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

In the Matter of:	**FDA DOCKET: 00N-1571**
	DATE: August 15, 2003
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	

Center for Veterinary Medicine's Reply to Bayer's Post-Hearing Brief in the Matter of Enrofloxacin for Poultry: Withdrawal of Approval of New Animal Drug Application (NADA) 140-828 (Baytril)

I. Introduction

On July 18, 2003, the parties, Center for Veterinary Medicine ("CVM" or "the Center") and Bayer Corporation ("Bayer"), and non-party participant Animal Health Institute ("AHI") submitted initial post-hearing briefs on the issues of hearing for the above-captioned case. This reply brief addresses Bayer's initial post-hearing brief.

II. Legal Standards, Applicable Burdens, and Evidentiary Standards

Bayer incorporates AHI's arguments in its initial post-hearing brief with respect to legal standards, applicable burdens, and evidentiary standards. CVM addresses these issues in its reply to AHI's brief, and will not repeat them here. To the extent additional issues related to the legal standards are raised by Bayer, CVM addresses such issues in this brief.

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III. CVM Has Presented New Evidence From Which Serious Questions About the Safety of Baytril Use in Poultry May Be Inferred

A. CVM Has Presented New Evidence

Not every (or even any) single sub-issue in the hearing must involve new evidence. New evidence about any one sub-issue (or even new evidence that is revealed when existing evidence from all sub-issues is taken together as a whole) would be sufficient to meet CVM's burden. Regardless, CVM has presented new evidence about each of the sub-issues in this hearing.

CVM presented new evidence that Baytril acts as a selection pressure. Despite Bayer's claims to the contrary, Dr. McDermott's study does not merely mirror existing studies. The results of Dr. McDermott's study showed, for the first time, the actual shift in the MICs of *Campylobacter* organisms exposed to Baytril. CVM Br. P10, P16-17; WDT G-1465: P3, L1-3 and L18-27; P4, L17-19. This was not done in the earlier studies by Jacobs-Reitsma who only measured whether the *Campylobacter* organisms were "resistant." WDT G-1465: P4, L13-17. Moreover, Dr. McDermott's study used a new method, agar dilution, Ex. B-868, not available at the time Baytril was approved, and not available to Jacobs-Reitsma, WDT G-1465: P4, L17-20. Other scientists have observed similar findings. See CVM Br. P17.

Bayer also claims that the fact that there is *Campylobacter* on retail meat is not new evidence. Bayer's Br. P45. However, the retail meat studies, especially the retail meat studies conducted in the United States which specifically measure FQ-resistant *Campylobacter*, are new. See Ex. G-746; Ex. G-763; Ex. G-589; Ex. G-541; WDT G-1484: P3, L45 - P4, L16 and P6, L29 - P8, L2. Further, the methods used in Ex. G-746 and Ex. G-763 included agar dilution. See Tr. P218, L3-8. Thus, these studies constitute tests by new methods and are "new" evidence. See 21 U.S.C. §360b(e)(1)(B).

Bayer admits that the transfer of FQ-resistant *Campylobacter* from poultry to humans is occurring and causing FQ-resistant campylobacteriosis in humans, but believes that this does not

constitute new evidence. Bayer claims that the Netherlands' experience in FQ-resistant *Campylobacter* should have alerted FDA to expect a similar experience in the United States if FDA approved the NADA for Baytril. It is curious that Bayer argues that the level of FQ resistance in humans is not really the result of enrofloxacin use and FQ resistance in poultry, but yet that CVM should have forecasted that, as a result of FDA's approval of Baytril, the U.S. would experience the level of resistance that it is currently experiencing. Compare Bayer Br. P19 with Bayer Br. P11. Nevertheless, there is no threshold level of transfer of bacteria and contribution to human illness needed in order to infer serious questions about the drug's safety. The evidence presented by CVM on the occurrence of the transfer of *Campylobacter*, including FQ-resistant *Campylobacter*, from poultry to humans, in conjunction with the potential to cause adverse health effects, is new evidence that raises serious questions about the drug's safety.

In addition, there is no substantiation in the record for the level of FQ resistance that Bayer claims existed in the Netherlands in 1990. Bayer states that in 1994 CVM knew that in 1990 the prevalence of FQ-resistant *Campylobacter* rose to 25% in the Netherlands. See Bayer Br. P18. For this proposition, Bayer cites to Exhibit G-219, which is a transcript of a Joint Meeting of the Veterinary Medicine Advisory Committee and Anti-Infective Drugs Advisory Committee at FDA in May 1994 ("VMAC Meeting"). The specific page cited by Bayer (p. 135) refers to a presentation by an industry representative who purports to summarize the FQ resistance findings of Dr. Hubert Endtz (a CVM witness in this hearing). Despite the presenter's statement that the quoted 1990 figure (25%) had been published, Bayer has not provided a citation to any such published data. Further, Dr. Endtz's published data that are in the evidentiary record show a substantially lower level of quinolone resistance in isolates collected around that time. See Ex. G-190: P1 (referring to resistance levels of 11% and 14% in humans and poultry, respectively).

At the time of approval of the NADA for Baytril, CVM was aware of foreign studies that demonstrated that FQ use in poultry could cause selection pressure that would result in the emergence and dissemination of FQ-resistant *Campylobacter*. WDT G-1478: P13, L22-25. However, contrary to the facts offered by Bayer (Bayer Br. P18), all indications were that poultry production practices in the U.S. were different from industry operations in other countries. See WDT G-1478: P13, L33-44. Even the industry representative mentioned above conveyed at the VMAC Meeting that there were few limitations to the use of FQs by veterinarians in the Netherlands and that misuse or overuse of FQs was the most likely cause of the increased resistance observed in *Campylobacter* in that country and others. See Ex. G-219: P136 - P141. When Baytril was approved by FDA, it was CVM's belief that stringent controls and close monitoring (prescription only, no extra-label use, resistance monitoring by NARMS) would prevent the emergence and dissemination of FQ-resistant enteric bacteria in the United States. WDT G-1478: P14, L1-43.

Bayer dismisses the post-approval evidence on the transfer of FQ-resistant *Campylobacter* from poultry to humans as nothing new. Bayer Br. P17. In part, Bayer reaches this conclusion by ignoring numerous studies published after approval of the NADA for Baytril. A tally of the studies cited in CVM's initial brief shows that approximately one-half of the epidemiological studies and nearly all of the microbiological and molecular studies were published after approval of the NADA for Baytril. These studies are not redundant of pre-approval evidence and cannot be discarded as mere surplusage. The later epidemiological studies are more abundant, have larger sample sizes, and in some cases are nationally based. The analytical methods used in post-approval molecular typing studies provide genotyping information that was previously unattainable. Unlike earlier data, some later epidemiological studies and molecular studies focus specifically on FQ-resistant infections. Temporal data

necessarily require the passage of time to impart valuable information. There can be no question that CVM has presented new evidence on the transfer of FQ-resistant *Campylobacter* from poultry to humans that contributes to FQ-resistant campylobacteriosis.

Bayer argues that CVM's risk assessment is not new evidence because the data used existed at the time Baytril was approved (Bayer Br. P49), and that the duration of diarrhea studies are not new evidence because CVM knew that FQ-resistant *Campylobacter* had the potential to affect human health at the time Baytril was approved, Bayer Br. P69-70. However, CVM's risk assessment and the duration of diarrhea studies allow, for the first time, a quantification of the potential impact on human health from FQ-resistant *Campylobacter* from the use of Baytril in chickens. Therefore, CVM's risk assessment and the duration of diarrhea studies constitute new evidence.

B. CVM Has Presented Evidence on Selection Pressure, and Emergence and Dissemination of FQ-Resistant *Campylobacter*, From Which Serious Questions About the Safety of Baytril May Be Inferred

Bayer makes several arguments in an attempt to support its claim that CVM's evidence, with respect to selection pressure, and the emergence and dissemination of FQ-resistant *Campylobacter*, do not raise serious questions about the safety of Baytril. First, Bayer claims that there are other sources of FQ resistance in *Campylobacter* besides the use of enrofloxacin in poultry. Bayer Br. P12. There are numerous flaws in this argument. As CVM's evidence demonstrates, there is no rational explanation for the levels of FQ resistance observed in poultry other than the use of Baytril in poultry. See CVM Br. P16. Bayer's discussion of waterborne *Campylobacter* (not specifically FQ-resistant *Campylobacter*) and its citation to Patterson's written direct testimony do not support an argument that water is an important source of FQ-resistant *Campylobacter*. See CVM Br. P72-73. Further, the cited portion of Patterson's testimony is merely an assertion by the witness, unsupported by any documents on the record.

See WDT B-1910: P6, L20-22. Moreover, even though CVM has shown that there is no evidence to suggest any major source of FQ-resistant *Campylobacter* other than poultry treated with or otherwise exposed to Baytril, CVM is not required to show that poultry is the only source of FQ-resistant *Campylobacter*. When faced with similar finger-pointing by industry in the context of an appeal of FDA's withdrawal of diethylstilbestrol implants in poultry ("the amount of estrogen exposure in the diet from a variety of common foodstuffs is greater than any exposure from caponette residue"), the Seventh Circuit stated, "If estrogens are contained naturally in certain items of diet, there is no justification for adding more by an artificial method." Bell v. Goddard, 366 F. 2d 177, 182 (7th Cir. 1966). Similarly here, even if Bayer's unsupported allegations had merit, there is no justification for adding more FQ-resistant *Campylobacter* by an artificial method, i.e., by the selection pressure caused by Baytril use in poultry.

