasonable certainty of no harm" definition of safety to humans in approving animal drugs by determining the level at which a substance formed in or on food as a result of the use of a new animal drug has no effect

on humans.[4] In determining whether a drug is "safe," pursuant to § 512(d)(2)(A) of the Act the FDA is to consider "the probable consumption of such drug and any substance formed in or on food because of the use of such drug." *See* H.R. 2284, 85th Cong., 2d. Sess., 4-5 (1958); S.R. 1308, 90th Cong., 2d Sess., 1 (1968).

The threshold burden of CVM includes a new look at the evidence that justifies a finding that the prior approval of enrofloxacin is no longer valid. New evidence is to show serious questions about the drug's safety "under the conditions of use upon the basis of which the application was approved." 21 U.S.C. § 360b(e)(1)(B). Bayer and AHI contend that many of the studies cited and relied upon by CVM are not material to this proceeding because CVM's purported new evidence was already known by FDA when the drug was initially approved. A witness for CVM stated that controversy "surrounded the use of fluoroquinolones in food-producing animals even before they were approved in the United States." (Exhibit No. G-1478, P. 4, L. 18-20). However, the scope of "new evidence" is not limited to data developed after an NADA is approved, but includes a re-evaluation or novel application of preexisting data. *See Bell v. Goddard*, 366 F.2d 177, 181 (7th Cir. 1966). A drug application could be withdrawn if "clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective" show a drug is unsafe. *Id.* In *Bell* the Commissioner's findings were based on an extensive re-evaluation of the evidence. *Id.* The court in that case stated found that to interpret the Act as "prohibiting such a new application of existing information would do violence to the paramount interest in protecting the public from unsafe drugs." *Id.*

[4] FDA, CVM, Guideline, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals," revised July 1994.

As a further reference is the Commissioner's statement concerning the diethylstilbestrol (DES) withdrawal hearing: "approval may be withdrawn pursuant to the 'safety clause' if new evidence, evaluated together with previously existing evidence, shows the drug is not shown to be safe." (44 Fed. Reg. 54,851, 54,861). In the DES matter, FDA sought to withdraw approval for DES, a synthetic estrogen used as a growth promotant in cattle and sheep.

Even though a number of the studies cited by CVM were prior to the approval of fluoroquinolones in poultry, they were known about prior to enrofloxacin's approval and may establish conclusions that were known prior to enrofloxacin's approval, the findings here may nevertheless be based on an extensive re-evaluation of the evidence. To hold otherwise would mean that should the FDA have erred in its initial approval, it would be powerless to correct that error in the absence of totally new evidence. Such a conclusion flies in the face of reason and ignores the public safety interest inherent in FDA regulation. Therefore, "new evidence" can be found based on the re-evaluation or novel application of preexisting data.

2. Bayer's Burden of Showing Safety of Enrofloxacin

If CVM meets its initial burden, the burden shifts to Bayer to establish that Baytril is "shown to be safe," i.e. that its benefits to human health outweigh its risks to human health. *See Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 992-94 (D.C. Cir. 1974). Pursuant to 21 C.F.R. §12.87(d),

> At a hearing involving issuing, amending, or revoking a regulation or order relating to the safety or effectiveness of a drug, device, food additive, or color additive, the participant who is contending that the product is safe or effective or both and who is requesting approval or contesting withdrawal of approval has the burden of proof in establishing safety or effectiveness or both and thus the right to approval. The burden of proof remains on that participant in an amendment or revocation proceeding.

An approved NADA means that the product is safe and effective for its intended use, and that the methods, facilities and controls used for the manufacturing, processing and packaging of the drug are adequate to preserve its identity, strength, quality, and purity.

In *Hess & Clark* it was held that in considering whether an animal drug is "safe" within the meaning of § 512(e)(1)(b) of the Act, "the typical issue for the FDA is not the absolute safety of a drug...the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use." 495 F.2d at 993-94. In *FDA v. Brown & Williamson Tobacco Corp.*, the Supreme Court noted that " [s]everal provisions in the Act require the FDA to determine that the *product itself* is safe as used by consumers. That is, the product's probable therapeutic benefits must outweigh its risk of harm." 529 U.S. 120, 140 (2000) citing *United States v. Rutherford*, 442 U.S. 544, 555 (1979) (noting that "[t]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use").

"Reasonable certainty of no harm" is the standard that CVM applies when determining an animal drug's safety, and Bayer's determination of safety by weighing the risks and benefits of enrofloxacin does not run afoul of this standard. Applying either or both definitions, the result remains steady. "Reasonable certainty of no harm" does not mean zero risk. Therefore, it is acceptable to look at both the risks and benefits of enrofloxacin when determining whether it is safe.

B. <u>Risk-Benefit Analysis</u>

In Bayer's Motion to Reformulate the Issues for Hearing and in the briefs filed by Respondents, Bayer and AHI argued that the issues for hearing should include a risk-benefit

consideration of animal welfare, economic, environmental, as well as direct and indirect human health impacts of enrofloxacin's withdrawal. However, the safety concern in this matter is limited to human food safety and human health impact, and the proper risk-benefit analysis considers only whether the benefits to human health from the use of enrofloxacin in poultry are proven to outweigh the risk to human health from such use.

Bayer contends that the use of enrofloxacin in poultry has animal health and welfare benefits that outweigh any risks to animals from its use, contending that animals deserve to be treated with effective therapies when they become ill and that veterinarians should have available effective drugs such as enrofloxacin for use in animals. However, there are effective alternatives to enrofloxacin for chickens and turkeys. Furthermore, the consumers of chickens and turkeys are humans, and there is no obligation upon CVM to subject the public to risk for the benefit of animals. In *Brown & Williamson Tobacco Corp.* the Court noted that "any product regulated by the FDA...must be safe for its intended use...the FDA must determine that there is a reasonable assurance that the product's therapeutic benefits outweigh the risk of harm to the consumer." 529 U.S. at 142.

Bayer also contends that economic harm to the chicken and turkey industries well in excess of $200 million annually would result from enrofloxacin's withdrawal. Even if this were shown, however, without explicit statutory authorization, economic costs—including the costs associated with lost revenue for poultry producers and drug manufacturers, as well as environmental and other costs—may not be considered in determining the safety of this drug. In *American Textile Manufacturers Institute, Inc. v. Donovan*, the Court held that "[w]hen Congress has intended that an agency engage in cost-benefit analysis, it has clearly indicated such intent on the face of the statute." 452 U.S. 490, 510 (1981); *See also Whitman v. American Trucking*

Association, 531 U.S. 457, 469 (2001) (finding that, in the context of the Clean Air Act, consideration of implementation costs "is both so indirectly related to public health and so full of potential for canceling the conclusions drawn from direct health effects that it would have been expressly mentioned...had Congress meant it to be considered.").

Finally, Bayer contends that withdrawal of enrofloxacin would have an adverse environmental impact that should be considered in this proceeding. Environmental damage may ensue, for example, because disposal of dead poultry results in contamination of ground water and lowering of air quality, and because increased mortality in poultry due to an enrofloxacin withdrawal would cause a need to increase the number of poultry raised for slaughter in order to account for chickens not treated with enrofloxacin.

Pursuant to § 102(2)(C) (42 U.S.C. § 4332) of the National Environmental Policy Act of 1969 (NEPA), all federal government agencies must include in their proposals for major federal actions significantly affecting the quality of the human environment a detailed statement on, among other things, the environmental impact of the proposed action, any adverse environmental effects which cannot be avoided should the proposal be implemented, and alternatives to the proposed action. For major federal actions with potentially significant impacts, agencies must prepare an Environmental Assessment (EA) and sometimes a more extensive Environmental Impact Statement (EIS), or claim a categorical exclusion. 40 C.F.R. § 1508.4.

Pursuant to 21 C.F.R. § 25.33, withdrawals of approval for NADAs "ordinarily do not require the preparation of an EA or an EIS." Alternatively, the FDA can claim a categorical exclusion. *See Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 174 (D.C. Dist. 2000); *see also Rhone-Poulenc*, 636 F.2d at 755 quoting *Asphalt Roofing Mfrs. Ass'n v. ICC*, 567 F.2d 994, 1005 (1977) ("'[w]hen the agency determines that (an EIS) is unnecessary, it must give a

statement of its reasons, and where the agency's statement of explanation is sufficient, the NEPA criteria are satisfied.'"). In *Rhone-Poulenc*, an EIS was unnecessary when the FDA's "Environmental Impact Analysis Report" showed that continued use of an animal drug would decrease animal waste and decrease the amount of feed grown for the animal. *Id.* The report noted that there were alternatives to the drug being withdrawn, and therefore any environmental harm would be mitigated. *Id.*

A withdrawal of Baytril from the market would not constitute one of "major Federal actions significantly affecting the quality of the human environment." There are alternatives, as there were in *Rhone-Poulenc*, to enrofloxacin. The consideration of adverse environmental consequences is beyond the scope of this proceeding because Bayer and AHI have not shown that the impact of enrofloxacin's withdrawal would be of such magnitude as to require an EA or an EIS. Even if the allegations set forth by Bayer were substantiated, they fall far short of the quality and quantity of evidence necessary to require the preparation of an EA or EIS.

As noted above, the risk-benefit analysis in this matter is limited in scope. CVM and Respondents are only required to present evidence on the direct human health effects of enrofloxacin's withdrawal. In any event, the evidence in this proceeding does not establish that the social and economic benefits of enrofloxacin outweigh the risks to public health.

C. <u>Epidemiological Studies</u>

The parties utilize evidence supporting their cases on the withdrawal of Baytril with epidemiological studies. Epidemiology has been defined as "the study of the incidence, distribution, and control of disease in a population." *Castillo v. E.I. Du Pont De Nemours & Co., Inc.*, 854 So. 2d 1264, 1269 (Fla. 2003) citing *Merriam-Webster's Collegiate Dictionary* 389 (10th ed.1998). In *In re TMI Litig.*, the court noted that "epidemiology is the 'study of the

distribution and determinants of health-related states and events in populations and the application of this study to control of health problems.'" 193 F.3d 613, 660 (3rd Cir. 1999) citing Federal Judicial Center, Reference Manual on Scientific Evidence 174 (1994). "Epidemiology is concerned with the incidence of disease in populations and does not address the question of the cause of an individual's disease." *Id.* citing Reference Manual on Scientific Evidence at 167.

A typical epidemiological study involves interviewing infected patients and asking them what they had to eat or drink or what other exposures they had in the week before they became ill, and 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 the same infections. This technique is known as the case-control study and is used to identify specific risk factors and exposures. (Exhibit No. G-1475, P. 7, L. 25-31).

The reliability of epidemiology has been questioned by the courts. In *In Re Joint E. & S. Dist. Asbestos Litig.*, the court deemed, "[b]y its nature, epidemiology is ill-suited to lead a factfinder toward definitive answers, dealing as it does in statistical probabilities and the continual possibility of confounding causal factors." 52 F.3d 1124, 1133 (2d Cir. 1995) citing *Brock v. Merrell Dow Pharmaceuticals, Inc.*, 874 F.2d 307, 311 (5th Cir. 1989). Potential problems with epidemiological studies in evidence include the presence of confounding factors which can distort the results if they are not accounted for. The FDA's "Guidelines for Ensuring the Quality of Information Disseminated to the Public" (FDA Guidelines) require that the FDA disseminates information that "is accurate and unbiased, as well as substantially reproducible and replicable. The goal is accomplished by using reliable data sources and sound analytical techniques." FDA Guidelines, § VII B. An Administrative Law Judge's "duty to screen

evidence for reliability, probativeness, and substantiality...ensures that final agency decisions will be based on evidence of requisite quality and quantity." *U.S. Steel Mining Co., Inc. v. Director, Office of Workers' Compensation Programs*, 187 F.3d 384, 389 (4th Cir. 1999).

Epidemiological findings individually may not be relied upon to prove a cause and effect. In other words, each of the studies and/or analyses thereof relied on in this proceeding, standing alone, would not support a finding that the use of enrofloxacin in poultry has resulted in a significant increase in drug resistant *Campylobacter* that would be sufficient to call the safety of Baytril into question. However, the focus in epidemiology is on general causation, rather than specific. *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 590 (D.N.J. 2002). Therefore, the record must be viewed in its entirety to reach a conclusion.

D. Reliability of Expert Witness Testimony

The opinion testimony of qualified experts is relied on in varying degree in evaluating evidence in proceedings that involve technical and scientific issues. The level of expertise as well as the studies relied on as the bases for expert opinions must be considered when evaluating that testimony.

CVM asserts that Dr. Louis Anthony Cox (Exhibit Nos. B-1901 and B-1020) is not a credible witness and that Bayer's reliance on his testimony is therefore groundless. In support thereof, CVM asserts that the witness' opinion seems to change depending on who is asking for it. (CVM Brief, P. 74). As a consultant to CVM, Dr. Cox agreed with the methodology of CVM's risk assessment. (Tr. P. 866, L. 3-9, P. 871, L. 20 – P. 872, L. 13). At a December 1999 meeting with CVM, he indicated that CVM's approach was good. (Tr. P. 866, L. 3-9, P. 869, L. 13-15, P. 872, L. 6-13; Exhibit No. G-1810). In that meeting, Dr. Cox agreed explicitly with CVM's "Big K" principle, i.e. the aggregation of the end sequences into one probability that a

pound of *Campylobacter* contaminated chicken will result in a case of campylobacteriosis. (Tr. P. 877, L. 15 – P. 878, L. 4; Exhibit No. G-1810, P. 143, L. 15-21). Dr. Cox acknowledged that the "Big K" principle that he had agreed with in 1999 exists in CVM's 2001 published risk assessment. (Tr. P. 879, L. 4-9). Thereafter, Dr. Cox became a consultant to AHI. (Tr. P. 881, L. 18-22). As a consultant to AHI and witness for Bayer, he disagreed with CVM's model and other CVM points. In his written direct testimony, he described CVM's risk assessment as "meaningless" and "technically deficient." (Exhibit No. B-1901, P. 25).