Second, Bayer's arguments that quinolone and FQ resistance found in poultry prior to approval of Baytril somehow detract from the serious questions raised by CVM must fail. Bayer Br. P13. The two studies cited by Bayer, Ex. G-62 and Ex. B-1851, do not preclude the evidence on the record from raising serious questions from which the safety of Baytril may be inferred. Ex. G-62 reports 4.5% of *Campylobacter* isolates being resistant to enrofloxacin. Several factors could have been responsible for the findings of this study. For example, although the authors mention that no antimicrobials were used on the chicken flocks where the resistant isolates were recovered, they do not report the prior antimicrobial history of those chicken houses, or other chicken houses on that or neighboring farms. Ex. B-1851 is a 1981 study which looked at the antimicrobial susceptibility of several antimicrobials. The study results are questionable given the addendum printed in the study report which states:

> Addendum: After this study was submitted for publication, a study by Vanhoof *et al.*, appeared on MIC's and MBC's for 84 strains of

> Campylobacter fetus ssp. jejuni performed in broth (Vanhoof, R., Gordits, B., Dierikx, R., Coignan, H. and Butzler, J.P. (1980) Antimicrobial Agents and Chemotherapy 18, 118-21). We found higher proportions of resistant strains to the drugs tested.

This addendum calls into question the findings of this study.

Third, Bayer says that the Luo study[1] shows recovery of susceptible organisms before slaughter and therefore this study cannot show serious questions linking FQ use in poultry to FQ-resistant *Campylobacter* in humans. Bayer Br. P15. However, in support of its argument, Bayer cites to Ex. A-190 which is not the final published report of Luo's study, but rather a poster presentation from a scientific meeting. A review of Ex. G-1800, the published version of the Luo study, shows the opposite of what Bayer claims – in fact, FQ-resistant *Campylobacter* does persist after treatment with Baytril is stopped. Ex. G-1800: P3, Figure 2. Ex. G-1800 shows that approximately 60% of the broilers treated with the low dose of 25 ppm were still colonized with FQ-resistant *Campylobacter* 12 days after initiation of Baytril treatment. Ex. G-1800: P3, Figure 2. For those chickens treated with 50 ppm, 100% or nearly 100% remained colonized with FQ-resistant *Campylobacter* 12 days after initiation of Baytril treatment. Ex. G-1800: P3, Figure 2.

Fourth, Bayer argues that CVM failed to raise serious questions about the safety of Baytril because the use of Baytril is low and selection pressure is low and controlled. See Bayer Br. P14. In support of its argument, Bayer cites to Dr. McDermott's study (Ex. B-868) arguing that Dr. McDermott used a higher dose and duration than is typical in the industry. Bayer Br. P14-15. This argument too must fail because Dr. McDermott used an approved dose and duration of Baytril in his study. See CVM Br. P16. Further, Bayer itself points out that a 50 ppm dose is sometimes given as a 12-24 hour loading dose. Bayer Br. P15, n.8. The high level resistance observed by McDermott appeared within that timeframe. CVM Br. P16.

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[1] Bayer refers to this study by one of its authors, Luo. CVM has referred to the same study in its initial brief by a different author, Zhang.

Fifth, Bayer's claim that McDermott overstates resistance by pooling feces and, therefore, his study cannot raise serious questions about the safety of Baytril, is unfounded. Bayer Br. P16. There is no indication that quinolones were present in the growth medium used by McDermott to decrease the recovery of susceptible strains in the pooled sample. See Ex. B-868. Therefore, if only 1 of the 5 composite samples contained FQ-resistant *Campylobacter,* there was at least an 80% chance the sample would be reported as susceptible. In any case, McDermott picked 10 colonies from each composite sample, not just one – thus, 50 isolates from each pen per collection day were subjected to agar dilution susceptibility testing. See Ex. B-868, P2. Bayer's arguments with respect to Dr. McDermott's study fail. The results of Dr. McDermott's study are indeed reliable and present new evidence from which serious questions about the safety of Baytril use in poultry may be inferred.

Sixth, Bayer claims the retail meat studies are not representative of the United States as a whole. Bayer Br. P45. The consistent findings of retail meat studies in the United States effectively negate this argument. While it is true that the retail meat studies can only sample a small percentage of the 8.5 billion chickens and 270 million turkeys slaughtered in the United States each year, the results of the studies show remarkably similar numbers with regard to prevalence of *Campylobacter* and FQ-resistant *Campylobacter*. Similar findings from several different retail meat studies from different geographical regions of the United States demonstrate that the studies are indicative of the United States retail poultry market as a whole. CVM Br. P22-23. In sum, Bayer's argument with respect to the representativeness of retail meat studies fails.

Bayer makes a number of other very speculative allegations about the retail food studies. Bayer claims that the food samples yield sublethally damaged cells which can be cultured but cannot cause disease, and that incorporation of antimicrobials in selective media introduce bias.

Bayer Br. P46. Bayer fails to substantiate these claims. The only evidence that sublethally damaged cells might not be able to cause disease comes from speculation of Dr. Silley, with no basis in the evidentiary record for such speculation. See WDT B-1913: P8, L16-18, P18, L19 - P19, L3.

Bayer incorrectly contends that the use of a pre-enrichment step and that the use of antimicrobials in selective media are somehow improper and/or introduce confounding factors. Bayer Br. P46. CVM agrees that the use of a pre-enrichment step allows *Campylobacter* to multiply; that is the purpose of pre-enrichment. See WDT G-1466: P2, L2-7. Moreover, the use of antimicrobials in selective media does not introduce bias. There are good reasons for using antimicrobials in selective media. The use of antimicrobials in selective media is to eliminate other competing microorganisms which would hamper the identification of the bacteria in question, in this case *Campylobacter*. See G-1466: P2, L45 - P3, L3; WDT B-1913: P6, L8-10 ("Antimicrobials in selective media developed for *Campylobacter* have been chosen . . . on . . . those most effective in inhibiting competitive flora."). Both of these techniques allow a finding of the presence of *Campylobacter* only when *Campylobacter* does, in fact, exist.

Bayer next tries to attack the importance of the retail meat studies by arguing that there is no evidence that *Campylobacter* or FQ-resistant *Campylobacter* are found in sufficient quantity on retail meat to produce an infective dose. See Bayer Br. P47. While Bayer is correct that most of the retail meat studies do not indicate the pathogen load per carcass, Bayer reports that studies from 1987-1992 report contamination levels on fresh chicken ranging from between 100 and 100,000 cells per carcass. Bayer Br. P62. Evidence presented at the hearing demonstrates that an infective dose of *Campylobacter* can be low, with a tested dose of 500 CFUs producing symptomatic illness. Ex. G-1816. Therefore, not only are Bayer's arguments speculative, they

are easily countered by data on the evidentiary record that show the *Campylobacter* load on chicken is sufficient to provide an infectious dose.

Bayer continues its baseless attack on the retail meat studies, claiming that the mere presence of *Campylobacter* on retail meat is not important because not all strains of *Campylobacter* are capable of colonizing humans and causing disease. As an example, Bayer claims Meng's report of a study with 54% erythromycin resistance in *Campylobacter* from poultry meat, but only 3% resistance to erythromycin reported by human NARMS data, show that the mere presence of bacteria on meat does not mean it is causing the disease. Bayer Br. P48-49. Bayer cannot use these studies as a basis for this argument because Bayer has not shown that erythromycin-resistant *Campylobacter* has any relevance to the issues of the hearing and has not shown that these two studies are comparable.

C. CVM Has Presented Evidence on the Transfer of FQ-Resistant *Campylobacter* from Poultry to Humans From Which Serious Questions About the Safety of Baytril May Be Inferred

According to Bayer, CVM has not presented sufficient evidence on the transfer of FQ-resistant *Campylobacter* to create a reasonable basis from which serious questions about Baytril's safety can be inferred. Bayer's view of the evidence is fraught with error and contradiction. Bayer begins by asserting that there is a decrease in the incidence per 100,000 population of FQ-resistant *Campylobacter* infections between 1997 and 2001.[2] Bayer Br. P20. Bayer's simplistic, non-statistical approach is patently unreliable and cannot take the place of multivariate analyses that could be done to reach a precise and accurate result. More importantly, Bayer does not dispute the fact that the percent of resistant *Campylobacter* has increased between 1997 and 2001. The following subsections on epidemiological, molecular, microbiological, and temporal

[2] It is curious that the very numbers (i.e., the percentages of isolates that were ciprofloxacin-resistant from 1997 to 2001) Bayer chose to use in its calculations were the NARMS data, which Bayer has repeatedly decried as unreliable. See, e.g., Bayer Br. P37.

evidence reveal additional deficiencies in Bayer's arguments. These sub-sections will show that Bayer has not successfully challenged CVM's evidence of a reasonable basis from which serious questions about Baytril's safety can be inferred.

1. Epidemiological Evidence

With respect to the epidemiological evidence, Bayer: (a) ignores relevant studies; (b) offers unsupported speculation; (c) draws conclusions from an illogical premise; (d) mischaracterizes study design and outcome; (e) misstates study results; and (f) relies on an inappropriate witness to conduct and interpret epidemiological analyses.

a. Bayer ignores relevant studies

In an attempt to discount the strong association between poultry and the risk of acquiring campylobacteriosis, Bayer's evaluation simply ignores many relevant studies. Bayer's coverage of epidemiological studies includes only: the Friedman and Kassenborg analyses of the 1998-1999 FoodNet *Campylobacter* case-control study; the Deming and Harris studies; and the Smith (Minnesota) study.[3] Bayer Br. P21-25. On the other hand, CVM's initial brief evaluated the results of those five studies plus the results of an additional 18 epidemiological studies. A full and fair review of all of these studies, or even a more limited review of the studies cited by Bayer, shows that poultry is an important risk factor for acquiring campylobacteriosis. See CVM Br. P25-37.

b. Bayer offers unsupported speculation

Without any basis in fact, Bayer accuses the entire "public health community," including CVM's expert witnesses, of being biased by an "assumption" that poultry is associated with

[3] Bayer mentions the Effler study but only in the context of questionnaire design, not in results of data analysis. See Bayer Br. P25. In a later section of its brief, Bayer cites to other epidemiological studies that allegedly do not support CVM's position – Effler, Hopkins, Ikram, Iowa, Adak, and a U.K. case-comparison study. See Bayer Br. P60-61. CVM adequately addressed the relevance and importance of all of these studies in its initial brief. See CVM Br. P30-32, 34, 36-37.

Campylobacter. Bayer Br. P24. Bayer supports its "assumption" theory with citations to testimony from Bayer witness Cox (Bayer Br. P24-25), who is not an epidemiologist. The association of poultry and *Campylobacter* is not an assumption, despite Bayer's contention to the contrary. As thoroughly briefed by CVM, poultry's role as a risk factor has been statistically evaluated and confirmed in numerous epidemiological studies. CVM Br. P25-37.

Bayer states that Friedman's analysis shows a decline in the risk of acquiring campylobacteriosis from chicken and turkey (Bayer Br. P23); but Bayer does not support this hypothesis with any citation to expert epidemiological testimony. Neither Friedman nor CVM's expert witness epidemiologists drew such a conclusion from the Friedman analysis; nor, apparently, did Bayer's or AHI's expert witness epidemiologists. Bayer's unsupported speculation is invalid.

Bayer attempts to discount the results of Kassenborg's analysis in several ways by calling them "suspect" because (a) the findings depended on a "selective choice of models" and (b) the analytical method was "conclusion driven." Bayer Br. P28. It is difficult to determine how either of these criticisms actually reveals a flawed analysis and unreliable results. All analytical model selection is inherently selective. A researcher must choose which model is best at explaining the data, which is exactly what Kassenborg did.[4] Tr. P601, L5-6. Moreover, all analysis is driven by conclusions drawn from the existing body of scientific knowledge. On cross-examination, Kassenborg explained why it is unlikely that "some other factor" is causing FQ-resistant *Campylobacter* infections rather than the epidemiologically supported finding that

[4] Contrary to Bayer's opinion (Bayer Br. P57), Kassenborg's choice of models was directed by her scientific expertise, not by the "FJCRMSE." Kassenborg's study methods and results were also thoroughly reviewed by a large panel of scientific experts. Tr. P618, L11 – P619, L5.

Moreover, assuming Bayer is correct that the FJCRMSE is subject to judicial notice, Bayer's use of the material contained therein is not. See, e.g., Bayer Br. P55 (providing an example of a contention more properly suited to expert testimony rather than lawyers' argument).

consumption of poultry in a restaurant is a risk for acquiring campylobacteriosis.[5] Tr. P598, L9 – P599, L6. Kassenborg showed the logic of accepting the findings of epidemiological studies in light of the indisputable fact that chicken is contaminated with *Campylobacter* and that a lot of people eat chicken. Such an approach is not suspect -- it is science-based and reasonable. When a large body of evidence points in one direction, it would be inappropriate to simply avoid that evidence.

c. Bayer draws conclusions from an illogical premise

Bayer claims that certain epidemiological data in the U.S. from the late 1990s do not show that "all poultry consumption" is a sufficiently serious risk factor for campylobacteriosis. Bayer Br. P23, 27-28. Although never clearly explained, it appears Bayer is asserting that CVM must show that poultry consumption of every kind, in every location, and under every circumstance must be determined to be risk factors for acquiring *Campylobacter* infections. Bayer implies that, if CVM cannot do this, then poultry consumption must not be an important risk factor for campylobacteriosis.

An exposure can be an important risk factor even if it is not a universal risk factor. It is unrealistic to expect that all exposures to a causative agent under every condition would be a risk factor in an epidemiological study. Bayer's rationale would severely restrict FDA's ability to protect the public from the adverse health effects of a new animal drug because it creates a prohibitively wide gap between the identification of risk factors for disease and the consideration of those risk factors as causes for concern about the public health. FDA's ability to regulate the safety of new animal drugs cannot be constrained by unanswerable questions such as, "Is the

[5] Furthermore, the strength of the association between consuming chicken in a restaurant and acquiring an FQ-resistant *Campylobacter* infection is so strong (OR = 10) that it is extremely unlikely that the finding could be explained by anything other than a causal relationship or that the finding is a consequence of an "analytical trick" with the data.

antibiotic intended to be administered to chickens whose post-slaughter destination is a restaurant's kitchen or a consumer's kitchen?"

d. Bayer mischaracterizes study design and outcome

Although Bayer continues to insist that it is where you eat that causes campylobacteriosis, in reality the disease is caused by *Campylobacter* organisms and the source of bacteria is poultry. Consistently missing from Bayer's analysis is the fact that *Campylobacter* is in, on, and all over poultry, especially chicken. Bayer does not dispute this fact but seems to ignore it at critical moments. One of those moments is exemplified in Bayer's discussion of the population attributable fractions calculated in Friedman's analysis. See Bayer Br. P24. 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. See CVM Br. P29. Although the population attributable fraction was 21% for eating non-poultry (beef, lamb, pork, veal) 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*. CVM Br. P22. It follows that poultry must be the vehicle on which *Campylobacter* is carried into the restaurant. Given the probable volume of poultry entering the restaurant and the high prevalence of *Campylobacter* contamination of poultry relative to other food, it is logical to conclude that the highly contaminated poultry meat could have cross-contaminated the non-poultry meat during handling and preparation at the restaurant.

Moreover, Bayer misinterprets findings from epidemiological studies that were published after approval of the NADA for Baytril. Compare Bayer Br. P23, 27-28 with CVM Br. P27-34. In some studies, the risk was associated with consumption of chicken / poultry (Studhal, Neal). In other studies, the risk was associated with consumption of chicken / poultry that was

undercooked or raw (Michaud, Friedman, Neimann, Eberhart-Phillips)[6] or with consumption of poultry at specific locations, i.e., at a restaurant (Friedman, Kassenborg, Effler, Rodrigues, Eberhart-Phillips). The Kassenborg, Effler, and Rodriques studies do not stand for the proposition, for example, that chicken / poultry consumption only in a restaurant is a risk factor for campylobacteriosis. Rather, they stand for the proposition that chicken / poultry consumption in a restaurant is at least one of the poultry-related risk factors for campylobacteriosis. Similarly, results from the Friedman and Eberhart-Phillips studies represent that the consumption of undercooked chicken / poultry and the consumption of chicken / poultry in a restaurant are two, but not necessarily the only two, of the poultry-related risk factors for campylobacteriosis.

One reason that epidemiological studies may not identify all of the poultry-related risk factors is the difficulty of designing and conducting epidemiological studies that are capable of identifying risk factors in a group of people (i.e., cases) where many people in the population from which the study sample (cases and controls) is drawn experience the exposure in question. CVM Br. P36. The absence of a finding of risk does not mean that the exposure is not a risk factor, but rather that the risk factor may be difficult to identify epidemiologically.

The complexity of ascertaining risk factors where exposures are common in the population (cases and controls) is greatly magnified in epidemiological studies comparing risk factors for FQ-resistant *Campylobacter* infections with risk factors for FQ-susceptible *Campylobacter* infections (i.e., case-comparison studies). The absence of a finding that poultry is a risk factor in such case-comparison studies does not mean that poultry is not a risk factor, but that poultry was the likely risk factor in both groups of cases, i.e., that poultry was responsible

[6] These studies, including Friedman's (Ex. G-1488:P10), found that consuming undercooked chicken, regardless of where it was prepared, was independently associated with acquiring campylobacteriosis. In other words, this variable was not specific to the location of consumption.

for campylobacteriosis in the FQ-resistant and the FQ-susceptible cases. See CVM Br. P36-37. For this reason, it is misleading to use such case-comparison studies as evidence that poultry is not a risk factor for *Campylobacter* (including FQ-resistant *Campylobacter*) infections.

Another reason that epidemiological studies may not identify all of the existing poultry-related risk factors is the likelihood that poultry may be responsible for *Campylobacter* illness through the process of cross-contamination. Because the infectious dose of *Campylobacter* can be small, *Campylobacter* on poultry can be easily transferred in the kitchen to other surfaces, equipment, or other foods at a level sufficient to cause infection. WDT G-1475: P9, L29 – P10, L24; WDT G-1452: P12, L36-48; WDT G-1483: P10, L3-14. If *Campylobacter*-contaminated poultry in the kitchen contaminates salad greens with *Campylobacter*, it may not be obvious that enteritis in the person who ate the salad was actually the result of cross-contamination from poultry. Even if such poultry-related illness is not likely to be attributed to poultry during epidemiological investigations, it is nevertheless the poultry itself, which carries the *Campylobacter* into the kitchen, that is responsible for the *Campylobacter* illness. That chicken is a frequent cause of disease mainly through cross-contamination rather than direct consumption may be a more likely occurrence in the home than in restaurants. See Ex. G-1711: P6.