In addition to changing his position, CVM argues that Dr. Cox misrepresents published articles by misquoting the text of the articles he relies on in his testimony, referring specifically to the Dr. Hanne Rosenquist article referenced in his direct testimony. (Exhibit No. B-1901, P. 16). This witness admits to altering quoted material from published articles. (Tr. PP. 947-965). He contends that editing quoted material is fair as long as it does not change the context and admitted that this is the way he quotes other sources throughout his testimony. (Tr. PP. 967-8). He further indicates that his use of quotation marks does not necessarily mean that the quoted words can be attributed to another source, and goes so far as to attempt to justify the indiscriminate use of quotation marks in his sworn testimony by claiming it was merely to emphasize important concepts. (Tr. P. 1003).

Bayer and AHI argue that Dr. Cox's quote of Dr. Rosenquist accurately portrayed the substance of the article. (AHI Reply Brief, P. 20). They further assert that Dr. Cox's opinion regarding CVM's "Big K" model only changed after he was unable to validate the model. (AHI Reply Brief, P. 19).

While the explanation of his apparently differing opinions before and after being hired by AHI as a consultant may be partially explanatory, an additional question as to credibility

remains. It seems that Dr. Cox edits referenced material, prefers his edited version to the original, and quotes the edited version in his testimony. Apparently, this is his usual way of presenting cited material.

The explanation of Dr. Cox's misquotes of published articles does little to resolve the issue. Bayer and AHI assert "that when all is said and done, Cox's quote of Dr. Rosenquist accurately portrayed the substance of the article." (AHI Reply Brief, P. 20). Why anyone would use quotation marks when meaning only to convey the substance of referenced material remains a mystery. Having to determine whether or not the edited versions accurately portray the substance of the referenced material would require an unnecessarily burdensome word-for-word examination of each and every reference.

There can be no justification for excerpting the substance of material from publications and presenting it in quotes attributed to that publication. If a witness is merely referring to the substance of a portion of a published article relied on, the use of quotation marks is totally inaccurate and misleading. Under the circumstances, this witness' credibility is severely compromised and his testimony cannot be relied on.

E. <u>Standards and Guidelines</u>

The National Committee for Clinical Laboratory Standards (NCCLS) promotes the development and use of standards and interpretive criteria guidelines within the healthcare community. FDA has accepted the NCCLS as the standards setting body for antimicrobial susceptibility testing. The NCCLS has defined quality control standards, the definitions of susceptible, intermediate and resistant (SIR) and also the criteria to determine the breakpoints for SIR.[5]

[5] A breakpoint is the concentration—expressed as an MIC—that distinguishes between susceptible, intermediate and resistant bacteria. (Exhibit No. G-1481, P. 5, L. 1-4).

Currently there are no NCCLS interpretive criteria for any antimicrobial agent for the *in vitro* antimicrobial susceptibility testing of *Campylobacter*. However, there are NCCLS approved standardized testing method and quality control ranges for five antimicrobial agents (ciprofloxacin, doxycycline, erythromycin, gentamicin, and meropenem). (Exhibit No. G-1481, P. 6). Many scientific reports use the NCCLS interpretive criteria generated for *Enterobacteriaceae* to determine susceptibility and resistance to ciprofloxacin (a fluoroquinolone used in humans) for *Campylobacter*, which is ≥4 μg/ml. (Exhibit Nos. G-1481, P. 7 and G-1473, P. 4, L. 4-13).

There are a number of *in vitro* antimicrobial susceptibility testing (AST) procedures including agar dilution, broth dilution, and agar diffusion. (Exhibit No. G-1481, P. 3). The only standardized *in vitro* AST method approved by the NCCLS for the testing of bacteria belonging to the genus *Campylobacteris* is the agar dilution testing method. (Exhibit No. G-1481, PP. 7-8). However, the NCCLS approved method for animal-origin *Campylobacter* susceptibility testing was not available until May 2002.

In vitro antimicrobial susceptibility testing is performed by exposing a known concentration of a pure bacterial culture, in the appropriate growth phase, to increasing concentrations of selected antimicrobial agents. The results may be reported qualitatively (susceptible, intermediate or resistant) or quantitatively via a numerical value representing the MIC value expressed in terms of micrograms per milliliter or milligrams per liter.

Many of the studies in evidence used ciprofloxacin to measure MIC values. However, the MIC value from these studies cannot be extrapolated to calculate the MIC value for enrofloxacin. For instance, the Danish DANMAP study defines resistance with an MIC of ≥ 1

μg/ml for ciprofloxacin. However, this MIC value cannot be extrapolated to calculate MIC value for enrofloxacin. (Tr. PP. 692-694).

Campylobacter isolates in the human National Antimicrobial Resistance Monitoring System (NARMS)[6] surveillance program, exhibited two distinct populations with respect to their MICs to ciprofloxacin: nearly all isolates either had a MIC of ≤ 0.5 μg/ml (susceptible isolates), or a MIC of ≥ 32 μg/ml (resistant isolates). Bayer disputes the characterization of 32 μg/ml as clinically "resistant" and notes that a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Bayer contends that clinical cure can be demonstrated for a *Campylobacter* with an MIC of 32 μg/ml.

AHI contends that the CVM *Campylobacter* risk assessment on the human health impact of fluoroquinolone-resistant *Campylobacter* attributed to the consumption of chicken (CVM risk assessment)[7] does not comport with accepted National Academy of Sciences (NAS) and National Research Council (NRC) guidelines and standards. This issue is discussed infra.

Any consideration of the studies cited by all parties to this proceeding is accompanied by an understanding that the MIC breakpoint values distinguishing resistant from susceptible *Campylobacter* are not uniformly applied. Owing to the bimodal nature of *Campylobacter*—making it generally either highly susceptible or highly resistant—this does not appear to compromise the studies in a significant way. Furthermore, the fact that the agar dilution method of susceptibility testing is not the sole AST method utilized in the studies also does not compromise the reliability of studies in evidence.

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[6] NARMS is a collaboration among the CDC, FDA's CVM, and Food Safety and Inspection Service (FSIS) and Agricultural Research Services of the USDA, and became operational in January 1996. Approximately 50 state and 4 local public health laboratories participate in NARMS. It allows the FDA to monitor resistance to antimicrobial drugs used in humans and in food animals.

[7] The CVM risk assessment was dated October 18, 2000 and revised January 5, 2001. (Exhibit No. G-953, P. 2).

F. Chickens and Turkeys

A concern in this proceeding is whether the evidence submitted made a showing as to enrofloxacin's effects on both chickens and turkeys or just chickens. Bayer and AHI contend that CVM has not presented new evidence on the effects of enrofloxacin on turkeys, and that evidence on turkeys overall is lacking. CVM, however, has offered new evidence on turkeys which, when taken together with existing information available at the time of Baytril approval, presents a reasonable basis from which questions on the safety of Baytril use in turkeys may be inferred.

One of the exhibits showing data on turkeys was that of Dr. Catherine M. Logue. Dr. Logue conducted a study in the late 1990s at two turkey slaughterhouses in the mid-west in order to determine the prevalence of foodborne pathogens, including *Campylobacter*, studied their antimicrobial susceptibility, and found fluoroquinolone-resistant *Campylobacter* in turkeys. (Exhibit No. G-1464, P. 2, L. 26-P. 3, L. 5, and P. 5, L. 22-P. 6, L. 25). Also, Dr. Cindy R. Friedman's analysis of the FoodNet case-control study contains new epidemiological findings with respect to turkeys. (Exhibit No. G-1488). Data from the retail meat studies showing fluoroquinolone-resistant *Campylobacter* on retail turkey is new evidence. (Exhibit No. G-763).

CVM contends that if Baytril is withdrawn for use in chickens, it must also be withdrawn for use in turkeys. These is some evidence that almost 100% of turkeys are colonized with *Campylobacter*. (Exhibit Nos. G-686, G-1459, P. 4, L. 9-11). CVM contends that there is no biological reason that Baytril's effect on *Campylobacter* in *Campylobacter*-colonized turkeys is any different than its effect on *Campylobacter* in *Campylobacter*-colonized chickens. Dr. Stuart B. Levy stated that "[t]he emergence, selection, and mechanism of fluoroquinolone resistance in

bacteria is characteristic of the bacterium and not the host animal in which resistance is selected." (Exhibit No. G-1463, P. 4, L. 9-11).

Studies in evidence show that turkey is second only to chicken in prevalence of *Campylobacter* on retail meat. Retail meat studies find a lower prevalence of *Campylobacter* in retail turkey than in retail chicken (i.e., the finding in Exhibit No. G-727 that 70.7% of chicken contaminated with *Campylobacter* but only 14.5% of turkeys contaminated with *Campylobacter*); the prevalence of *Campylobacter* contamination in turkeys is much higher than in other retail meat except chicken. (Exhibit No. G-1466, P. 2, L. 30-35). In only 1.7% of pork and 0.5% of beef in one study, in which 14% of turkeys yielded *Campylobacter*, were contaminated with *Campylobacter*. (Exhibit No. G-1484, P. 3, L. 13-15).

Bayer and AHI assert that data on turkeys is limited and that CVM lumps together turkeys and chickens as "poultry," and obscures the fact that turkeys have a lower risk factor than chickens. Bayer and AHI assert that despite the evidence demonstrating that chickens and turkeys have significant differences which ultimately affect both prevalence of *Campylobacter* on turkeys and the incidence rate of human campylobacteriosis attributable to turkey, CVM's case rests on the proposition that all evidence specific to chicken may be extrapolated to turkeys.

AHI argues that the CVM risk assessment measures only the human health impact of fluoroquinolone-resistant *Campylobacter* from chicken and not from turkeys and that animal NARMS monitors only resistance in chicken, not turkeys. CVM indicates that the risk assessment is simply a way to quantify the potential human health impact of fluoroquinolone-resistant *Campylobacter* acquired from chicken.

There is precedent for withdrawing the approval of an animal drug in multiple species, even though the evidence is mainly from one species. *See Rhone-Poulenc*, 636 F.2d at 753 n.3.

In the evidentiary hearing held on the proposal to withdraw the NADA for DES, most of the evidence presented was with respect to DES in cattle. The Commissioner, however, ordered withdrawal of the NADA in both cattle and sheep, and the Court of Appeals upheld the Commissioner on this point. *Id.* Given the precedent of the DES decision, and given that Bayer and AHI did not present evidence of the pertaining biological differences between chickens and turkeys that may be responsible for differential effects of enrofloxacin on chickens and turkeys, this proceeding is controlling for turkeys as well as chickens.

G. CVM *Campylobacter* Risk Assessment

An information quality complaint in the form of a Request for Correction of Information Under Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554, was filed with the FDA by AHI on January 23, 2003. It deals with the question of whether CVM's *Campylobacter* risk assessment complies with the Office of Management and Budget (OMB), HHS, and FDA guidelines.[8] Section 515 of P.L. 106-554 requires the Director of OMB to issue guidelines providing policy and procedural guidance to federal agencies regarding the information they disseminate.

By a communication dated March 20, 2003, CVM Director Dr. Stephen F. Sundlof, informed AHI that the Request for Correction would be handled within 60 days after the final determination in this proceeding. By letter dated April 16, 2003 AHI appealed that determination and alleged that the deferral amounted to a denial of its Request for Correction due to the fact of CVM's reliance on the very same risk assessment in this proceeding.

By letter dated September 16, 2003, the FDA Principal Associate Commissioner, Dr. Murray M. Lumpkin, indicated that he, acting for the Commissioner, had determined on behalf

[8] The FDA Guidelines are designed to help ensure and maximize the quality, objectivity, utility and integrity of information disseminated by the agency. *See* FDA Guidelines, *available at* www.hhs.gov/infoquality/fda.html.

of the agency, that the information quality complaint filed by AHI under Section 515 of P.L. 106-554, should be considered as part of this proceeding. Accordingly, the question of whether the CVM risk assessment is consistent with the OMB, HHS and FDA Guidelines will be considered along with similar issues dealing with the CVM risk assessment and raised in this proceeding.

IV. EVIDENCE AND CONTENTIONS OF THE PARTIES

CVM concludes that enrofloxacin use in poultry acts as a selection pressure that results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry that are transferred to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans. CVM contends that it has presented evidence meeting its burden of proof in this matter, and that Bayer has not demonstrated the safety of enrofloxacin. Bayer asserts that CVM's evidence is faulty, that enrofloxacin is safe under the approved conditions of use in chickens, and that turkeys and that the use of enrofloxacin in poultry has a substantial human health benefit that outweighs its purported risks. The parties' evidence and contentions are considered below.

A. SERIOUS QUESTIONS ABOUT ENROFLOXACIN USE IN POULTRY

1. Selection Pressure and the Emergence and Dissemination of Fluoroquinolone-Resistant *Campylobacter* in Poultry

CVM has the burden to demonstrate that there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred. A sub issue of this inquiry is "[w]hether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in poultry?"

There are studies indicating that most retail chicken in the U.S. have *Campylobacter* (Exhibit Nos. G-701, G-727, G-541, G-589, G-1785, and G-1484) and CVM contends that the

use of fluoroquinolones in poultry causes the selection of fluoroquinolone-resistant *Campylobacter*. Resistance occurs naturally, and selection and dissemination of resistance is an inevitable result of any antibiotic use. According to Bayer, however, CVM overestimates the impact of enrofloxacin on selection pressure, emergence, and dissemination of fluoroquinolone-resistant *Campylobacter*.