In addition, Bayer inappropriately seems to suggest that odds ratios can cancel each other out. Bayer Br. P23, 27. For example, Friedman's multivariate analysis found that eating chicken in a restaurant and eating turkey in a restaurant were independent risks for acquiring campylobacteriosis. In light of that result, it is patently incorrect to assert that the (apparent) lesser risk of acquiring campylobacteriosis from consuming poultry in the home negates the greater risk of acquiring campylobacteriosis from consuming poultry in a restaurant. The risk of

acquiring campylobacteriosis from poultry consumption in a restaurant and the relationship between a *Campylobacter* infection and poultry consumption at home[7] are mutually exclusive.

e. Bayer misstates study results

Bayer states that Kassenborg's analysis does not find a connection between poultry and FQ-resistant campylobacteriosis. Bayer Br. P26, 56, 57, 64. Bayer's statement is not only without merit but is actually contradicted later in Bayer's brief, which acknowledges that Kassenborg found a statistically significant independent association between eating chicken or turkey at a commercial establishment and an increased risk of acquiring FQ-resistant campylobacteriosis. See Bayer Br. P27-28. Bayer also inappropriately recites Kassenborg's univariate findings as if they are the final result of her analyses (see Bayer Br. P27); they are not. Only one of the three risk factors discussed by Bayer was determined to be independently associated with *Campylobacter* infection.[8]

Bayer also misstates several findings from Friedman's analysis.[9] See Bayer Br. P23. Friedman's final multivariate results plainly contradict Bayer's assertion that people who did not eat chicken at home were "twice as likely" to acquire *Campylobacter* infections as were people who did eat chicken at home. Although the odds ratio for "eating chicken prepared at home" was 0.5 in Friedman's univariate analysis, the odds ratio for "eating chicken prepared at home" was

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[7] Merely because some studies found that eating chicken in the home has an odds ratio below one, chicken consumption at home does not protect one from contracting campylobacteriosis. Cf. Bayer Br. P23 (implying the contrary). For reasons not well-established, people with campylobacteriosis appear to be less likely to eat chicken in the home than people without campylobacteriosis. If this effect is the result of developing an acquired immunity to campylobacteriosis by people who eat chicken at home (CVM Br. P37), it stands to reason that those people had to be previously exposed to *Campylobacter*, which gave them the opportunity to become immune to the bacterial effects. It also stands to reason that the immune-person's previous exposure to *Campylobacter* may have come from eating or handling *Campylobacter*-contaminated chicken in the home. One thing is for certain – eating chicken in the home is no less a risk for campylobacteriosis than, for example, not eating chicken (or food that was cross-contaminated by chicken) at all.

[8] Bayer also errs when discussing the variable "eating any meat at home" in Kassenborg's analysis. See Bayer Br. P27. Despite Bayer's presumption to the contrary, this variable clearly does not include chicken and turkey. In fact, it explicitly excludes chicken and turkey. WDT G-1460: P8, L16.

not 0.5 in the multivariate analysis. Ex. G-1488: P23. Moreover, two other variables Bayer claims are statistically significantly associated with a lower risk of *Campylobacter* infection ("had raw chicken in home refrigerator" and "touched raw chicken") were not even in the final multivariate model constructed by Friedman. Ex. G-1488: P23. Further, Bayer's contention that illnesses in one-half of the cases in Friedman's analysis were attributed to an unknown source is contradicted by the information revealed in Bayer's supporting citation, which suggests that approximately one-quarter of the cases had an unattributed source of infection. Compare Bayer Br. P68 with Tr. P810, L1 - P815, L13 and WDT G-1452 Attach. 3, P101 (Table 4).

Bayer inappropriately cites to Effler for supporting its hypothesis that study questionnaires are biased because of the "assumption" that poultry causes campylobacteriosis. See Bayer Br. P25. According to Effler, "the agreement of these separate studies [i.e., the studies of Effler, Ikram, Eberhart-Phillips] conducted by different investigators and across countries, greatly reduces the likelihood that the association [between *Campylobacter* illness and commercially prepared chicken] is spurious." Ex. G-185, P4. As can be seen by the conclusion Effler draws from his study, Effler does not support Bayer's assertion that the poultry-causes-campylobacteriosis "assumption" is invalid.

Bayer improperly claims that Friedman's analysis (and other unidentified U.S. data) supports Bayer witness Newell's conclusion, which questions whether poultry is a major source of *Campylobacter* infections. See Bayer Br. P25-26. According to Friedman:

> The 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, this indicates that poultry was the dominant food source for *Campylobacter* infection during the study period.

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[9] Bayer's reference on page 23 to the variable "eating poultry meat at home" in conjunction with Friedman's analysis is unclear. The Friedman analysis does not contain this particular variable.

Ex. G-1488: P11. Friedman's analysis, therefore, squarely contradicts Newell's conclusion.

f. Bayer relies on an inappropriate witness to conduct and interpret epidemiological analyses

Bayer cites to Cox for the following propositions: (1) the more chicken consumption, the less illness (Bayer Br. P63); and (2) the lack of a causal relationship between chicken and FQ-resistant illness (Bayer Br. P65). The underpinning of the first proposition is an admittedly "exploratory analysis" conducted by Cox, who implies that his approach should not be given much weight. Tr. P1069, L13 – P1074, L14. The underpinning of the second proposition is Cox's "conditional independent tests for causality" examining the relationship between chicken and FQ resistance in the Friedman, Effler, and Smith data sets. It is unclear how Cox managed to conduct his Effler re-analysis, for example. According to Effler's study, the isolates were not subject to antimicrobial sensitivity testing, G-185: P3, which indicates that FQ resistance status was unknown, thus making an evaluation of causality between chicken and FQ resistance impossible.

2. Molecular and Microbiological Evidence

With respect to the molecular and microbiological evidence, Bayer: (a) ignores relevant studies; (b) misconstrues study applicability; (c) misinterprets study methods; and (d) misuses study results.

a. Bayer ignores relevant studies

In an attempt to discount the strong evidence from genetic typing studies, Bayer simply ignores many relevant studies. See Bayer Br. P30-33. Bayer's coverage of microbiological and molecular studies is comprised of the results of three studies and citations to a handful of others. Conversely, CVM's initial brief evaluates the results of twelve studies. A full and fair review of the studies shows that the molecular and microbiological evidence strongly supports the

conclusion that poultry is an important risk factor for acquiring campylobacteriosis. See CVM Br. P38-43.

b. Bayer misconstrues study applicability

Bayer suggests that CVM witness Smith's molecular typing results warrant closer scrutiny because they are not in accordance with results from his case-comparison study. See Bayer Br. P32. Bayer does not understand the appropriate use of bacterial DNA fingerprinting. The fact that the Smith case-comparison study did not find a difference between poultry as a risk factor for campylobacteriosis when comparing FQ-resistant and FQ-susceptible cases does not preclude Dr. Smith from conducting a valid molecular typing study comparing strain overlap between human and poultry isolates. First, the results of the Smith case-comparison study were reasonable. See CVM Br. P36-37. Second, Smith's molecular typing study was not conducted in an epidemiological vacuum. As Smith's New England Journal of Medicine article stated, "Poultry has been documented repeatedly as a major food reservoir of *Campylobacter* for infections in humans . . . ." Ex. G-589: P6. Molecular typing studies are conducted and interpreted in light of all available epidemiological knowledge. It is this epidemiological context that is relevant in the evaluation of molecular typing results and to which CVM's expert witnesses refer. See Bayer Br. P29.

c. Bayer misinterprets study methods

Although the Clow study (U.K.) states that not all poultry strains are potentially pathogenic to humans, it is illogical for Bayer to rely on that statement to conclude that, because every poultry strain cannot be found among human strains, poultry is no longer an important source of campylobacteriosis. See Bayer Br. P31. If the purpose of scientific investigation is to examine whether poultry could be the source of human illness, the relevant determination is how many strains found in humans are also found in poultry (i.e., how much of human illness can be

explained by a poultry source). Put another way, the inquiry begins by examining the molecular patterns of bacterial strains from human isolates to see if those strains can be matched to molecular patterns of bacterial strains from poultry isolates. The fact that some poultry strains may be "left over," i.e., cannot be matched with strains from human isolates, does not detract from the strain overlap detected.

Bayer criticizes the sample size (i.e., too small) of the chicken isolates in the Smith study. Bayer Br. P32. However, a small sample size would seem to work against the likelihood of finding strain similarities between human and chicken isolates. A smaller universe of chicken isolates would make it less likely that bacterial strains found in human isolates would be able to be matched to bacterial strains from chicken isolates. In addition, because the chicken isolates were not collected over the full time period during which the human isolates were collected,[10] it would again seem less likely that an overlap in the two sets of bacterial strains could be identified.[11]

d. Bayer misuses study results

Bayer's comparison between the percentage of strain similarity in the Smith study and the population attributable fractions from the Harris (Ex. G-268) and Deming (Ex. G-162) studies cannot withstand scrutiny. See Bayer Br. P33. Results from molecular subtyping are not equivalent to population attributable fractions. Population attributable fractions are derived from risk factor data from epidemiological studies, not from strain overlap data from molecular typing studies. Bayer's comparison is impermissible, unscientific, and invalid.

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[10] The time frames for isolate collection, however, are not nearly as disparate as Bayer states. As is evident from Smith's published study, Smith's statistical comparisons were conducted on patients with infections during 1997 and chicken isolates collected during a two-month period in 1997. Therefore, an 18-month gap between collection of human and poultry isolates would be impossible.