While examining the evidence presented by both CVM and Bayer as to selection pressure, emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry, it is noted that there is no scientific consensus on the MIC breakpoint value for the determination of "resistant" versus "susceptible" *Campylobacter*. Considering the evidence as a whole, however, it is apparent that despite some limitations of the data presented, the use of enrofloxacin in poultry acts as a selection pressure for fluoroquinolone-resistant *Campylobacter* and results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*.

a. Background on Selection for Fluoroquinolone-Resistant *Campylobacter* in Poultry

Campylobacter are a common inhabitant of the intestinal tracts of poultry. (Exhibit Nos. G-1483, P. 4, L. 14–15, G-1459, P. 2, L. 28-30, and G-1484, P. 2, L. 44-45). They do not usually cause disease in the poultry. (Exhibit No. G-1483, P. 4, L. 2-4). A single point mutation in the gyrase gene (gyrA) of *Campylobacter* occurring in approximately 1 to 5 in 100 million cells is sufficient to confer fluoroquinolone resistance in *Campylobacter*. (Exhibit Nos. G-1465, P. 5, L. 8-10, P. 2, L. 17-19, P. 4, L. 5-9, and B-826).

Studies indicate that there is a bimodal MIC distribution of fluoroquinolone susceptibility of *Campylobacter* isolates in both chickens and humans. (Exhibit Nos. G-1465, P. 4, L. 44 – P. 5, L. 6, G-1517, and B-868, P. 3). *Campylobacter* are either highly susceptible or highly

resistant to fluoroquinolones. (Exhibit Nos. G-1465, P. 5, L. 4-6, and G-1455, P. 5, L. 33-37). This bimodal MIC distribution is present in both poultry and human fluoroquinolone-resistant *Campylobacter* isolates.

The low range of common breakpoints for *Campylobacter* resistance is ≥1 to ≥4 μg/ml and thus it is acceptable to use methods such as the E-test even though it uses higher MICs. Some countries such as Denmark and France use relatively low breakpoints for resistance to ciprofloxacin, such as ≥1 μg/ml in Denmark and >2 μg/ml in France. (Exhibit No. G-1481, P. 6, L. 42 – P. 7, L. 6). A witness for CVM, Dr. Robert D. Walker testified on cross-examination that there is freedom in the type of testing that may be utilized. (Tr. P. 249, L. 16-21). It is irrelevant that there is no official NCCLS breakpoint for *Campylobacter* because of its bimodal nature. Methods of resistance testing on *Campylobacter* can vary as to what MIC values are used when denoting resistant or susceptible. (Tr. P. 249, L. 13-21).

Although there is no single MIC breakpoint value established for *Campylobacter*, the studies relied on in this proceeding are not thereby unreliable or otherwise ill-suited for drawing certain conclusions. Complete uniformity in testing methods is an ideal but unfortunately unrealistic goal.

b. <u>Cross-Contamination of Poultry</u>

The effects of fluoroquinolone use in poultry exceeds their actual use in poultry because of cross contamination. Poultry that are not treated with Baytril via drinking water can acquire fluoroquinolone-resistant *Campylobacter* via cross-contamination. A witness for CVM, Dr. Carolyn Harris Minnich, stated that "there are numerous places where cross-contamination may occur between animals or carcasses with *Campylobacter*, and if present, fluoroquinolone-

resistant *Campylobacter*, and those carcasses without *Campylobacter*." (Exhibit No. G-1467, P. 7, L. 25-28).

Cross contamination of fecal matter during processing results in increased levels of human pathogens on poultry. The gut of birds can contaminate other birds during slaughter and processing. Transporting poultry from farms to commercial slaughter facilities can increase pathogen populations of *Campylobacter* 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. (Exhibit No. G-1464, P. 2, L. 4–11). During slaughter, intestinal contents of poultry may spread on the carcasses causing contamination of end-products. (Exhibit No. G-1459, P. 2, L. 19–21). One researcher demonstrated that visible fecal contamination on carcasses had a significant impact on the microbiological profile of roaster chickens. (Exhibit No. B-1912, P. 38, L. 17–19). Cross-contamination during the slaughter and processing of turkeys also occurs, though probably to a lesser degree. This result is in part a consequence of the less automated nature of the slaughter of turkeys as compared to that of broilers. (Exhibit Nos. G-1467, P. 2, L. 16–18, and A-201, P. 12, L. 4–5).

In sum, the evidence presented indicates that poultry directly treated with Baytril are not the only birds exposed to fluoroquinolone-resistant *Campylobacter*. Therefore, the use of enrofloxacin has been shown to have an affect on birds beyond those that are directly treated with the fluoroquinolone.

c. Poultry as a Major Source of Fluoroquinolone-Resistant *Campylobacter*

Retail poultry is a reservoir for *Campylobacter* and beef, pork and other retail meat are not as contaminated with *Campylobacter* as are poultry. (Exhibit Nos. G-727, P. 3, G-1484, PP.

2-4, and G-1466, P. 3). A witness for CVM, Dr. Patrick F. McDermott, estimates that approximately one quarter to one third of retail *Campylobacter*-contaminated chicken carry fluoroquinolone-resistant strains of *Campylobacter*. (Exhibit No. G-1465, P. 7, L. 17-23). The significance of this finding is highlighted by the fact that only about 2% of broilers are treated with Baytril. CVM argues that no evidence suggests any major source of fluoroquinolone-resistant *Campylobacter* other than poultry treated with or otherwise exposed to Baytril.

In 1996 a witness for CVM, Dr. Kirk Smith, led a study on quinolone drug resistance in *Campylobacter* isolates from Minnesota residents (Smith study) where domestic chicken was evaluated as a potential source of resistant *Campylobacter*. (Exhibit No. G-589). The Smith study evaluated resistance to quinolones among *Campylobacter* isolates from Minnesota from 1992 through 1998. Resistant isolates and selected sensitive isolates were tested for resistance to ciprofloxacin and Dr. Smith found that 20% of retail chicken products analyzed were infected with resistant *Campylobacter*. (Exhibit No. G-589, P. 5). For ciprofloxacin, resistance was defined as an MIC of $\geq$4 μg/ml, and resistance to enrofloxacin and sarafloxacin (the two fluoroquinolones used in veterinary medicine at that time) was defined as the same as for ciprofloxacin. By the study's definition of MIC of $\geq$4 μg/ml, 96 % of isolates that were resistant to fluoroquinolones actually had MICs of $\geq$32 μg/ml. According to Dr. Smith, an MIC of $\geq$32 μg/ml represents much stronger resistance than one of $\geq$4 μg/ml. (Exhibit No. G-1473, P. 4).

Enrofloxacin is not the only selection pressure that acts upon *Campylobacter* to select for populations that are fluoroquinolone-resistant. Resistant *Campylobacter* had been found in humans when it was not possible for enrofloxacin use to be the cause. Fluoroquinolone use in humans can itself lead to emergence of fluoroquinolone-resistant *Campylobacter* in the treated

individual. (Exhibit No. B-1851). For instance, Dr. Smith found around 6% resistance in humans in the U.S. in 1995. (Exhibit No. G-589, P. 3).

Among the potential sources for *Campylobacter* cited by Bayer is water. Water gets contaminated with *Campylobacter* via animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. (Exhibit Nos. B-1910, P. 4, L. 12–13, and B-1908, P. 8, L. 1–3). However, Bayer's discussion deals with waterborne *Campylobacter*, not specifically fluoroquinolone-resistant *Campylobacter*, and therefore does not support the position that water is an important source of fluoroquinolone-resistant *Campylobacter*. In addition, nearly all wild and domesticated animals, including domesticated pets, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract, and insects can be carriers of *Campylobacter* as well. (Exhibit Nos. G-1483, P. 4, L. 14–15, G-1612, P. 6, G-1719, P. 3, and G-572).

A question is raised as to whether CVM's data on poultry as a source of *Campylobacter* from retail meat studies is representative of the U.S. population as a whole. The Zhao study (Exhibit No. G-727), for example, tested only 184 chicken samples and 172 turkey samples. Bayer contends that such a small sample cannot be considered statistically representative of the U.S. retail market as a whole. However, the studies show similar numbers with regard to prevalence of *Campylobacter* and fluoroquinolone-resistant *Campylobacter*; similar findings from several different retail meat studies from different geographical regions of the U.S. demonstrate that the studies are indicative of the U.S. retail poultry market as a whole.

The Respondent asserts that retail food study samples yield sub-lethally damaged bacteria which can be cultured but cannot cause disease. Bayer also contends that the use of antimicrobials for enrichment in selective media in retail food studies cited by CVM may introduce confounding factors and render the studies unreliable. However, the pre-enrichment

step is acceptable because the purpose of the use of antimicrobials in selective media is to eliminate other competing microorganisms which would hamper the identification of *Campylobacter*. (Exhibit No. G-1466, P. 2, L. 2-11, P. 2, L. 45-P. 3, L. 2).

Because *Campylobacter* are present in retail poultry, it is possible that an infective dose will remain on poultry at the point of consumption. The best kitchen hygiene cannot completely eliminate *Campylobacter*.

There is evidence of record indicating that there are other potential sources of fluoroquinolone-resistant *Campylobacter* including non-poultry animals, retail meats, contaminated water and fluoroquinolone use in humans. Nevertheless, a preponderance of the evidence demonstrates that poultry is in fact a major source of fluoroquinolone-resistant *Campylobacter*.

d. Increase of Resistance Post Enrofloxacin Use

A fluoroquinolone has the effect of killing off all fluoroquinolone-susceptible bacteria, including both the target pathogen (in the case of enrofloxacin, *E. coli*) and other bacteria in the poultry, including *Campylobacter*, but resistant bacteria survive. (Exhibit Nos. G-1463, P. 7, L. 9-11, and G-1465, P. 4, L. 20-25). These surviving bacteria are mutated bacteria, which reproduce and pass on their acquired resistance to daughter bacteria.

With fluoroquinolone treatment, susceptible *Campylobacter* rapidly die off allowing the naturally occurring fluoroquinolone-resistant *Campylobacter* to quickly take over, multiply and colonize the chicken. (Exhibit Nos. G-1465, P. 5, L. 20-24, B-868, P. 3, and G-1800, PP. 2-3). Dr. McDermott wrote, "the use of veterinary-specific fluoroquinolones in chickens generates a rapid increase in the ciprofloxacin MICs of *C. jejuni* (from 0.250 μg/ml to 32 μg/ml) and that this increase appears within the treatment time frame and persists long after treatment is

stopped." (Exhibit No. B-868, P. 3). Dr. McDermott found that within 24 hours of enrofloxacin use *Campylobacter* became seven-fold more resistant to ciprofloxacin than before treatment. (Exhibit No. G-1465, P. 3, L. 1-3).

Bayer contends that Dr. McDermott used high enrofloxacin dosages and long treatment durations not typically used by the broiler industry. (Exhibit Nos. G-1465, P. 2, L. 33-34, and B-1903, P. 5, L. 10-12). Bayer also contends that Dr. McDermott used pooled feces samples and thus his results are misleading and may overestimate resistance levels. However, there is no indication that quinolones were present in the growth medium used by Dr. McDermott to decrease the recovery of susceptible strains in the pooled sample. Dr. McDermott chose 10 colonies from each composite sample, thus, 50 isolates from each pen per collection day were subjected to agar dilution susceptibility testing. (Exhibit No. B-868, P. 2). Furthermore, Dr. McDermott used an approved dose and duration of Baytril treatment in his study. Therefore, Dr. McDermott's findings do not overestimate resistance and his findings are reliable.

The 2002 Qijing Zhang study noted that antibiotic treatment reduced the numbers of fluoroqinolone-sensitive *Campylobacter* and other competing bacterial flora in the gut, and resulted in a favorable environment for the rapid spread and transmission of fluoroquinolone-resistant mutants in the chickens studied. (Exhibit No. G-1800, P. 3). A Jacobs-Reitsma study found that exposure to enrofloxacin selected for resistant *Campylobacter*. (Exhibit Nos. G-1459, P. 7, L. 7-22, and G-315, PP. 2-3). A witness for Bayer, Dr. Dianne Newell found resistance to enrofloxacin and ciprofloxacin as seen by a 7-8 fold increase in MICs in *C. jejuni* recovered 48 hours after starting Baytril treatment in chickens. (Exhibit No. G-1465, P. 4, L. 38-39, Attach., P. 25).

A survey on the animal arm of NARMS showed an overall increase of *Campylobacter* resistance from 1998 to 2001. (Exhibit No. G-1478, P. 12, L. 6-7). CVM believes that from 1998 until 2001 the fluoroquinolone resistance among *Campylobacter* found on chicken and turkey carcasses from the animal arm of NARMS was underestimated due to the methods employed in isolating the organisms, where only nalidixic acid susceptible organisms were selected. (Exhibit No. G-1478, P. 19, L. 22-27).

Dr. Logue examined the antimicrobial susceptibility of *Campylobacter* in turkeys processed at two poultry processing plants in 2000-2001. (Exhibit No. G-1464, P. 2, L. 27 – P. 3, L. 4). At the smaller of the two slaughter plants 8.8% of *Campylobacter* recovered from turkeys were resistant to ciprofloxacin and at the larger of the two plants, 65.3% of the *Campylobacter* were found to be resistant to ciprofloxacin. (Exhibit No. G-1464, P. 6, L. 14-19).

In a study of retail meat bought in the greater Washington D.C. metropolitan area in 1999-2000, 35% of the *Campylobacter* poultry isolates were found to be resistant to ciprofloxacin and 41% were found to be resistant to nalidixic acid. (Exhibit Nos. G-1466, P. 3, L. 24-29, and G-1778, PP. 9-10). In a 1999 CDC study of retail chicken bought in Georgia, Maryland, and Minnesota, 24% of the *Campylobacter* isolates tested were resistant to ciprofloxacin, and a total of 11% of the retail chicken tested contained ciprofloxacin-resistant *Campylobacter*. (Exhibit Nos. G-1484, P. 5, L. 35 – P. 6, L. 3, and G-541, P. 1). In a study conducted in Iowa, 27% of the *C. jejuni* isolates from retail chicken and turkey purchased March 2001 to March 2002 exhibited ciprofloxacin resistance and 27% of the *C. coli* from retail chicken and turkey exhibited ciprofloxacin resistance. (Exhibit No. G-1484, P. 7, L. 43).