[11] For the same reason, the overlap between the poultry and human strains may be artificially low in the Dickens molecular typing study of retail meat. See Bayer Br. P30.

3. Temporal Evidence

Bayer argues that temporal data do not favor CVM's position that temporal association data provide strong support for the conclusion that enrofloxacin administered to poultry causes the proliferation of FQ-resistant *Campylobacter* in poultry which contributes to FQ-resistant *Campylobacter* infections in humans. Bayer attempts to show that several non-U.S. countries do not "fit" the temporal association model. Bayer points to Finland (Bayer Br. P40-42) and Sweden (Bayer Br. P13, 36, 41) for the proposition that there can be elevated resistance in animals and/or humans without FQ use in animals and to Canada (Bayer Br. P42-43) as an example of a country with low resistance in poultry but high resistance in humans.[12] For the reasons described below, none of Bayer's examples supports Bayer's theory.

In Finland, norfloxacin resistance was 4% and ciprofloxacin resistance was non-existent in human isolates collected between 1978 and 1980. Ex. G-524: P2. Resistance increased among human isolates collected in 1990 (11% norfloxacin resistance; 9% ciprofloxacin resistance). Id. According to the researchers, the increase in resistance likely reflected the levels of resistance in countries other than Finland because of the high rate of foreign travel in the Finnish patients. Ex. G-524: P4. The researchers also stated: "None of the resistant strains [from 1990] were known for certain to be of domestic origin." Id.

In addition to Exhibit G-524, Bayer cites to two other references for data on Finland. One exhibit (B-881) refers to the study discussed above and also attributes a 17% resistance level in 1993 to unpublished data only. Because of the high rate of foreign travel in this population, particularly to countries with documented high levels of FQ resistance (e.g., Spain), see Ex. G-524: P2-3; WDT G-1458: P3-4, it is quite likely that the percentage of resistance in 1993 is not

[12] In passing, Bayer also cites to Exhibit B-1936 to show that Germany is another example of a disparity in FQ use and FQ resistance levels in humans. Bayer Br. P13. This exhibit, which Bayer introduced during cross-examination, is an abstract of a paper published in 1983. As CVM witness Hanninen testified on cross-examination, the source of the isolates is not clear in the abstract. Tr. P713, L10 – P714, L16.

representative of indigenous cases.[13] The other exhibit (B-44) is a table that references two possible sources for the 1997 resistance level cited by Bayer. One source is a personal communication, the other source is an article. The article, Exhibit G-262, is a study of domestically acquired *Campylobacter* cases in Finland that found that the ciprofloxacin resistance was 0.9% (3 of 107 isolates). Based on published data, therefore, Finland -- a country that has not approved the use of enrofloxacin (RJS 54) -- has an extremely low level of domestically acquired FQ-resistant *Campylobacter* infections.

In Sweden, enrofloxacin has not been used for treatment of chickens. WDT G-1458: P4. Bayer cites to Exhibit G-62 to show that Sweden has high levels of resistance among chicken isolates. The exhibit reveals a resistance level of 4.5%. Bayer also cites to Exhibit B-1851 for the same proposition among human and chicken isolates. As discussed above, this study is unreliable because even the researchers who conducted it questioned its reliability. See Ex. B-1851: P4 (Addendum).

To show that Canada has allegedly experienced low resistance levels in poultry but high resistance levels in humans in the presence of limited FQ use, Bayer provides citations to six studies but no expert witness testimony. Bayer's evidence deserves no weight because the purportedly supporting documentation is unavailable for evaluation. Bayer cites to: (a) Exhibit B-29, which contains only the last two pages of a study; (b) Exhibit B-28, which contains no document at all; (c) Exhibit B-63, which is illegible; and (d) Exhibit B-1(A) P8,[14] which refers

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[13] Bayer argues that the high rate of foreign travel found in the studies from Finland raises questions about the validity of NARMS data because, according to Bayer, there is no way to know whether the same amount of resistance seen in the NARMS data can be attributed to foreign travel. Bayer is wrong. The 1998-1999 FoodNet Campylobacter case-control study found that the majority of persons with FQ-resistant infections had not been out of the United States in the week preceding illness; therefore, their illnesses were not acquired during foreign travel. WDT G-1460: P7, L19-22. Because NARMS is conducted exclusively within FoodNet sites, the information from the case-control study can be informative in estimating the level of foreign travel that may be occurring in the NARMS surveillance population.

[14] Bayer's citation to the Canadian studies in Bayer's NOOH Response is incorrect – it should be B-1(A) P10.

without detail to two additional studies that do not appear to be in the evidentiary record or anywhere on the docket. That leaves Bayer's Exhibit B-32 to tell the whole story, which it cannot. Because the study described in Exhibit B-32 involved human isolates only, Bayer has not shown that Canada fits its "low poultry, high human resistance" theory.

Finally, Bayer proposes that data from Denmark and Spain show that FQ resistance can be controlled by prudent use. See Bayer Br. P43. Given Bayer's denial of the existence of a relationship between FQ use and FQ resistance levels, it is surprising that Bayer would offer this theory, for, if FQ resistance can be affected by controlling FQ use, Bayer must concede that such a relationship exists. Indeed, Bayer has so conceded.

Bayer also attempts to discredit conclusions drawn from the United States data by claiming that estimates of levels of quinolone / FQ resistance in the U.S. before approval of enrofloxacin are similar to the resistance levels measured by NARMS after approval. Bayer Br. P34-35. Bayer completely ignores data from the only systematic national study in the United States conducted before enrofloxacin approval. The systematic 1989 – 1990 national study found the level of ciprofloxacin resistance among 332 *Campylobacter* isolates tested to be nearly zero (1 of 332 = 0.3% resistance). CVM Br. P49.

Although Bayer suggests that "CVM's citation to temporal examples is selective at best," CVM addressed all of the three relevant and reliable studies (Barrett, Nachamkin, and Smith) of the five cited by Bayer. Compare CVM Br. P48-50 with Bayer Br. P13-14, 34-35, 44. The remaining two studies Bayer cites were not considered by CVM. One (Williams) is inarguably irrelevant to the issues of the hearing.[15] The other (Kiehlbauch) is unreliable for the issues in this case.[16]

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[15] The Williams study that Bayer cites is an abstract about an unusual outbreak that occurred in 1993 among nursing home residents aged 86 to 97. Ex. B-67. The study is irrelevant because the level of resistance is derived from an enteritis outbreak, not from a sampling of sporadic cases. Even so, the study found a low level of quinolone resistance (3.3%) in this population.

Although Bayer cites to the Barrett, Nachamkin, and Smith studies for the proposition that there were high pre-approval levels of resistance, CVM believes these studies are examples of low pre-approval levels of quinolone or FQ resistance in the U.S. The Barrett study found that in 1988 only 2 of 42 *Campylobacter jejuni* ("*C. jejuni*") isolates and 0 of 25 *C. coli* isolates were resistant to nalidixic acid (5% resistance in *C. jejuni* isolates or 3% combined resistance in *C. jejuni/coli* isolates).[17] Ex. G-1609; WDT G-1453: P3. Nachamkin reported that no FQ resistance was observed in isolates from 1982 to 1992.[18] The Smith study found a 1.3% quinolone resistance level in 1992.[19] In CVM's assessment, 5%, 3%, 0%, 1.3% represent low levels of resistance compared to the levels observed after the NADA for Baytril was approved.

The post-approval national data from NARMS (high level of resistance and increasing trend) and pre-approval national data from the Sentinel County Study (nearly zero resistance), which are the most robust and reliable data available, show the stark contrast between FQ resistance levels in the United States before and after the approval of enrofloxacin. Nevertheless, Bayer continues to attempt to discredit the U.S. data by claiming that the NARMS estimates do not show an increasing trend in FQ resistance.[20] Bayer contends that the human NARMS data

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[16] The article appears to be a laboratory study examining methods for isolating bacteria and does not describe the population from which the sample isolates were taken. See Ex. B-39.

[17] Contrary to Bayer's assertion (Bayer Br. P13, N7), CVM witness Barrett did not testify that resistance levels were underestimated around 1988. See WDT G-1453: P3, L29-44.

[18] It appears that the 1995 level in Nachamkin's study may have been anomalous because it does not fit the trend seen in the populations studied by Nachamkin in the years before (1982 to 1992: no FQ resistance) and after (1996: 8% resistance (CVM Br. P49)).

[19] Bayer cites to page one of Smith's article as a reference for 6% resistance in 1995. Bayer Br. P35. Smith did not report a 6% quinolone resistance level in isolates from 1995 on that page or anywhere else in the article. Perhaps Bayer estimated this percentage from a graph on page three of the article. Even assuming that the resistance may be somewhere between 4% - 6%, this level does not support Bayer's contention of high pre-approval levels of resistance.

[20] With respect to animal NARMS data, CVM has already acknowledged that the data from the first several years of monitoring underestimated resistance levels. CVM Br. P20. However, after this problem was resolved, the level of FQ resistance among *C. jejuni* isolates from poultry in 2001 was measured at 17.6%. CVM Br. P20.

are not generalizable to the U.S., that the sampling scheme is not representative of the U.S., and that the sampling scheme skews the results. Bayer Br. 37-39.

Although CVM has adequately rebutted Bayer's criticisms of human NARMS data (CVM Br. P70-72), one additional point is worth noting. The comparison between pre- and post-approval resistance levels attributed to CVM witness Angulo at the end of page 35 of Bayer's brief is flatly wrong. Nowhere in Dr. Angulo's written direct testimony or in his testimony on cross-examination is there any statement even remotely similar to the one Bayer claims he made.