The evidence discussed above, including Dr. McDermott's findings, the Zhang study, and NARMS findings indicate that since enrofloxacin approval, the prevalence of fluroquinolone-

resistant *Campylobacter* on poultry has increased. While the studies and data relied on by the parties may have some individual limitations, the evidence as a whole supports the conclusion that the use of enrofloxacin in poultry acts as a selection pressure for fluoroquinolone-resistant *Campylobacter* and results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*.

2. Transfer of Fluoroquinolone-Resistant *Campylobacter* to Humans

CVM contends that fluoroquinolone-resistant *Campylobacter* in poultry are transferred to humans and are a significant cause of fluoroquinolone-resistant *Campylobacter* infections. Bayer agrees that fluoroquinolone-resistant *Campylobacter* in poultry can be transferred to humans and can contribute to fluoroquinolone-resistant *Campylobacter* infections in humans but says that the issue is whether or not the phenomenon is happening and if so, whether it occurs at a level to raise serious questions about safety.

Bayer contends that CVM's evidence on the transfer of *Campylobacter* to humans contain (a) *a priori* assumptions about poultry as a source of campylobacteriosis that are not supported by the most recent, relevant, and robust epidemiological data, (b) outdated studies that conflict with more recent, relevant, and robust data, (c) non-causal temporal associations between enrofloxacin use in poultry and fluoroquinolone-resistant *Campylobacter* 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, and (d) a selective view of the data which ignores contradictory data. According to Bayer, CVM has submitted only two U.S. epidemiology studies that examine the link between poultry consumption and fluoroquinolone-resistant *Campylobacter* infections in humans, Dr. Smith's (Exhibit No. G-589) and Dr. Heidi D. Kassenborg's (Exhibit No. G-337).

Nevertheless, the evidence of record indicates that poultry is in fact a significant source of fluoroquinolone-resistant *Campylobacter* in humans. CVM's analysis is the result of the review of many more studies (including those available pre-Baytril approval) than the two studies referred to by Bayer. (Exhibit Nos. G-228, G-1644, G-299, G-162, G-268, G-953). The evidence as a whole indicates that fluoroquinolone-resistant *Campylobacter* are transferred from poultry to humans and contribute to *Campylobacter* infections in humans.

a. Poultry as a Major Source of Fluoroquinolone-Resistant *Campylobacter* in Humans

The data indicate that there are a number of potential sources of fluoroquinolone-resistant *Campylobacter* in humans. Risk factors for *Campylobacter* infections other than contact with poultry include foreign travel, pets' feces, unpasteurized milk, water, and non-poultry animal foods. (*See* Exhibit Nos. G-1460, G-1457, G-1483, G-1475, B-1908, G-1452, P. 9, L. 40-41, and G-10, PP. 4-5). However, poultry are the most important source of foodborne campylobacteriosis in the industrialized world. (Exhibit No. G-1483, P. 11, L. 1-2). Bayer contends that this position may be due to a faulty and widely held assumption that poultry is the principal or major source of *Campylobacter* infections. (Exhibit Nos. G-185 and B-1908).

A person's most likely exposure to fluoroquinolone-resistant *Campylobacter* is uncooked or undercooked food that contains fluoroquinolone-resistant *Campylobacter*. *Campylobacter* can reach humans who consume poultry at home, consume poultry that is raw or undercooked, consume poultry in a restaurant, handle raw chicken, and fail to clean utensils during food preparation. (Exhibit Nos. G-162, G-268, G-1686, G-602, G-1718, G-334, G-474, G-307, G-1488, G-299, B-561, G-1681, G-182, G-337, G-185, G-1711, and G-1644). Consuming poultry

has been estimated by some U.S. studies to account for around 50% to 70% of *Campylobacter* cases. (Exhibit Nos. G-1644, P. 10 and G-1457 P. 4, L. 15-17).

Bayer argues that if all poultry consumption were a major risk factor for acquiring fluoroquinolone-resistant *Campylobacter*, then poultry would be a risk factor no matter where it is consumed. However Dr. Friedman's data suggest that poultry consumption at home is associated with a lower risk of campylobacteriosis than poultry eaten away from home. (Exhibit No. G-1488). Dr. Friedman's analysis of the FoodNet study suggests that many presumed poultry risk factors, such as eating chicken or turkey prepared at home, touching raw chickens, and chicken prepared at home that required cutting while raw were statistically associated with a lower risk of *Campylobacter* illness. (Exhibit No. G-1452, and Attach. 3, PP. 98–99). Dr. Friedman pointed to some non-chicken sources of *Campylobacter* in restaurants. (Exhibit No. G-1488, P. 23). According to Bayer, people who did not eat chicken at home were twice as likely to acquire *Campylobacter* infections as people who did eat chicken at home. However, while some studies suggest that preparing chicken at home is associated with a lower risk, this can be due to the acquired immunity that may occur with repeated contact with contaminated poultry. (Exhibit No. G-1457, P. 4, L. 23-25).

Temporal and spatial data from various epidemiological and molecular studies have been presented on the transfer of fluoroquinolone-resistant *Campylobacter* from poultry to humans. These studies point to the conclusion that while sources such as contaminated water, non-poultry meats, and pets' feces may contribute to the presence of fluoroquinolone-resistant *Campylobacter* in humans, the chief cause appears to be poultry. Even if Bayer's arguments on eating poultry away from home were substantiated, they are not relevant to the specific issue of whether the use of fluoroquinolones in poultry has resulted in an increase of fluoroquinolone-

resistant *Campylobacter* which thereby presents a significant human health risk, e.g. to those persons eating chicken (poultry) away from the home. CVM was correct in its contention that "FDA's ability to regulate the safety of new animal drugs cannot be constrained by unanswerable questions such as, '[i]s the antibiotic intended to be administered to chickens whose post-slaughter destination is a restaurant's kitchen or a consumer's kitchen?'" Exposure of humans to poultry with fluoroquinolone-resistant *Campylobacter* appears to be an important risk factor.

i. CVM Risk Assessment

The CVM risk assessment was initiated to estimate the likelihood of human health impact of fluoroquinolone-resistant *Campylobacter* from fluoroquinolone-resistant *Campylobacter* on poultry. It found that in 1998, the mean number of people in the U.S. who acquired fluoroquinolone-resistant *Campylobacter* infections associated with consumption of chicken and who subsequently received treatment with a fluoroquinolone was 8,678; in 1999, this number increased to 9,261. (Exhibit No. G-953, PP. 63-64).

CVM developed a mathematical model for microbial food safety to relate the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens. (Exhibit No. G-953, P. 6). The model 1) estimates the expected annual number of cases seeking care that are fluoroquinolone-resistant and attributed to the use of fluoroquinolones in chickens, λ, 2) estimates the quantity of consumed chicken with fluoroquinolone-resistant *Campylobacter,* V_i, and, 3) estimates a parameter, K_{res} linking the quantity of chicken with fluoroquinolone-resistant *Campylobacter* and λ. The formula illustrating the link is $K_{res} \times V_i = \lambda$. (Exhibit No. G-1454, PP. 4-5). The goals of this model were to assess the impact of fluoroquinolone-resistant *Campylobacter* from broilers on human health; provide a transparent

and robust assessment based on published and, where necessary, regularly revised data to the extent that it is available; and allow future changes in the system being modeled. (Exhibit No. G-953, P. 8). The model produced a number of findings including estimates of the probability a person would be affected by the risk in question for various U.S. sub-populations, estimates of nominal mean number of *Campylobacter* cases in the U.S. population, and estimates of the nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken. (Exhibit No. G-953, P. 12).

Bayer and AHI argue that the CVM risk assessment should be disqualified for a number of reasons. One reason is that CVM allegedly did not follow traditional microbial risk assessment methodology and should have conducted a farm-to-fork risk assessment that would have relied on a dose-response model. (*See* Exhibit No. G-953, P. 8). However, a farm-to-fork analysis would be problematic for several reasons. Among those reasons is that that type of analysis would have resulted in greater data gaps because such analysis would require significant assumptions that could not be supported by data. (Exhibit Nos. G-1480, P. 10, L. 26-27 and G-1479, P. 17, L. 8-17). Also, a farm-to-fork analysis would be very costly to maintain as new studies and data could be required to reflect any changes in husbandry, transportation, processing, and human behavior. (Exhibit No. G-1480, P. 10, L. 30-32). Additionally, a dose-response model was inappropriate for CVM's purposes because of insufficient dose-response data on *Campylobacter* and because there is no generally agreed upon analysis. (Exhibit No. WDT G-1480, P. 10, L. 33-35). Furthermore, a more intricate risk assessment model, such as a farm-to-fork model, would not have yielded additional information of use to CVM and would have increased the likelihood of error in the model's calculations. (Exhibit No. G-1480, P. 10, L. 6-8, L. 10-13, L. 26-29, and L. 33-35).

Bayer also points out that Dr. Friedman found that eating non-poultry meats at a restaurant constitutes a risk factor of similar magnitude to eating chicken at a restaurant, suggesting that the source of campylobacteriosis in restaurants could be something besides poultry. (Exhibit No. G-1488, P. 23). Bayer argues that when such a questionable variable exists, although there is no single approach that is entirely suitable, one possibility is to drop that variable from the regression to determine whether its exclusion makes a difference. Using backward step-wise regression, Dr. Kassenborg did this in her analysis of risk factors for domestically acquired fluoroquinolone-resistant *Campylobacter* infections and found that chicken was not a risk factor. (Tr. P. 603, L. 2–14). However, she testified that she did not report this finding. (Tr. P. 603, L. 15–21).

CVM pointed out that the population attributable fractions were 24% for eating chicken in a restaurant and 4% for eating turkey in a restaurant, suggesting that at least 28% of the domestically acquired *Campylobacter* infections could be eliminated if the risk from eating poultry in a restaurant were eliminated. Although the population attributable fraction was 21% for eating non-poultry meat in a restaurant, it is the poultry meat (and not the non-poultry meat) at slaughter and retail that has been found to be highly contaminated with *Campylobacter*. Given the probable volume of poultry entering the restaurant and the high prevalence of *Campylobacter* contamination of poultry relative to other food, it is possible that the highly contaminated poultry meat could have cross-contaminated the non-poultry meat during handling and preparation at the restaurant.

According to Bayer, the CVM risk assessment is flawed in its approach to calculating the fraction of resistant cases attributable to the use of Baytril on chickens because the risk assessment just subtracts cases attributable to foreign travel and prior treatment from the

aggregate of all resistant cases, and assumes that all the remaining resistant cases are due to the use of Baytril. In so doing, it ignores other sources of resistant *Campylobacter*, including water from wastewater treatment plants that do not receive meat-processing waste. (Exhibit No. G-953, PP. 49–50, Tr. P. 810, L. 1– P. 815, L. 20, and G-1488, P. 23).

CVM argues, however, that witness for Bayer, Dr. James W. Patterson, presented a comparison of the numbers of foodborne versus waterborne campylobacteriosis cases that is misleading. Dr. Patterson estimates that up to 500,000 annual incidences of U.S. waterborne infection can be attributed to *Campylobacter*. (Exhibit No. B-1910, P. 27, L. 9-15). However, according to Exhibit No. B-927, there were approximately 2.1 million total cases of campylobacteriosis, only 15% of which were attributed as waterborne. Fifteen percent of the total cases equal 320,000, far fewer than the "almost 500,000" cases Dr. Patterson asserts are waterborne. (Exhibit No. B-927, PP. 8-9).

Dr. Patterson also uses a 60,000 figure as an estimate of foodborne campylobacteriosis cases. (Exhibit No. B-1910, P. 27, L. 15-16). However, this 60,000 figure is based on actual reported cases, not an estimate of total cases of foodborne attributed campylobacteriosis. In order to get a correct figure, one first must multiply the 60,000 reported cases by 38, since CDC has estimated that the true incidence of campylobacteriosis is 38 times the reported cases. (Exhibit No. G-410, P. 12). Using Dr. Patterson's 60,000 figure, and multiplying it by 38, there would be 2,280,000 cases of foodborne related campylobacteriosis. If Dr. Patterson made a fair comparison, he would have found that waterborne cases of campylobacteriosis (320,000) fall far behind foodborne cases of campylobacteriosis (2.28 million). (Exhibit Nos. B-927, P. 9 and G-410). Even with the slight difference in the estimates of total campylobacteriosis (Exhibit No. B-927, P. 8 uses a 2.1 million total figure and Exhibit G-410, P. 5 uses a 2.4 million total figure), it

is clear that Patterson's assertion that most campylobacteriosis is waterborne is incorrect. Based on these figures, it can be concluded that annual waterborne incidences (500,000) are far less than total campylobacteriosis cases.

Bayer argues that the CVM risk assessment did not use recent data and thus overestimated the risk. In its support, Bayer cited the Hopkins study (Exhibit No. G-299), a study CVM dropped, having considered it faulty. The study found no overall correlation between chicken consumption and campylobacteriosis. Bayer also contends that CVM overlooked or disregarded certain relevant data from the FoodNet study, including Dr. Friedman's analysis showing that eating chicken and turkey is associated with a lower risk of *Campylobacter* illness. Dr. Friedman, however, did note that "[t]he most important food-specific risk factor was consumption of chicken prepared at a commercial food establishment. Combined with consumption of turkey prepared at a commercial food establishment and with consuming undercooked chicken, which were independent risk factors...indicates that poultry was the dominant food source for *Campylobacter* infection during the study period." (Exhibit No. G-1488, P. 11). Furthermore, Bayer looked at a limited number of studies including the Friedman and Kassenborg analyses of the 1998-1999 FoodNet *Campylobacter* case-control study; the Dr. Deming and Dr. Harris studies; and the Smith study, while CVM evaluated the results of those studies plus an additional number of studies to find that poultry is an important risk factor for acquiring campylobacteriosis.

AHI argues that the CVM risk assessment does not comport with an accepted NAS paradigm as produced by the NRC, it does not comport with Data Quality Act Standards, and its "predictive model approach" has not been generally accepted in the risk assessment field. AHI says that the risks of enrofloxacin are no greater than those accepted by FDA under the Safe

Drinking Water Act (SDWA). The CVM risk assessment does not have to follow the NRC guidelines because they are not necessary for developing a scientifically sound antimicrobial risk assessment, they are not standards that must be followed.

Finally, Bayer and AHI argue that the CVM risk assessment fails to meet FDA Guidelines. The FDA Guidelines follow Office of Management and Budget (OMB) guidelines implementing section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001. (Public Law 106-554; H.R. 5658). The FDA Guidelines are designed to ensure and maximize the quality, objectivity, utility, and integrity of information disseminated by the FDA. (67 Fed. Reg. 8,452, February 22, 2002). In the case of influential information, special care is required under the FDA Guidelines. Influential information is "disseminated information that results from or is used in support of agency actions that are expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities." (FDA Guidelines § VII (A)).[9] If information is influential information, it must meet higher standards of transparency and methods to facilitate its reproducibility.

FDA strives to ensure its information is reproducible, replicable, accurate, and unbiased, a goal that is served by the use of reliable data sources and sound analytical techniques and by using high degree of transparency. (FDA Guidelines § VII (B)). In the case of influential risk assessments, FDA Guidelines state that "[w]ith regard to analysis of risks to human health, safety, and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and

[9] FDA Guidelines, *available at* www.hhs.gov/infoquality/fda.html.

disseminated pursuant to the SDWA Amendments of 1996 (42 U.S.C. 300g-1(b)(3)(A) and (B))." (FDA Guidelines § VII (C)).

The SDWA risk assessment guidelines state that the agency shall use the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices, and data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data). (FDA Guidelines § VII (C)). In addition, for quantitative risk assessments FDA is to specify a) each population addressed by any estimate of applicable effects; b) the expected or central estimate of risk for the specific populations affected; c) each appropriate upper-bound and/or lower-bound risk estimate and the methodology used to reconcile the inconsistencies in the scientific data; d) data gaps and other significant uncertainties identified in the process of the risk assessment and the studies that would assist in characterizing the uncertainties; and e) additional studies not used to produce the risk estimate that support or fail to support the findings of the assessment, and the rationale of why they were not used. (FDA Guidelines § VII (C)).

AHI alleges that the evidence in this proceeding constitutes influential information because the proposed withdrawal of Baytril is reasonably expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the poultry industry, productivity in the poultry industry, the environment, and/or public health or safety. Furthermore, AHI contends that even if the FDA Guidelines are not strictly applicable to this proceeding, they are influential in determining the reliability of CVM's testimony and evidence in this proceeding.

AHI contends that the CVM risk assessment fails to meet the FDA Guidelines. It contends that the CVM risk assessment model 1) does not use the best available science and

supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available; 2) uses data not collected by accepted methods (where reliability of the method and the nature of the decision justifies use of the data); and 3) does not identify, use, or explain why additional studies were not used to produce the risk estimate to support or fail to support the findings of the assessment; and 4) does not follow the SDWA approach for quantitative risk assessment. Thus, the CVM risk assessment is unreliable and irrelevant, according to AHI.

CVM's risk assessment does in fact comport with the FDA Guidelines. First, CVM used realiable science and supporting studies, including the Dr. Harris and Dr. Deming case-control studies that provided the best, supportable attributable fractions at the time CVM conducted its risk assessment. (*See* Exhibit Nos. G-1480 and G-1454). Although the CVM risk assessment model's findings have not been published in a peer reviewed journal, the model went through a rigorous review that usually accompanies peer reviewed journal publication. (Exhibit No. G-1480, P. 6, L. 25-34). Furthermore, while CVM's risk assessment model was not published in a peer review journal, it was subject to scrutiny by the public and scientific experts and through this process adequately peer reviewed.

Second, the data used in the risk assessment was collected by adequate methods. The data was compiled by federal agencies, including the CDC and the USDA, and not for the hearing or any regulatory action with respect to specific drug products.

Third, the CVM risk assessment did not use some additional studies because its final risk assessment report was published in January 2001. At the time that the CVM risk assessment was conducted, Dr. Friedman's analysis of the CDC data had not been completed and Dr. Effler's study was not published until February 2001. (Exhibit Nos. G-185 and G-228). Since neither

Dr. Friedman's analysis of the CDC data, nor Effler's study, had been completed prior to CVM publishing its risk assessment report, CVM could not use those data in its report. In addition, CVM reviewed the draft results produced by Dr. Friedman which found an attributable fraction of 28% for poultry meats consumed at a restaurant. Since Dr. Friedman's results were consistent with the estimates of attributable risk fractions from the Dr. Harris and Dr. Deming studies, CVM saw no need to revise its model.

Fourth, CVM acknowledges that the risk assessment model does not follow the SDWA approach for quantitative risk assessments. However, the OMB Guidelines state, "agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996. The word 'adapt' is intended to provide agencies flexibility in applying these principles to various types of risk assessment." OMB Guidelines, 67 Fed. Reg. at 8,458. In line with the OMB Guidelines, the FDA Guidelines *adapted* the general principles for risk assessments from the SDWA.[10]

If the withdrawal of Baytril would have an effect of $100 million or more on the economy, the CVM risk assessment would need to meet FDA's more stringent guidelines for "influential information." However, Exhibit No. B-1907, containing the written direct testimony of G. Thomas Martin, Jr., the exhibit AHI cites to as showing that the withdrawal would have such an influential effect, was stricken in its entirety from the record. It was stricken because it was found to be altogether unreliable, and not just on the issue of economic effects of Baytril's withdrawal.

Overall the CVM risk assessment is reliable and presents valuable information regarding poultry as a major source of fluoroquinolone-resistant campylobacteriosis. As to the criticisms

[10] FDA Guidelines and Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by HHS Agencies. (67 Fed. Reg. 61,343, Sept. 30, 2002).

leveled against the CVM risk assessment in the information quality complaint of January 23, 2003, the record establishes that the risk assessment falls within the OMB Guidelines, and it has not been shown that the risk assessment has to meet the more stringent risk assessment guidelines for "influential information." The risk assessment provides a reliable source of evidence on the effects of Baytril use in poultry.

ii. FoodNet Study

One of the main epidemiological studies on *Campylobacter* infections in the U.S. is the CDC's 1998-1999 FoodNet *Campylobacter* Case-Control Study (FoodNet study).[11] The FoodNet study, led by Dr. Heidi Kassenborg, considered approximately 7.7% of the U.S. population and was conducted in several states. (Exhibit Nos. G-1460, P. 3, L. 10-12 and G-228, P. 1). *Campylobacter* was tested for susceptibility to eight antimicrobial agents including ciprofloxacin and nalidixic acid. (Exhibit No. G-1452, P. 14, L. 12-14). *Campylobacter* isolates were tested beginning in 1997. (Exhibit Nos. G-1452, P. 3, line 36 and G-749, P. 9). Risk factors associated with fluoroquinolone-resistant *Campylobacter* and *Campylobacter* infections were analyzed and it was found that poultry, particularly chicken, is the dominant source of domestic *Campylobacter* infections in humans. (Exhibit Nos. G-1452, P. 10, L. 46 – P. 11, L. 1 and G-1488, P. 3).

In the FoodNet study, cases and controls (1316 of each) were asked about foreign travel, food and water exposures, and food handling practices in the seven days prior to illness onset. (Exhibit No. G-1452, P. 10). The population attributable fraction for foreign travel was 12%,

[11] FoodNet is the principal foodborne disease component of the CDC's Emerging Infections Program and a part of the human branch of NARMS. (Exhibit Nos. G-1478, P. 6, and G-1452, P. 2, L. 15-21). It is designed to augment longstanding activities at the CDC, participating state health departments, the FSIS and FDA, to identify, control, and prevent foodborne disease hazards. Its primary purpose is to monitor antimicrobial resistance among foodborne enteric bacteria including *Campylobacter, Salmonella,* and *E. coli*. (Exhibit No. G-1452, P. 3, L. 17-19). *Campylobacter* isolates are sent to the CDC for susceptibility testing at a rate of one isolate per week. (Exhibit No. G-1478, P. 7, L. 30-34).

suggesting that 12% of sporadic cases of campylobacteriosis in the United States are due to travel outside the United States. (Exhibit No. G-1452, P. 10, L 18-20). Among study subjects with no foreign travel the following exposures were significant risk factors for infection: eating undercooked poultry (7% patients versus 4% controls), eating chicken or turkey that was cooked outside the home (46% patients versus 28% controls), eating non-poultry meat that was cooked outside the home (51% patients versus 34% controls), eating raw seafood (5% patients versus 3% controls), drinking raw milk (2% patients versus 1% controls), living or visiting a farm (16% patients versus 9% controls), having contact with farm animals (11% patients versus 5% controls), and having contact with puppies (11% patients versus 6% controls). Eating chicken or turkey cooked in the home was a protective factor (53% patients versus 69% controls). (Exhibit No. B-27, P. 1-2). The percent of *Campylobacter* isolates resistant to ciprofloxacin was reported as 13% in 1997, 14% in 1998, 18% in 1999, 14% in 2000, and 19% in 2001. (Exhibit Nos. G-1452, P. 8, L. 9-11 and G-1487).

In analyzing the FoodNet data, Dr. Friedman used a multivariate logistic regression model to determine independent risk factors for acquiring a *Campylobacter* infection among persons who did not travel outside the U.S. (Exhibit No. G-1452, P. 10, L. 22-23). Friedman found that the largest population attributable factor for *Campylobacter* infections was eating chicken in a restaurant, at 24%, and eating non-poultry meat in a restaurant, at 21%. (Exhibit Nos. G-1452, P. 10, L. 36-39 and G-1488, P. 23). Friedman's final multivariate logistic regression model found that (a) cases were 2.2 times more likely to have eaten chicken in a restaurant in the seven days prior to illness onset than controls (44% of cases ate chicken in a restaurant compared with 26% of controls), (b) cases were 2.5 times more likely to have eaten turkey in a restaurant in the seven days prior to illness onset than controls (6% of cases ate turkey

in a restaurant compared with 3% of controls), and (c) cases were 1.7 times more likely to have eaten non-poultry meat in a restaurant in the seven days prior to illness onset than controls (52% of cases ate non-poultry meat in a restaurant compared with 35% of controls). (Exhibit No. G-1452, P. 10, L. 23-32).

Dr. Kassenborg found that 58% of those with a fluoroquinolone-resistant *Campylobacter* infection acquired the infection domestically. (Exhibit No. G-1460, P. 7, L. 19-22). Effler's case-control study of an analysis conducted in Hawaii had findings similar to Dr. Friedman's and Dr. Kassenborg's. (Exhibit Nos. G-1483, P. 14, and G-185).

Bayer and AHI argue that the Friedman and Kassenborg studies show that poultry are statistically associated with campylobacteriosis and fluoroquinolone-resistant campylobacteriosis only under limited conditions such as whether the poultry is prepared at a restaurant or cooked at a commercial establishment. (Exhibit Nos. 1488, P. 23 and G-337, P. 15). They argue that Dr. Burkhart and Dr. Cox reviewed the data of Dr. Kassenborg's analysis and were unable to replicate her findings. (Exhibit Nos. B-1901, and B-1900, P. 31, L. 25-32, P. 32, L. 32-44). Dr. Kassenborg did testify that she found that eating chicken or turkey at a commercial establishment was the only risk factor that remained independently associated with fluoroquinolone-resistant campylobacteriosis. (Tr. P. 601, L. 20 – P. 602, L. 5).

Bayer argues that there are flaws in the logistic regression model such as that it was not able to successfully account for the potentially confounding effects of the changing population base and the site variability in ciprofloxacin resistance. Bayer contends that in conducting the logistic regression model, CDC failed to explore how the independent variables and outcome measured vary with the passage of time, and the analysis obliterated the sequential relationship

among temporal identifiers which precluded analysis of trends because each year was considered in isolation.

Dr. Kare Molbak noted that FoodNet figures are not reflective of the entire U.S. population. (Exhibit No. G-1468, P. 5, L. 20-21). The data collected and analyzed by FoodNet indicate some demographic differences between the populations residing in the FoodNet surveillance area and the U.S., but despite these differences, the distribution of the FoodNet population across several other demographic factors such as age, gender, and health indicators, is similar to that of the U.S. population. (Exhibit No. G-1452, P. 4, L. 21-26).

Bayer and AHI claim that FoodNet analyses did not find a connection between poultry and fluoroquinolone-resistant campylobacteriosis. Bayer did acknowledge, however, that there was a statistically significant association between eating chicken or turkey at a commercial establishment and an increased risk of acquiring fluoroquinolone-resistant campylobacteriosis.

It is not practical for investigators to consider all available studies or all existing analytical methods. They must make a reasonable plan for their analysis. Bayer and AHI have not shown why the methods utilized by FoodNet analysis studies were inadequate. That, coupled with the fact that Bayer acknowledges that there is a connection to campylobacteriosis and eating poultry at a commercial establishment, leads to the conclusion that FoodNet analysis is reasonable and reliable and points to the conclusion that eating poultry is associated with an increased level of campylobacteriosis in humans.

iii. <u>Microbiological and Molecular Studies</u>

Microbiological and molecular studies were presented in this proceeding. Bacterial typing studies characterize bacterial isolates below the species level, and serotyping compares strain similarity at the cellular level. (*See* Exhibit Nos. G-1453, P. 4 and G-1475, P. 11).