D. CVM Has Presented Evidence that FQ-Resistant *Campylobacter* Infections in Humans Have the Potential to Adversely Affect Human Health From Which Serious Questions About the Safety of Baytril May Be Inferred

Bayer attacks the credibility of the studies showing that FQ-resistant *Campylobacter* infections lead to an increased duration of diarrhea. See Bayer Br. P 70-72. However, a careful reading of these well-conducted studies shows that there is an increase in the duration of diarrhea when proper comparisons are made between FQ-resistant and FQ-susceptible *Campylobacter* infections.

1. Foreign Travel is Not a Confounder In Determining Duration of Diarrhea

Bayer asserts that *Campylobacter* cases associated with foreign travel must be excluded from duration of diarrhea analyses. Bayer Br. P71-72. For example, Bayer argues that, when foreign travel-acquired cases are removed from an analysis of data from the Smith study, there is no statistically significant difference in the duration of diarrhea between patients with quinolone-resistant *Campylobacter* infections and patients with quinolone-susceptible *Campylobacter* infections.

Bayer attempts to support its contention that duration of diarrhea analyses are confounded by foreign travel by referencing CVM's risk assessment at Ex. G-953: P25, 55-57, and 103. CVM's risk assessment does not support Bayer's contention. Moreover, the cited portions of

CVM's risk assessment do not even address the issue raised by Bayer and, therefore, cannot be relied on by Bayer for support.

There is no reason to exclude foreign travel-related cases when analyzing the association between the duration of diarrhea and FQ (or quinolone) susceptibility status of *Campylobacter* infections. See Tr. P462, L17 - P463, L6. For example, there are no data in the evidentiary record to support the premise that FQ-resistant *Campylobacter* acquired abroad is any more virulent than FQ-resistant *Campylobacter* acquired in the United States. Further, since FQ resistance in *Campylobacter* is chromosomally-mediated, rather than plasmid-mediated (i.e., resistance results from a mutation in the organism itself rather than the transfer of genetic material from other bacteria to *Campylobacter*), there is no reason to believe that FQ-resistant *Campylobacter* infections acquired during foreign travel would be any different (i.e., have greater adverse consequences, such as a longer duration of diarrhea) than FQ-resistant *Campylobacter* infections acquired domestically. See WDT G-1463: P3, L1-4, L17-25, P4, L1-7. As thoroughly addressed in CVM's initial brief, foreign travel is not a confounder. See CVM Br. P58-59; see also Tr. P463, L16 - P464, L10.

2. Studies Consistently Show That FQ-Resistant *Campylobacter* is Associated with Longer Duration of Diarrhea

Contrary to Bayer's assertion, see Bayer Br. P71, the epidemiological studies find an increased duration of diarrhea in persons with FQ-resistant *Campylobacter* infections compared to persons with FQ-susceptible *Campylobacter* infections. See CVM Br. P56-59. Although not every analysis assessing the impact of FQ resistance on duration of diarrhea has results that are statistically significant at a p-value of less than or equal to .05, they all find a longer duration of diarrhea associated with FQ-resistant Campylobacter infections when compared to FQ-susceptible Campylobacter infections. The fact that the studies consistently point to the same conclusion, whether or not their findings meet a specified level of statistical significance, is

evidence of the validity and reliability of their results. Discounting the results based on a numerical cutoff for statistical significance testing would cause the improper rejection of valid scientific findings, the reliability of which has been further supported by credible expert testimony.

3. Case Control Studies Do Not Show that FQ-Resistant *Campylobacter* Infections Respond to FQ Treatment and FQ-Susceptible *Campylobacter* Infections Fail to Respond to FQ Treatment

Bayer argues that patients with FQ-resistant *Campylobacter* infections who are treated with FQs respond to treatment, Bayer Br. P58-59, P73, and that patients with FQ-susceptible *Campylobacter* infections who are treated with FQs do not respond to treatment, Bayer Br. P58-59. These arguments are not supported, and in fact are controverted, by the evidentiary record.

Bayer's interpretation of the analyses of the CDC case-control data is flawed. The duration of diarrhea analyses of the CDC case-control data (by Marano and McClellan/Nelson), compared FQ-resistant cases with FQ susceptible cases. These analyses did not compare FQ-treated resistant cases with non-FQ-treated resistant cases. Similarly, the analyses did not compare FQ-treated susceptible cases with non-FQ-treated susceptible cases. Bayer inappropriately takes the results of the statistical analyses that were done and attempts to draw conclusions about statistical analyses that were not done.

The additional studies (Ex. B-50, Ex. G-354, and Ex. B-1920) cited by Bayer (see Bayer Br. P59) further demonstrate the unfounded nature of Bayer's argument. Ex. B-50 is a short narrative about antimicrobial resistance, which includes one sentence about some preliminary *Campylobacter* data. For many reasons, one cannot draw any scientifically valid conclusions about the efficacy of treatment from this statement. Most importantly, there was no comparison group (all patients had FQ-resistant *Campylobacter* and all were treated). In Ex. B-1920, the comparison group consisted of only three resistant cases who were not treated. Ex. B-1920: P4.

In Ex. G-354, 4 of 7 patients with FQ-susceptible *Campylobacter* isolates treated with ciprofloxacin recovered within 48 hours compared with 2 of 7 patients with FQ-resistant *Campylobacter* isolates treated with ciprofloxacin. It is unclear how that result could be considered supportive of Bayer's position.

In further support of its contention, Bayer states that the in vitro definition of resistance does not equate to clinical resistance. See Bayer Br. P74. According to Bayer, the disconnect exists because of: 1) the use of blood-level concentrations to develop the 4 μg/ml breakpoint used by CVM and other researchers, rather than the concentration of the drug in the cell lining of the gastrointestinal tract; and 2) the lack of a National Committee for Clinical Laboratory Standards (NCCLS) breakpoint for establishing clinical resistance for FQ use in *Campylobacter* infections in humans. These claims have been addressed.. See CVM Br. P18-19.

4. CVM's Risk Assessment Quantifies the Potential Adverse Health Impact to Humans of FQ-Resistant *Campylobacter* Infections Acquired From Chickens

CVM's risk assessment model estimated that, in 1999, the mean number of people in the United States who acquired FQ-resistant *Campylobacter* infections attributed to chicken consumption and who were prescribed an FQ was 9,261. CVM Br. P61. According to Bayer, Cox calculated the estimated number of people in the United States who acquired FQ-resistant *Campylobacter* infections attributed to chicken consumption that were prescribed FQs using both CVM's risk assessment model and Bayer's risk assessment model. Bayer Br. P75-76. When Cox changed the attributable fraction and treatment failure rate in CVM's risk assessment model, Cox found that the estimated number of people who acquired FQ-resistant *Campylobacter* infections attributed to chicken consumption and who were treated with an FQ was 975. Bayer Br. P75. Although CVM believes that the data inputs used in Cox's analysis were incorrect, when Cox used his own dose-response model, which applied farm-to-fork methodology, he found that the estimated number of such people was 985. Bayer Br. P76. Both CVM's and Bayer's risk

assessment models found that people with FQ-resistant *Campylobacter* infections suffered harm. The difference between Cox's results using CVM's risk assessment and Cox's results using his own risk assessment is 10 people. This nominal difference between the two models suggests that if the inputs for both models are similar, the outputs would also be similar—i.e, if the attributable fractions and treatment failure rates were the same in both models, the results would be the same. Thus, contrary to Bayer's assertions, CVM's model does not suffer from conceptual problems. In fact, the nominal difference between the two models demonstrates that, even according to Bayer's calculations, CVM's risk assessment model is scientifically sound as discussed below.

a. CVM's Risk Assessment Model is Robust

CVM's risk assessment assumes that there is a positive, linear relationship between contaminated poultry meat produced in a year and the resulting number of campylobacteriosis cases. See CVM Br. P66. Bayer criticizes CVM's assumption and relies on Cox's analysis of the FoodNet data to support the notion that there is a negative association between consumption of per capita chicken and cases of campylobacteriosis, i.e., that the more chicken consumed, the fewer campylobacteriosis cases. Bayer Br. P63; see also WDT B-1901: P17, 37. Cox's analysis is flawed.

In his analysis, Cox extrapolated data from FoodNet sites and constructed a linear regression chart with seven data points to show a negative association between chicken consumption and campylobacteriosis. See WDT B-1901: P37. But, when questioned on cross-examination, Cox admitted that his linear regression was just "a proxy" of the FoodNet survey data because he lacked measurements for the actual chicken consumed for the seven sites. Tr. P1069, L13-17. Moreover, although Cox testified, during cross-examination, that the statistical analysis he used for his linear regression was "just exploratory," Tr. P1071, L21 - P.1073, L6, Cox included this analysis in his written direct testimony without such caveat. See WDT B-

1901: P37. Cox also testified that his linear regression failed to include a confidence interval and R square values, basic factors in scientific analysis, because he did not consider the regression in his testimony to be "serious data analysis." Tr. P1071, L21-P1073, L6. Yet this "nonserious" analysis also appeared in Cox's article, in a journal supplement sponsored by Bayer, which is on the record in its pre-published form. Ex. B-1252: P3.

Additionally, during cross-examination, when Cox was questioned about Rosenquist's farm-to-fork model which included microbial load distributions and a dose-response model, Ex. G-1788: P10, Cox conceded that Rosenquist's model produced the same linear relationship that CVM assumed under the same fixed load distribution in CVM's model, Tr. P970, L14 - P972, L7. Moreover, it is unclear whether any of Bayer's witnesses ever tested the linear relationship in CVM's model to determine whether they would have found the same result as did CVM. See Tr. P1023, L15 - P1024, L1.