Subtyping compares strain similarity at the genetic level; strain subtypes are called genotypes. Several subtyping techniques, most of which generate a form of DNA fingerprint, exist. DNA fingerprinting is used to strengthen statistical associations found in epidemiological analyses. (Exhibit No. G-1455, P. 6, L. 27-30). It does not tend to show proof of the causation of a disease. (Tr. P. 518, L. 20 – P. 521, L. 4, Exhibit No. G-1455, P. 7, L. 1-3).

DNA fingerprinting methods have different levels of resolution and CVM argues that using a method that provides a higher level of resolution is not necessarily better for revealing information on bacterial strain relatedness because if there is too much resolution, all the bacterium may appear different. (Exhibit No. G-1455, P. 7, L. 5 – P. 8, L. 8). Two DNA fingerprinting methods commonly used to study *C. jejuni* are pulsed-filed gel electrophoresis (PFGE) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).[12] (Exhibit No. G-1470, P. 8, L. 1-2). Other methods, including ribotyping, amplified fragment length polymorphism (AFLP), and multilocus sequence typing (MLST) have also been used. (Exhibit No. G-1470, P. 7, L. 34-40).

Typing studies have repeatedly isolated bacterial types from human *Campylobacter* isolates that are related to *Campylobacter* from poultry. Though microbiological and molecular studies do not show a complete overlap between poultry and human *Campylobacter* isolates, their findings are significant. Dr. Smith stated that it is unlikely that a common third source accounts for the overlap results. (Tr. P. 557, L. 15-19).

Dr. Smith found 92.3% of isolates from humans overlapping with chicken retail samples. (Exhibit No. G-1455, P. 10, L. 7-10). Using PCR-RFLP, a study in the U.K. by Clow (Exhibit

[12] PFGE examines gene sequences that could occur on any part of the bacterial genome. (Exhibit No. G-1455, P. 9, L. 37 – L. 44). PCR-RFLP, specifically of the *flaA* gene (*flaA*-RFLP), examines DNA sequences in the flagellin (or flagellar) gene, which codes for the bacteria's motility appendage (the flagellum). (Exhibit No. G-1455, P. 9, L. 23-33).

No. B-250) found "at least 77% of human [*Campylobacter*] infections could potentially be explained by poultry exposure." (Exhibit No. G-1453, P. 6, L. 43-44). Studies with similar findings include an MLST study from the U.K. (Exhibit No. G-1629), a Netherlands study using AFLP analysis (Exhibit No. G-176), and a study in Canada using PFGE (Exhibit No. G-1684).

Bayer contends that *flaA*-RFLP subtyping (used by Dr. Smith in Exhibit No. G-589, Dr. Clow in Exhibit No. B-250, Dr. Wu in Exhibit No. G-1775) may be of limited value because the technique has low discriminatory power. (Exhibit No. B-1927, P. 7). However, *flaA*-RFLP subtyping is adequately discriminating to allow for conclusions about the relatedness of bacterial isolates. (Exhibit Nos. G-1453, P. 5, L. 6-34 and G-1470, P. 8, L. 13-16). Furthermore, *fla* typing is widely accepted. (Exhibit Nos. B-1927 and G-1453, P. 7, L. 30-32).

Bayer contends that Smith's (Exhibit No. G-589) and Dickins' (Exhibit No. G-1785) are the only genetic typing studies in evidence that compare retail poultry *Campylobacter* isolates with those of human campylobacteriosis isolates that are based solely on U.S. data and conducted and reported since the approval of Baytril. The Dickins study reported a clonal overlap of only 4 chicken isolates out of 54 human isolates. (Exhibit No. G-1785, P. 5). However, this study was not performed to trace Campylobacter movement from chickens to humans. In fact, the study undercuts Bayer's point and concluded, "most cases of campylobacteriosis are sporadic and...the variation of PFGE patterns present on possible sources of infection (e.g., retail poultry carcasses) makes traceback studies difficult." (Exhibit No. G-1785, P. 5).

According to Bayer, Dr. Smith's epidemiology did not show poultry as a source of fluoroquinolone-resistant *Campylobacter* infections and misuses genetic typing to establish a link because genetic typing should not be used independently of epidemiological analysis. Dr.

Smith did not compare isolates to a potential third source though there is evidence that there may be such sources of *Campylobacter* common to chickens and humans. (Tr. P. 533, L. 8 - P. 534, L. 3 and Exhibit No. B-1901, PP. 20–21, P. 45).

A molecular subtyping study in Finland of human and chicken isolates showed overlapping genotypes among human and chicken strains. (Exhibit Nos. G-1458, P. 7 and G-264). The results were corroborated with three subtyping methods (PFGE, AFLP ribotyping) applied in combination with serotyping. (Exhibit Nos. G-1458, P. 7 and B-380). In Iceland, researchers subtyped a portion of the *flaA* gene called the SVR DNA sequence and reported that *Campylobacter* with identical *flaA* SVR DNA sequences were found in broilers and in human disease. (Exhibit Nos. G-771, and G-1475, P. 12, L. 41-42). Using PFGE and *fla* typing, a researcher in the U.K. found that turkeys were a reservoir of *Campylobacter* subtypes found in human clinical isolates. (Exhibit Nos. G-1470, P. 9, L. 8-11, and G-218).

A comparison of serotypes in the Netherlands of human and animal isolates of *C. jejuni* published in 1985 showed that four of the five most common types present in human isolates were also common in poultry and that there was little overlap between human and hog serotypes. (Exhibit Nos. G-1698, P. 4, and G-1475, P. 11, L. 44 – P. 12, L. 6). A study in Denmark published in 1997 observed a large overlap of in distribution of *Campylobacter* serotypes between human serotypes and serotypes found in broiler chickens and cattle isolates. (Exhibit No. G-1457, P. 5, L. 17-22). The study concluded that poultry (as opposed to cattle) is likely to be a major source of campylobacteriosis. (Exhibit No. G-459, P. 8). A study in Denmark published in 2001of *C. jejuni* isolates found an overlap in genotypes between poultry and human *Campylobacter* isolates. (Exhibit No. G-494, P. 5).

Researchers in Taiwan conducted an evaluation specifically of quinolone-resistant *Campylobacter* isolates from poultry and from humans. (Exhibit Nos. G-1457, P. 5, L. 26-29). When combining PFGE and *flaA*-RFLP methods, the study found that the quinolone-resistant genotypes that were identified in nearly 40% of the human isolates were also identified in the poultry isolates. (Exhibit Nos. G-1457, P. 5, L. 29-30, and G-1775, PP. 3-4).

Microbiological and molecular data are strong indicators of a causal relationship between poultry and campylobacteriosis. However, these data are more beneficial when they are combined with epidemiological analysis. Respondent suggests that studies conducted outside of the U.S. are often given less weight than those conducted in this country. However, there is nothing in this record to support such a conclusion. Accordingly, the results of these studies are relevant and add to the totality of the evidence supporting a causal relationship between poultry and campylobacteriosis.

b. Prevalence of *Campylobacter* Post-Enrofloxacin's Approval

i. U.S. Studies

CVM has shown that post-enrofloxacin approval, there has been an increase in fluoroquinolone-resistance in the U.S. Dr. Smith's study found that the proportion of nalidixic acid-resistant *C. jejuni* isolates from Minnesota residents increased from 1.3% in 1992 to 10.2% in 1998. (Exhibit No. G-1473, P. 7, L. 9-12). In the Smith study, the rates of resistance appeared to carry a seasonal pattern where the percentage of isolates that were resistant to nalidixic acid peaked during the first quarter of each year and showed valleys during the third quarter of each year; both the peaks and the valleys generally increased over time. (Exhibit No. G-1473, P. 7, L. 14-18). When Dr. Smith looked at domestically-acquired *C. jejuni* infections, he found four times more cases in 1998 than 1996. (Exhibit No. G-1473, P. 12, L. 13-19).

A national study conducted 1989 to 1990 found the level of ciprofloxacin resistance among 332 *Campylobacter* isolates tested to be nearly zero, at 0.3% resistance. (Exhibit Nos. G-624, and B-589). In isolates collected from patients between 1982 and 1992 in a U.S. study, none of the isolates were resistant to ciprofloxacin. (Exhibit Nos. G-440, PP. 2-3 and G-1470, P. 6, L. 31-36). A follow-up study by the same researcher, Dr. Irving Nachamkin, on isolates collected between 1995 and 2001 reported resistance of 8.3% in 1996 and 40.5% in 2001. (Exhibit No. G-1470, P. 6, L. 36-45).

There is no established baseline for pre-approval resistance levels of *Campylobacter* in the U.S. Bayer claims that resistance levels of up to 20% existed in the U.S. prior to enrofloxacin's approval. In 1988 Dr. Barrett found 5% quinolone resistance in *C. jejuni* isolated from humans. (Exhibit Nos. G-1453, P. 3, L. 3-10). In *Campylobacter* isolated from humans from August 1992 to April 1995 Dr. Kiehlbach found 12% of *C. jejuni* resistant to ciprofloxacin. (Exhibit No. B-39, P. 3). Dr. Smith found 1.3% fluoroquinolone resistance in *Campylobacter* isolated from humans in 1992, and 6% resistance in *C. jejuni* isolated from humans in 1995. (Exhibit No. G-589, P. 1, 3).

Despite the fact that there is imperfect information regarding pre-approval resistance levels of *Campylobacter*, NARMS data show that since enrofloxacin's approval, ciprofloxacin-resistant *Campylobacter* infections in the U.S. have risen. In human NARMS, the percent of *Campylobacter* isolates resistant to ciprofloxacin was 13% in 1997, 14% in 1998, 18% in 1999, 14% in 2000, and 19% in 2001. (Exhibit Nos. G-1452, P. 8, L. 9-11, and G-1487).

Bayer contends that neither the poultry NARMS data nor the human NARMS data are of value in demonstrating temporal trends in the U.S. Bayer claims that NARMS has no way of distinguishing whether the resistance it reports is from foreign travel or is domestically acquired,

because NARMS does not collect data on source of infection. (Tr. P. 116, L. 3-6). Additionally, Bayer notes that susceptibility testing of *Campylobacter* isolates from poultry was not added to the animal arm of NARMS until 1998, which to Bayer makes questionable any use of poultry NARMS data for temporal trend purposes. (Exhibit No. G-1478, P. 9, L. 4-5). Bayer contends that NARMS captures only a limited demographic area, and the data collected do not include information about whether the person took a fluoroquinolone antibiotic prior to submitting a sample. (Tr. P. 113, L. 12 - P. 114, L. 10).

There have been a number of changes in the poultry NARMS program over the years and Bayer argues that makes any year-to-year comparisons meaningless. Between 1998 through 2001, sources for *Campylobacter* isolates used in the animal NARMS program were very different; the source of isolates provided by FSIS has not been consistent from year to year. (Exhibit Nos. A-199, P. 6, L. 17-18, G-1478, P. 9, L. 15-P. 11, L. 8, and A-200, P. 6, L. 13-15). The culture techniques utilized to isolate *Campylobacter* in the animal NARMS program have not been consistent. (Exhibit No. A-199, P. 7, L. 2-3). Though NARMS did not employ the same methods yearly, the facts do not support the conclusion that the study's findings are meaningless.

Bayer argues that the Smith study has limitations. The study did not control for foreign travel and prior flouoroquinolone use. (Exhibit No. B-1900, P. 19, L. 6 – P. 20, L. 23). Bayer also contends that Dr. Smith's study sought to connect fluoroquinolone-resistant campylobacteriosis to chicken based largely on genetic typing. However, while the Smith study may have limitations including lack of control for foreign travel, the study's conclusions were not based exclusively on genetic typing data but epidemiological data were also considered. (Exhibit No. G-589).

It is not clear what was the exact pre-approval level of fluoroquinolone resistance in the U.S. Nevertheless, those levels appear significantly higher post-approval as compared to pre-approval.

ii. Non-U.S. Studies

The experiences of several countries provide support for the conclusion that poultry is a source of fluoroquinolone-resistant campylobacteriosis. Countries without enrofloxacin including Finland, Australia, and Sweden, have had infections linked to foreign travel, according to CVM, while in countries with enrofloxacin, fluoroquinolone-resistant strains are due to fluoroquinolone use in veterinary medicine. In countries including UK, Denmark, Sweden, Switzerland, Norway, Netherlands, and Canada, eating poultry was identified as a risk factor.

There are some analyses that do not support CVM's temporal association contentions. In Finland, fluoroquinolones were never marketed but resistance to ciprofloxacin went from 9% in 1990 to 17% in 1993. (Exhibit No. B-881, P. 2). Bayer contends that this cannot be accounted for by foreign travel, but partly by natural resistance. (Exhibit No. G-524, P. 4). In Sweden in 1981 where fluoroquinolones were not approved for use in poultry, a study found 39% quinolone resistance in poultry *Campylobacter* and 11% in human *C. jejuni*. (Exhibit Nos. B-1851 and A-201, P. 14, L. 8–14). Dr. 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 consumption of poultry meat, there was no detectable increase in campylobacteriosis. (Exhibit No. B-1908, P. 24, L. 10–14).

On the other hand, in 1999 in Belgium, all chicken and eggs were withdrawn from the market for four weeks due to a dioxin scare. A study on that incident reported a decline of 40% in the number of *Campylobacter* infections. (Exhibit No. G-672).

Fluoroquinolones have been used in the Netherlands in human medicine since 1985 and in animal medicine (enrofloxacin) since 1987. (Exhibit No. B-298). Between 1982 and 1989 in the Netherlands, *Campylobacter* fluoroquinolone resistance rose from 0% to 14% in poultry isolates and from 0% to 11% in human isolates. (Exhibit No. G-190, P. 1). In the Netherlands enrofloxacin was approved under very similar conditions of use as those required in the U.S. (Exhibit No. B-1916, P. 13, L. 3-5).

Bayer contends that countries with low poultry resistance such as Canada, where resistance in humans is high, disprove CVM's temporal relationship argument. A study of 309 *C. jejuni* isolates taken from humans in Ontario from 1992 to 1994 found that 13.6% of the isolates were resistant to nalidixic acid. (Exhibit No. B-32, P. 3). The study also analyzed 69 *C. coli* isolates gathered during the same time period, and found 29.0% were resistant to nalidixic acid. (Exhibit No. B-32, P. 4).

Bayer contends that prudent use restrictions, like those put in place when enrofloxacin was approved in the U.S., have been successful in controlling resistance levels. In Spain, according to witness Dr. Marja-Liisa Hanninen, fluoroquinolone use is not strictly regulated. (Tr. P. 675, L. 22 - P. 676, L. 1). In that country, between 1987 and 1997-1998 resistance on poultry *Campylobacter* isolates increased from near non existence to 99% and from 1987 and 1993 increased in human *Campylobacter* isolates from 0% to 48.8%. (Exhibit Nos. G-549, P. 2, and G-532, P. 2). Bayer asserts that in Denmark anti-microbial use has been strongly regulated and in 2000 Denmark was reporting only 8% and 10% ciprofloxacin resistance in broiler chicken *C. jejuni* and *C. coli* respectively.[13] (Exhibit No. G-151, P. 25). In humans, ciprofloxacin resistance in domestically-acquired cases in Denmark was 22%. (Exhibit No. G-151, P. 27).

[13] An internal Bayer email from 1997 acknowledged that "[r]esistance rates in Denmark are low because relatively few Baytril is being used." (Exhibit No. B-454).

While interesting, the experience in Spain does not overshadow the experiences in other countries, including Denmark. Data from foreign countries on prevalence of fluoroquinolone-resistant *Campylobacter* in humans and poultry pre- and post-enrofloxacin use contribute to national studies showing a link between enrofloxacin use and increase in fluoroquinolone resistant *Campylobacter* in humans that originated on poultry.

3. Potential of Fluoroquinolone-Resistant *Campylobacter* to Adversely Affect Human Health

CVM's final burden is to show that "fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?"

Bayer argues that CVM has presented no new evidence that fluoroquinolone-resistant *Campylobacter* illness in humans has the potential to affect certain symptoms differently than fluoroquinolone-susceptible *Campylobacter* illness. Bayer claims the lack of an established breakpoint for clinical resistance to fluoroquinolone use in *Campylobacter* may mean that the importance of campylobacteriosis has been overestimated. (Exhibit No. B-1900, P. 4, L. 22–24).

Campylobacteriosis is often a result of the consumption of poultry containing fluoroquinolone-resistant *Campylobacter*. The dangers of enrofloxacin use in poultry may have been over-emphasized and over-estimated, as the illness is often non-fatal and self-limiting. However, for the purposes of this proceeding, the lack of severity of complications in humans resulting from enrofloxacin use in poultry does not alter the pertinent fact that fluoroquinolone-resistant *Campylobacter* have a potential to adversely affect human health.

a. Pathogen Load and Infective Dose

There is evidence that *Campylobacter* or fluoroquinolone-resistant *Campylobacter* are found in sufficient quantity on retail meat to produce an infective dose. While most of the retail

meat studies do not indicate the pathogen load per carcass, studies from 1987-1992 report contamination levels on fresh chicken ranging from between 100 and 100,000 cells per carcass. (Exhibit No. B-1908, P. 23, L. 11–13). Even a drop of chicken juice can contain an infective dose of *Campylobacter*. (Exhibit Nos. G-1475, P. 10, L. 40-41 and G-1679, PP. 13-14).

Bayer argues that the Dr. Jianghong Meng report of a study with 54% erythromycin resistance in *Campylobacter* from poultry meat, but only 3% resistance to erythromycin reported by human NARMS data, shows that the mere presence of bacteria on meat does not mean it is causing the disease. (Exhibit Nos. G-1466, P. 3, L. 24–29 and G-1452, P. 74, Attach. 2). However, Bayer has not shown the relevance and comparability between erythromycin-resistant and enrofloxacin-resistant *Campylobacter*.

The mere presence of *Campylobacter* on retail meat may not be significant because not all strains of *Campylobacter* are capable of causing disease. The FSIS found less *Campylobacter* contamination levels on broiler carcass rinses in 1999–2000 than in 1994–1995. (Exhibit No. A-102, P. 3). And yet, despite this decrease in pathogen load, there is evidence in the record that campylobacteriosis has increased.

The exact infective dose of *Campylobacter* has not been established by the evidence and pathogen load on poultry can vary significantly. Nevertheless, the precise infective dose and pathogen load is not required to establish evidence of the potential of fluoroquinolone-resistant *Campylobacter* to adversely affect human health.

b. <u>Symptoms and Treatment of Campylobacteriosis</u>

Bayer's position is that overall, resistant *Campylobacter*-caused illnesses are not worse than susceptible ones and that illness due to *Campylobacter* and other foodborne bacteria will increase if enrofloxacin is removed from the market. CVM does not claim that the use of

enrofloxacin in poultry results in a net increase in incidence, frequency, or rise of *Campylobacter* infections in humans. The issue is whether the illnesses are caused by resistant infections are more adverse to human health than illnesses caused by susceptible infections.

There are an estimated 1.4 to 2.4 million cases of campylobacteriosis each year.[14] (Exhibit No. G-1452, P. 7, L. 5-14). Symptoms are often minor and include diarrhea, fever, cramps and nausea. The disease is often self-limiting and most patients recover in three to ten days without visiting a physician. However, the illness can also include more serious complications such as arthritis and Guillain-Barré syndrome. (Exhibit No. G-1477, P. 2). Furthermore, a fluoroquinolone-resistant *Campylobacter* infection is potentially life-threatening. (Exhibit No. G-1485, P. 14, L. 42-44). The patients that tend to be treated with antibiotics include those with more severe symptoms, those at higher risk of more severe illness (generally those who are immune-compromised) and those who are treated empirically (i.e., without waiting for results of stool cultures).

There is variation in the duration of diarrhea in patients with fluoroquinolone-resistant and those with fluoroquinolone-susceptible *Campylobacter* infections. FoodNet, Smith, Neimann, Molbak and others found an increased duration of diarrhea in fluoroquinolone-treated patients infected with resistant *Campylobacter* strains when compared to fluoroquinolone-treated patients infected with susceptible *Campylobacter* strains. (Exhibit Nos. G-1452, P. 15, L. 12 – L. 46, G-1473, P. 20, L. 31-38, and G-1468, P. 19, L. 15-37; Tr. P. 291). Dr. Jennifer M. Nelson reported that duration of diarrhea for those who did not take medication was 9 days for those with resistant *Campylobacter* infections and 7 days for those with a susceptible infection. (Exhibit Nos. G-1452, P. 15, L. 31-36 and G-1489).

[14] Bayer contends that CVM's high estimate of 2.4 million cases was for 1996-1997 and the low estimate 1.4 million is for 1999 and that CVM overstates the annual incidence of campylobacteriosis in the U.S. (Exhibit No. G-1452, P. 5, L. 20-21). Data for 2002 suggest a continuation of the downward trend in cases. (Exhibit No. B-1924).

There is evidence that patients who are infected with fluoroquinolone-resistant *Campylobacter* respond more slowly to treatment as compared to those infected with fluoroquinolone-susceptible *Campylobacter*. (Exhibit Nos. G-394, and G-1489, P. 11). CVM points out that FoodNet, contrary to Bayer's view, did not compare fluoroquinolone-treated susceptible cases with non-fluoroquinolone-treated susceptible cases. In FoodNet, 6 days was the average days of illness in fluoroquinolone-susceptible *Campylobacter* infected patients who were treated with fluoroquinolones and 7 days in those patients who were not treated. However, the focus in this proceeding is still on the effect on fluoroquinolone efficacy in treating fluoroquinolone-resistant *Campylobacter* infections in humans due to Baytril's use in poultry. Bayer has not demonstrated the significance of the efficacy of fluoroquinole treatment of patients with fluoroquinolone-susceptible *Campylobacter* caused infections.

Bayer notes that the FoodNet study found that generally persons with fluoroquinolone-resistant *Campylobacter* infections respond to fluoroquinolone treatment. However, FoodNet found patients with a fluoroquinolone-resistant *Campylobacter* infection who were treated with a fluoroquinolone had fewer days of illness than those who had a resistant infection and were not treated. (Exhibit Nos. G-394, and G-1489, P. 11).

Bayer argues that it is unclear that treatment failures will be common or will occur at a significantly greater rate than treatment failures among persons with susceptible infections. Dr. Laura Piddock reported that only 1 out of 39 patients with resistant infections failed to respond to treatment with ciprofloxacin. (Exhibit No. B-50, P. 2). In a more extensively-reported study, Sanders reported that between 58% and 75% of resistant cases responded to treatment with ciprofloxacin. (Exhibit No. B-1920, P. 4). In another study, among 37 patients with *Campylobacter* infections who were treated with fluoroquinolones, there were only two

failures—one of which was a susceptible infection, and one of which was a resistant case. (Exhibit No. G-354, P. 3). Bayer claims that the CVM risk assessment overlooked data that at a minimum would reduce the number of persons at risk and overlooked studies (particularly Marano G-394 and McClellan G-1679) which indicate that treatment of resistant cases is generally effective and may be equally or more effective than treatment of susceptible cases.

Dr. Smith stated that there was no statistically significant association between fluoroquinolone resistance and longer duration of diarrhea in domestically acquired cases in the data set used in his study. (Tr. P. 545, L. 1–5). Bayer argues that cases acquired through foreign travel are subject to uncontrolled confounding by other risk factors. However, there is no reason to exclude foreign travel-related cases when analyzing the association between the duration of diarrhea and fluoroquinolone susceptibility status of *Campylobacter* infections. (Tr. P. 462, L. 17 – P. 463, L. 6). There is no data in the evidentiary record to support the premise that fluoroquinolone-resistant *Campylobacter* acquired abroad is any more virulent than fluoroquinolone-resistant *Campylobacter* acquired in the U.S. and there is no reason to believe that fluoroquinolone-resistant *Campylobacter* infections acquired during foreign travel would be any different (i.e., result in a longer duration of diarrhea) than fluoroquinolone-resistant *Campylobacter* infections acquired domestically. (Exhibit No. G-1463, P. 3, L. 1-4, L. 17-25, P. 4, L. 1-7).

Bayer also argues that the increased days of diarrhea in fluoroquinolone-treated patients are not significant as there is no significant difference between duration of illness in fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections. (Exhibit Nos. G-394, G-1489, P. 11, B-1900, and B-1908).

Patients with mild symptoms generally do not need treatment of campylobacteriosis with antimicrobials. (Exhibit No. G-1485, P. 10, L. 1-7, P. 11, L. 11-29). Ciprofloxacin is the drug of choice for treatment of gastroenteritis, and antibiotic therapy for campylobacteriosis reduces the chance that a patient will have a relapse. (Exhibit No. G-1485, P. 13). Bayer argues that fluoroquinolone-resistant *Campylobacter* infections are treatable with macrolides or fluoroquinolones and other antibiotics, and are treated as effectively as fluoroquinolone-susceptible infections.

Bayer relies on studies that found no statistically significant association between fluoroquinolone resistance and longer duration of diarrhea. It has also asserted that the effect of resistance on treatment has been found to be slight in the case of *Campylobacter*. However, Bayer's analysis of the FoodNet and other studies is flawed. The evidence shows that fluoroquinolone-resistant strains of *Campylobacter* have a greater potential to adversely affect human health than do fluoroquinolone-susceptible strains of the bacterium. The difference between effects of fluoroquinolone-resistant and fluoroquinolone-susceptible strains is most evident in the increased duration of the symptom of diarrhea. The preponderance of the evidence establishes that fluoroquinolone-resistant *Campylobacter* results in an increased severity of campylobacteriosis in humans.

B. SAFETY OF ENROFLOXACIN

The evidence of record raises serious questions about the safety of Baytril use in poultry. Bayer's burden is to show that Baytril is safe under its approved conditions of use in poultry.

Bayer argues that a withdrawal of enrofloxacin would have negative consequences for the health of humans because enrofloxacin is the most effective antibiotic available in the U.S. for treatment of *E. coli* infections in broiler chickens and *E. coli* and *P. multocida* infections in

turkeys. (Exhibit No. B-1903, P. 5, L. 21-P. 6, L. 1). Bayer contends that poultry veterinarians have very few antibiotics available for treatment of *E. coli* infections. (Exhibit No. A-202, P. 24, L. 2–3).

According to Bayer, when a farm-to-fork approach to risk assessment is applied to U.S. data it is estimated that there are 985 cases per year of chicken-associated fluoroquinolone-resistant campylobacteriosis treated with fluoroquinolones. (Exhibit No. B-1020, P. 24). Bayer argues that if enrofloxacin were withdrawn, it would result in an increase in susceptible microbial loads and cases in excess of the hypothesized reduction in resistant microbial loads and cases.

Bayer asserts that without enrofloxacin, there may be increased risk of campylobacteriosis because sick birds will remain smaller and their intestines more fragile and therefore pose a greater risk to humans. When poultry become ill they can stop eating and become more susceptible to enteric problems, including parasites such as coccidiosis and the overgrowth of pathogenic bacteria such as *Salmonella*. (Exhibit No. B-1912, P. 17, L. 3–5). The broiler chickens and turkeys that stop eating early are more likely to be populated with both *Campylobacter* and *Salmonella*. (Exhibit No. B-1912, P. 17, L. 16–18). Dr. Scott Russell (Exhibit Nos. B-1912, and B-1014) found that chickens with air sacculitis infections (caused by organisms such as *E. coli*) are more likely to weigh less than uninfected birds, be contaminated with fecal material during processing, have a processing error or multiple processing errors during venting, opening and evisceration, and have higher *Campylobacter* counts. (Exhibit No. B-1912, P. 26, L. 8-11, and P. 18, L. 5). Dr. Russell claims that his findings "demonstrated that broilers that had air sacculitis and were treated with non-enrofloxacin alternatives such as oxytetracycline and sulfa drugs were underweight and less uniform." (Exhibit No. B-1912, P.