A farm-to-fork analysis, including a dose-response model, would have been inappropriate for the reasons discussed in CVM's initial brief. See CVM Br. P64-65. In spite of the limitations in that model, Bayer insists that CVM should have conducted a farm-to-fork risk assessment that would have relied on a dose-response model. Bayer Br. P62-64, P76. Bayer's criticisms fail because the dose-response models that Bayer relies on to support its contention are unreliable and based on data that undermines Bayer's argument.

The *Campylobacter* dose-response models that have been developed all rely on the only dose-response data set available for *Campylobacter*, contained in a study authored by Black. See Ex. G-67, Ex. G-1788; Ex. B-748; Ex. B-517; and Ex. B-147. Bayer relies on this data (Bayer Br. P62), as analyzed by Cox, to show that ingesting food with high doses of *Campylobacter* are disproportionately likely to cause illness compared to ingesting food with average doses. Bayer Br. P63; see also WDT G-1901: P22. Yet, Black's data do not indicate a traditional dose-

response in that they actually showed that people did not develop illnesses when given a relatively high dose of 10^8 CFUs of *Campylobacter* but did develop illnesses when given a lower dose of 9×10^4 CFUs. Ex. G-67: P4. In fact, one person even developed an illness at only 800 CFUs, the lowest dose given. Id.

Rosenquist's study, Ex. G-1788, states that "the dose-response relationship is based on only one study [Black's study] describing the response in young American volunteers to two strains of *C. jejuni*. Therefore, with the current state of knowledge, a model like the one presented cannot be used to generate true risk estimates." Ex. G-1788: P14. Clearly Rosenquist does not agree that Black's data supports Bayer's argument that higher doses of *Campylobacter* result in illnesses.

Teunis' study developed an experimental dose-response model in an attempt to explain why the probability of illness seemed to decrease at high doses in Black's data. Ex. B-748: P1. This resulted in a controversial model that showed a probability of illness that did not continuously increase with increasing doses (Ex. B-748: P7, Fig. 2c) as would normally be expected (Ex. B-748: P7, Fig. 1c). Teunis' dose-response model is not appropriate for *Campylobacter* risk modeling because it is biologically implausible; it shows that a person has a greater risk of illness from consuming 10 CFUs of *Campylobacter* than from consuming 10^8 CFUs of *Campylobacter*.

Medema also attempted to model the probability of illness based on Black's data, but noted that: "Although applicable to assess the risk of infection, the current dose-response data on *C. jejuni* and other enteropathogens do not allow assessment of the disease risk, since no clear relation was found between dose and the occurrence of symptoms." Ex. B-517: P9. A complete dose-response model requires the determination of both: (1) the probability of being infected (i.e., having *Campylobacter* recovered from the stool) given a particular dose; and (2) the

probability of illness (i.e., symptoms of disease) given infection by a certain dose. Medema's dose-response model is insufficient because it did not determine the probability of illness given the infection.

Anderson's study, Ex. B-147, does not support Bayer's position. Anderson discussed the lack of relationship in the available data between the dose and probability of illness. Ex. B-147: P5. Anderson then described how judgment-encoding methodology had to be used to bridge the gap in the data, indicating that the dose-response model was not based on actual data. Id. Anderson further expressed concerns about the limited use of the risk assessment in his study due to the lack of data. Id. at P7.

Bayer also relies on Robinson's study, Ex. G-1816, to show that any dose of *Campylobacter* below 500 CFUs has a zero probability of producing a *Campylobacter* illness. WDT G-1901: P14, P22; Ex. A-17: P29; Tr. P1026, L13 - P1021, L1. But during cross-examination, Cox admitted that the Robinson's study involves only "one guy administering to himself" one dose of 500 CFUs of *C. jejuni* resulted in him getting sick. Tr. P1032, L1 - P1033, L5. There is no evidence in Robinson's study that doses lower than 500 CFUs would not result in illness; no lower dose was administered.

b. CVM'S Risk Assessment Applied Standard Epidemiological Attribution Methods

Bayer argues that a 24% attributable fraction is more appropriate than the 57% attributable fraction used by CVM in its risk assessment. Bayer Br. P75. CVM's risk assessment, unlike Bayer's, applied a standard epidemiological approach for determining attributable fractions. Although attributable fractions cannot be negative numbers, see Tr. P800, L11-14, Cox's model presents negative attributable fractions (i.e., confidence bounds on the attributable fraction that are -11.6%, 0.72%), WDT B-1901: P57. An attributable fraction is based on the odds ratio between cases and controls and on an estimate of exposure in the general

population. An odds ratio less than one signifies that the cases were less likely than the controls to have been exposed to the risk factor of concern. Bayer, by misinterpreting Friedman's analysis, interprets an odds ratio less than one as being "protective." See Bayer Br. P56. But this ratio does not mean that there was negative risk to the cases. Tr. P801, L12-19. Bayer imagines that because eating chicken at home is supposedly "protective" some amount should be subtracted from the population attributable fraction for chicken overall to compensate. Bayer Br. P25, P63-64.

Bayer questions the validity of CVM's attributable fraction. Bayer Br. P23. Bayer claims that CVM's reliance on the Harris and Deming studies, rather than the CDC data set, indicates an a priori bias on the part of CVM. Bayer Br. P24. The Harris and Deming studies were the most robust studies available to CVM at the time it conducted its risk assessment. CVM Br. P68; Reply to AHI Br. P7. In the CDC data set, the attributable fraction for poultry, chicken and turkey combined, is 28%. The 21% attributable fraction for non-poultry meat, see Bayer Br. P24, would be viewed by CVM as being mostly attributed to cross-contamination from poultry in the restaurant kitchen. Bayer, on the other hand, views this 21% as indicating that there is some third common source contaminating both the poultry and non-poultry meats. Bayer Br. P56. The 21% value, however, is consistent with other, earlier, information on the attribution to cross-contamination from preparation of poultry. See WDT G-1454: P14, L38-41.

The combined value of these fractions (49%) is still insufficient for factoring in all potential exposures to *Campylobacter* derived from chicken because it omits direct contact with farm animals and exposure to raw water contaminated with poultry farm runoff. Thus, even if CVM were to re-calculate a global attributable fraction based on the CDC data and other information, the attributable fraction would be similar to the attributable fraction CVM used in its risk assessment (57%, see CVM Br. P68) based on the Harris and Deming studies. Bayer

misapplied the CDC data because Cox only used the attributable fraction for eating chicken at home and assumed that because the odds ratio was less than 1, he had an impossible negative risk. See Bayer Br. P63-64.

Bayer further insists that CVM should have performed causal analysis via conditional independence tests to determine if chicken is the cause of campylobacteriosis. Bayer Br. P64-65. On the other hand, Bayer (incorporating by reference AHI's brief) also insists that CVM should have modeled risk in the same way that other risk assessments modeled other risks. See AHI Br. P21 n.9. These two arguments are contradictory because none of the other risk assessments cited in the record used causal analysis via conditional independence tests. Ironically, AHI and Bayer rely on the Danish Veterinary and Food Administration *Campylobacter* risk assessment by Rosenquist (Ex. G-1788), the Health Canada *Campylobacter* risk assessment, and the Georgetown University *Campylobacter* in beef risk assessment by Anderson (Ex. B-147). Bayer Br. P76; AHI Br. P26. Yet none of those risk assessments used conditional independence tests. Bayer's argument that CVM's risk assessment should have used conditional independence tests lacks credibility.

Although CVM used older studies than those now available to estimate the population attributable fraction for national consumption of poultry, a current estimate incorporating the CDC case control data should consider many routes of exposure and would not differ substantially from the values used in CVM's risk assessment. On the other hand, Bayer relies heavily on Cox's causal analysis to show that the proportion of cases of campylobacteriosis attributed to chicken is much smaller than CVM's value. But Cox's analysis lacks credibility because he misinterprets information in the literature, analyzes data without knowledge of how it was collected, and apportions risk to factors that cannot be responsible for exposure to *Campylobacter* by permitting inappropriate software to make biologically implausible choices

and then claims that factors chosen by such a process are necessarily causal, Tr. P1112, L1 - P1118, L13.

IV. The Risk of Baytril Use in Poultry to Humans Exceeds its Benefits

Bayer relies on Cox's modeling of data generated by Russell to argue the risks to human health from the withdrawal of the NADA for Baytril use in poultry exceed the benefit to humans of such withdrawal. Bayer Br. P86-88. This study, however, fails to indicate the specific antimicrobial treatment histories of the birds tested, which makes it impossible to compare the various replications of the air sacculitis positive and negative birds.[21] The study does not indicate whether the broilers are from the same farm or different farms, how much and what each flock was fed, the management practices of each flock owner, whether the flock had any other disease present, how long the birds were held before slaughter, or how long the broilers were off feed until slaughter. All of these factors could impact the size, weight and uniformity of the birds tested. It is not even clear whether air sacculitis positive and negative birds were sampled the same day or what part of the day (i.e., at what point in the work shift) the birds were slaughtered, see Ex. B-1912: Attach. 1, which is important because the slaughter process presents many opportunities for cross-contamination, see WDT G-1467: P7, L25-31.