20, L. 2-4). Bayer argues that tetracycline usage for treatment of *E. coli* infections in poultry is usually ineffective or poorly effective because of widespread resistance to tetracyclines among bird *E. coli* isolates. (Exhibit No. B-1903, P. 7, L.11–17). A witness for AHI, Dr. Chuck Hofacre, found that nearly 90% of *E. coli* isolates are resistant to the tetracyclines.[15] (Exhibit No. A-202, P. 27, L. 2–3). Bayer contends that enrofloxacin is the only effective treatment for air sacculitis. 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. Bayer concludes that there are no suitable alternatives for enrofloxacin use and that birds with air sacculitis not treated with enrofloxacin have higher pathogen levels of *Campylobacter* and other pathogens.

The issue of the availability of alternative animal drug therapies is at best, marginal as it applies to this proceeding. Nevertheless, there are in fact effective alternatives to enrofloxacin including chlortetracycline, oxytetracycline, sulfomyxin, and tetracycline. (Exhibit No. G-1478, P. 18, L. 34-46, and Attach. A).

Bayer's analysis on air saculitis has limitations. In the Dr. Russell study none of the chickens were treated with fluoroquinolones, a fact that questions the accuracy of Bayer's contention that chickens not treated with fluoroquinolones will be smaller as there is no comparison of the alternate therapies with Baytril. Dr. Russell's study does not indicate antimicrobial treatment histories of the birds tested, and it does not indicate whether the air sacculitis positive and negative birds were sampled the same day or what part of the work shift the birds were slaughtered, which is important because the slaughtering process presents opportunities for cross-contamination. (Exhibit No. B-1912). This lack of standardization in the

[15] The *E. coli* resistance to tetracyclines, cited by Respondent, is interesting in light of its correlation to the issue of fluoroquinolone-resistant *Campylobacter* resulting from Baytril use in poultry.

study's protocol is problematic considering that one of the objectives of Dr. Russell's study was to measure lack of uniformity of the birds. (Exhibit No. B-1912, P. 19, L. 19-22).

Bayer argues that if enrofloxacin is withdrawn, a typical patient might suffer 8 days of illness rather than 10 days. On the other hand, assuming Bayer is correct, and removal of enrofloxacin will lead to additional *Campylobacter* and *Salmonella* infections, these are not additional days of illness, but additional cases of illness, and each additional case would consist of between 3 and 10 days of illness. Thus, Bayer argues that prevention outweighs any risks of additional days of illness from fluoroquinolone-resistant strains of *Campylobacter*.

However, Bayer's findings on increase of cases of *Campylobacter* and *Salmonella* infections resulting from a withdrawal are not reliable. Bayer relies on Dr. Cox's farm-to-fork analysis to demonstrate the alleged benefits of enrofloxacin on human health. Dr. Cox claims that a 1999 ban on several antimicrobials was "followed by sharp increases and record levels of campylobacteriosis and salmonellosis in multiple countries." (Exhibit No. B-1901, P. 83). Dr. Cox's testimony quoted a Eurosurveillance Weekly report that discussed the increasing *Campylobacter* infections in Norway, but Dr. Cox failed to note that there was a steady increase in domestically-acquired campylobacteriosis cases since 1992, well before the ban. (Exhibit No. B-1901, P. 83; http://www.eurosurveillance.org/ew/2002/020613.asp.). Dr. Cox's analysis underestimates the risk to humans of enrofloxacin use in poultry by underestimating the exposure itself, and overestimating the amount of exposure required to produce illness. (Tr. P. 1058, L. 2 – P. 1067, L. 20, Tr. P. 1026, L. 1 – P. 1049, L. 5). Apparently, Dr. Cox uses this same combination of faulty microbial load distribution with an unsubstantiated dose-response relationship to find a human health benefit for enrofloxacin. The estimate of the distribution of bacterial load was based on Dr. Stern's data (*See* Exhibit Nos. B-1020, P. 13, and A-17, P. 96.)

Dr. Stern's data measurements were, however, determined from rinses of carcasses, not from the actual carcasses themselves. Washing a carcass in a liquid and counting the bacteria in that liquid would necessarily underestimate the actual number of bacteria on the carcass itself because of the imperfect transfer of the bacteria from the carcass into the liquid. (*See* Tr. P. 1058, L. 2 – P. 1060, L. 10).

Bayer's arguments are inconsistent. Bayer presents Dr. Russell's study to make a case that poultry are a source of *Campylobacter* and that the withdrawal of Baytril will lead to additional cases of diarrhea from *Campylobacter* derived from poultry sources. At the same time Bayer argues that chicken is not a source of *Campylobacter* and seeks to discredit the evidence that poultry is a major source of campylobacteriosis and fluoroquinolone-resistant campylobacteriosis. In any event, the evidence of record is insufficient to support a finding of any significant benefit to human health as a result of Baytril use in poultry.

V. CONCLUSION

Throughout this proceeding, Bayer and AHI have criticized the evidence relied on by CVM as failing to qualify as scientific knowledge of the quality necessary to support CVM's position. The Supreme Court, in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, held that scientific testimony or evidence has to be relevant and reliable. 509 U.S. 579, 589 (1993). The Court listed a number of factors that may be considered in assessing reliability: whether a theory or technique can be, and has been, tested; whether it has been subjected to peer review and publication; whether the technique has a high known or potential rate of error and whether there are standards controlling its operation; and whether the theory or technique enjoys "general acceptance" within the relevant scientific community. *Id.* at 592-94.

CVM argues against strictly applying the *Daubert* standard for reliability/relevancy because "agencies are not bound by the evidentiary strictures of *Daubert*. *See Consolidation Coal Company v. Director, Office of Workers' Compensation Programs*, 294 F.3d 885, 893 (7th Cir. 2002). Although *Daubert* is not directly applicable to an administrative proceeding, its general principle that evidentiary reliability is dependent upon scientific reliability it is certainly useful in administrative proceedings where "litigants must still satisfy the ALJ that their experts are qualified by knowledge, training, or experience to, and have in fact applied recognized and accepted medical principles in a reliable way." *Id.* citing *Peabody Coal Co. v. McCandless*, 255 F.3d 465, 468-49 (7th Cir. 2001).

Various factors are considered when assessing evidential reliability and relevance and considerable flexibility is permitted. Respondent has alluded to various deficiencies in many of the studies (and/or evaluations thereof) relied on by CVM. After consideration of Respondent's specific criticisms and CVM's responses thereto, it appears that while each of the studies and/or analyses relied on by CVM, standing alone, would not support a finding that the use of fluoroquinolones in poultry has resulted in an increase in drug resistant *Campylobacter,* when the record is viewed in its entirety, there is substantial body of evidence supporting the conclusion that the increase in fluoroquinolone-resistant *Campylobacter* and resultant campylobacteriosis is a result of the extensive use of enrofloxacin in poultry.

Some of the evidence was unavailable at the time the FDA approved the NADA for enrofloxacin, and some of the evidence presented in this matter was available at the time of approval but has since been reexamined, in light of new evidence. This evidence confirms the earlier evidence and provides particularized information on the risks to humans of acquiring a fluoroquinolone-resistant *Campylobacter* infection from contamination by contact with poultry.

Exposure of poultry to enrofloxacin acts as a selection pressure for fluoroquinolone-resistant *Campylobacter* and results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry. While there are other potential sources of fluoroquinolone-resistant *Campylobacter* including non-poultry animals, contaminated water and fluoroquinolone use in humans, the preponderance of the evidence demonstrates that fluoroquinolone-resistant *Campylobacter* comes mainly from poultry. There has been a noticeable increase in the level of fluoroquinolone-resistant *Campylobacter* on poultry in the years since Baytril's approval.

The data indicate that poultry is a significant source of fluoroquinolone-resistant *Campylobacter* in humans. The evidence as a whole indicates that fluoroquinolone-resistant *Campylobacter* are transferred from poultry to humans and result in added *Campylobacter* infections in humans. There are a number of potential sources of fluoroquinolone-resistant *Campylobacter* in humans. However, poultry are the most important source. The CVM risk assessment is reliable and presents valuable information. The CVM risk assessment falls within the OMB Guidelines. FoodNet analysis is reasonable and reliable and points to the conclusion that eating poultry is associated with an increased level of campylobacteriosis in humans. Also, various microbiological and molecular studies on U.S. and foreign data support this conclusion. Enrofloxacin use has resulted in an increase in fluoroquinolone-resistance *Campylobacter.*

Fluoroquinolone-resistant *Campylobacter* have a potential to adversely affect human health. *Campylobacter* are found in sufficient quantity on retail meat to produce a dose that will cause campylobacteriosis in humans. The evidence shows that fluoroquinolone-resistant strains of *Campylobacter* have a greater potential to adversely affect human health than do fluoroquinolone-susceptible strains of the bacterium. The preponderance of the evidence

establishes that fluoroquinolone-resistant *Campylobacter* results in an increased severity of campylobacteriosis in humans.

There is no evidence of record as to any significant benefit to human health of Baytril use in poultry. Baytril is effective in treating *E. coli* infections in broiler chickens and *E. coli* and *P. multocida* infections in turkeys which leads to less air sacculitis. However, there are alternatives to Baytril. Bayer has not shown Baytril use in poultry to be safe.

VI. ULTIMATE FINDINGS AND ORDER

Consideration of the entire record in this proceeding leads to the following ultimate findings:

1. There is a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred.

2. Fluoroquinolone-resistant *Campylobacter* are naturally present in the environment and are found even in poultry flocks that have not been treated with fluoroquinolones.

3. Use of Baytril in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*.

4. Baytril treated poultry, with fluoroquinolone-resistant *Campylobacter*, cross contaminate untreated poultry by various means such as during transportation and slaughtering, by fecal matter and other processing activities.

5. There is evidence showing that fluoroquinolone-resistant *Campylobacter* in poultry can be transferred to humans and can contribute to fluoroquinolone-resistant *Campylobacter* infections in humans.

6. Emergence of resistance to fluoroquinolones in poultry increases after Baytril treatment.

7. Fluoroquinolones are the drugs of choice to treat *Campylobacter* infections in humans.

8. The fact that no standard official breakpoint that distinguishes between susceptible, intermediate, and resistant bacteria has been adopted for *Campylobacter* susceptibility to fluoroquinolones does not affect the designation of *Campylobacter* isolates as fluoroquinolone-susceptible or fluoroquinolone-resistant due to the bimodal nature of *Campylobacter*.

9. Epidemiological studies show that poultry is responsible for fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter* infections in humans. Microbiological and molecular

studies strengthen the results of the epidemiological studies, and temporal data provide further support for the conclusion that poultry is a source of campylobacteriosis, specifically fluoroquinolone-resistant campylobacteriosis.

10. Fluoroquinolone-resistant *Campylobacter* in poultry are transferred to humans and cause fluoroquinolone-resistant *Campylobacter* infections in humans.

11. Sources of human exposure to *Campylobacter* include consuming poultry that is raw or undercooked, consuming poultry in a restaurant, handling raw chicken, and failing to clean food preparation/cutting board surfaces.

12. In several countries, the introduction of fluoroquinolones including enrofloxacin in veterinary medicine has been followed by an increase in fluoroquinolone-resistant campylobacteriosis in humans.

13. Fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health.

14. The prevalence of fluoroquinolone-resistant campylobacteriosis in the U.S. is significant. Over one million people suffer from campylobacteriosis each year.

15. Complications of *Campylobacter* infections often include diarrhea, fever, cramps, nausea, and sometimes reactive arthritis, Guillain-Barré syndrome, and blood stream infections.

16. The duration of diarrhea is statistically significantly longer for patients infected with fluoroquinolone-resistant *Campylobacter* than for patients with fluoroquinolone-susceptible *Campylobacter.*

17. Among patients who were treated with a fluoroquinolone, the duration of diarrhea was statistically significantly longer for the patients with quinolone-resistant *Campylobacter* infections (median, 10 days) than for the patients with quinolone-susceptible *Campylobacter* infections (median, 7 days). Patients with resistant infections may suffer a significantly longer course of illness because the antibiotic provided to them does not work against resistant *Campylobacter.*

18. CVM's risk assessment model was developed to relate the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chicken. The risk assessment was based on reliable scientific data and was in line with OMB Guidelines, and FDA Guidelines for risk assessments.

19. In a NADA withdrawal proceeding, the effects of withdrawal on the economy and animal welfare are not relevant. Effects on the environment are only considered under exceptional circumstances, which this case does not present. Moreover, even if it were appropriate to consider enrofloxacin withdrawal's effects on the economy and animal welfare, the evidence presented in this proceeding is insufficient to warrant such a finding.

20. There are alternative treatments other than Baytril available to treat poultry respiratory diseases, and thus the withdrawal of enrofloxacin will not adversely affect human health.

21. Bayer's evidence on safety of enrofloxacin use in poultry is insufficient to find that the drug is safe.

22. Fluoroquinolone usage has the same effects in turkeys as in chickens.

23. Enrofloxacin is not shown to be safe under the conditions of use upon the basis of which the application was approved as required under § 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b(e)(1)(B)).

It is ORDERED that the approval of NADA 140-828 for Baytril be withdrawn, effective on the date this initial decision becomes final.

And it is further ORDERED that pursuant to 21 C.F.R. § 12.120(e) this initial decision will become the final decision of the Commissioner by operation of law in the absence of the timely filing of exceptions under § 12.125(a) or the filing of a notice of review under 21 C.F.R. § 12.125(f), and shall be effective as of the date of publication of a notice to that effect in the Federal Register pursuant to 21 C.F.R. § 12.120(f).

DATED this 16th day of March, 2004.

/s/ Daniel J. Davidson

Daniel J. Davidson
Administrative Law Judge