Moreover, it appears that the age of the broilers in the study differed, requiring the use of an artificial calculation to adjust the size of the bird for the age of the bird. Ex. B-1912: Attach. 1, P42, L21-23. Considering that one of the objectives of the study was to measure the lack of uniformity of the birds, WDT B-1912: Attach. 1, P36, L2-4, it seems unusual that the protocol

[21] Russell states that "[B]oth air sacculitis-positive and air sacculitis-negative flocks of chickens were treated with tetracycline and sulfa drugs. None of the chickens evaluated in this study were treated using fluoroquinolones." WDT B-1912: P20, L18-21. Russell does not indicate how often the birds were treated, at what dose were they treated, or at what age were they treated. Further the fact that the chickens were not treated with FQs questions the accuracy of Bayer's contention that chickens not treated with FQs will be smaller because there is no comparison of the alternate therapies with Baytril.

would not require standardization among the birds tested with respect to all the variables listed above.

Further, the sampling point used by Russell for the microbiological evaluation is questionable. Russell's study states that the carcasses were collected after slaughter but before being washed. See WDT B-1912: Attach. 1, P41, L21-22. However, there is testimony from Bayer witness Robach that the spray wash is effective at removing some of the fecal contamination acquired during evisceration. WDT B-1911: P14, L14-16. Thus, it seems likely that Russell's sampling point would find higher contamination rates than would be the case after washing.

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 days of diarrhea from *Campylobacter* derived from poultry sources. See Bayer Br. P86. Bayer presents other witnesses to attempt to show that chicken is not a source of *Campylobacter* and to discredit CVM's evidence that poultry is a major source of campylobacteriosis and FQ-resistant campylobacteriosis. See Bayer Br. P21-24. The inconsistencies in Bayer's various arguments are evident.

A. Bayer's Model Grossly Underestimates the Human Health Risk of Enrofloxacin Use

Bayer claims that withdrawing enrofloxacin will actually harm humans because the risk of campylobacteriosis and salmonellosis will increase. Bayer Br. P86-89. Bayer relies on Cox's farm-to-fork analysis to demonstrate the alleged benefits of enrofloxacin on human health. As discussed below, Bayer's claims do not withstand scrutiny because Cox's model is flawed.

First, Cox overestimates the benefits of Baytril use in poultry to humans by erroneously interpreting foreign data as being supportive of Bayer's contention that withdrawing enrofloxacin will cause harm. Cox claims that a 1999 ban on several antimicrobials was

"followed by sharp increases and record levels of campylobacteriosis and salmonellosis in multiple countries." WDT B-1901: P83. Cox suggests that the ban supports his argument that withdrawing enrofloxacin will increase domestically-acquired campylobacteriosis cases. Cox's testimony quoted a Eurosurveillance Weekly report that discussed the increasing *Campylobacter* infections in Norway, but Cox failed to note that there was a steady increase in domestically-acquired campylobacteriosis cases since 1992, well before the ban. WDT B-1901: P83; http://www.eurosurveillance.org/ew/2002/020613.asp. Thus, Cox misrepresented the evidence he claims support his contention.

Next, Cox underestimates the risk to humans of enrofloxacin use in poultry in the United States by underestimating the exposure itself (microbial load on a serving of chicken and the number of servings consumed per person), Tr. P1058, L2 - P1067, L20, and overestimating the amount of exposure required to produce illness (dose-response), Tr. P1026, L1 - P1049, L5. Cox exploits this same combination of faulty microbial load distribution with an unsubstantiated dose-response relationship to contrive a human health benefit for enrofloxacin.

1. Bayer's Model Underestimates the Likely Exposure to *Campylobacter* on Chicken

Cox's estimate of the distribution of bacteria load in a chicken serving was based largely on Stern's data. See Ex. B-1020: P13, Table 3; Ex. A-17: P96; Tr. P1056, L16-19. In describing the data, Cox failed to mention that the measurements for Stern's data were determined from rinses of carcasses, not from the actual carcasses themselves. During cross examination, Cox had difficulty in appreciating that 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. P1058, L2 - P1060, L10.

More importantly, Cox used the Stern data incorrectly. The values reported in Stern's data are the *geometric* means of observations (i.e., averages of log bacterial counts, or of log reduction factors) of 10 samples in one study or 25 samples in the other. See Tr. P1067, L6-12. In his model, Cox used the values as though they represented individual observations. See Ex. B-1020: P13. This is an inaccurate reading of Stern, whose article clearly states that the values he is displaying are mean log CFU counts of 10 or 25 chickens, not CFU counts per chicken. Tr. P.1067, L6-13. Cox's error was perhaps explained during cross-examination, when he admitted that he did not know the details about how Stern's data was determined, Tr. P.1058, L2-12. In view of that error, Cox said that "The distribution [in his model] is not intended to be completely physically accurate. The distribution is intended to capture the approximate mean and variability for use in something called the central limit theorem." Tr. P1062, L10-14. By neglecting to recognize that the data involved geometric means of observations rather than actual observations, Cox's analysis completely failed to capture either the mean or the variance of the variables being modeled.

A. Error in estimating the mean. Cox based on his model on the arithmetic mean of Stern's geometric means. If Cox's model were corrected to recognize that Stern's data consisted of geometric means, the dose distribution from a serving would have a mean several times higher than Cox predicts. This error alone results in a gross underestimate of the risk and a gross overestimation of the benefits of enrofloxacin to human health.

B. Error in calculating the variance. Since Cox ignored the fact that the values in Stern's article were geometric means, he failed to increase the spread of his distribution of CFUs on a chicken carcass by a necessary factor. Cox's refusal to concede that this practice is in accordance with the central limit theorem is not credible, see Tr. P1066, L13 - P1068, L7, especially since it came only after FDA's counsel pointed out, Tr. P1067, L13-20, that this meant

that Cox's modeled population distribution of $\log_{10}$ bacteria would be between 3 and 5 times wider than the distribution of log means which he did fit, see Tr. P1067, L13-22. Cox then denied the applicability of the central limit theorem despite the fact that he was the one who first brought the central limit theorem up in this context. Tr. P1062, L10-14.

Cox's distribution of $\log_{10}$ CFUs in a serving ranged from 0 to about 3. WDT B-1901: P84, Figure 3. If Cox's distribution was calculated correctly, it would range from 0 to between 9 (3*3) and 15 (3*5) $\log_{10}$ CFUs. See Tr. P1062, L10-14. Although the lowest biologically meaningful dose is 1 CFU, or 0 $\log_{10}$ CFUs, Cox has dose distributions that lie almost entirely to the left of that value. Cox's model is not biologically plausible.

2. Bayer's Model Overestimates the Amount of Exposure Required to Produce Campylobacteriosis

The errors in Cox's dose-response model contribute to Bayer's mistaken belief that the continued use of enrofloxacin in poultry would be a benefit to humans. Cox's dose-response curve is misleading and not based on the data. See Ex. G-67. Black's data, which Teunis used to construct his dose-response curve, went up to doses of 8 $\log_{10}$ CFUs, Ex. G-67: P4, whereas Cox simply truncated Teunis' dose-response curve at 4 $\log_{10}$ CFUs, Ex. A-17: P112. The way Cox drew his dose-response curve avoided alerting the reader to the biologically remote idea, embedded in the model he uses, that the probability of illness becomes exceedingly small for very high doses. See Ex. A-17: P112. This omission is critical. A typical dose-response curve is monotonically increasing from zero probability of illness at a zero CFU dose to a non-zero probability of illness at high doses. See WDT G-1480: P9, L3-5. Teunis' model, and hence Cox's model, which arches up and then has to curve back down to fit a zero probability of illness for high doses, see WDT B-1901: P84, will be forced by its curvature to underestimate the probability of illness at all doses.

Cox decided that he would introduce a minimum infective dose threshold of 500 CFUs (which equals 2.7 $\log_{10}$), Ex. B-1020: P21, based on the Robinson study, which Cox admitted consisted of one person dosing himself with 500 CFUs and becoming ill, Tr. P1032, L8 – P1033, L5. With no known studies at lower doses there is no logical justification for making 500 CFUs the minimum infective dose. This contradicts even Cox's own understanding of the data, since he agreed that Teunis' composite, dose-response model has two components which give a finite probability that even just one bacterium could cause infection, and that illness could then result from that one bacterium. See Tr. P1034, L2-13.

B. Bayer's Model Grossly Overestimates the Human Health Benefit of Enrofloxacin Use

1. Bayer's Model Overestimates the Increased Risk of Campylobacteriosis that Would Follow the Withdrawal of the NADA for Enrofloxacin in Poultry

Bayer contends that without enrofloxacin, sick birds will remain smaller and their intestines more fragile resulting in more contamination of poultry carcasses and, therefore, more illness to humans. Bayer Br. P82-83, 86. In Cox's model, this means that the microbial load distribution on poultry will be shifted slightly to the right and will have a slightly longer right tail (jagged curve with slightly lower peak height to the right of the other jagged curve). See WDT B-1901: P84, Figure 3. Cox's model projects an increase in the number of cases of illness because more of the shifted exposure distribution exceeds his illness threshold.

Under Cox's modeling of the current situation, the right tail of the dose distribution does not exceed 500 CFUs (WDT B-1901: P84, Fig. 3), connoting as Cox has claimed that there are no cases of campylobacteriosis caused by chicken because "there is an overall negative (beneficial) association between chicken consumption and the risk of campylobacteriosis . . . ." WDT B-1901: P5-6. On the other hand, in Cox's modeling of the situation if enrofloxacin were not being used (WDT B-1901: P84, Fig. 3), Cox contends that a portion of the dose distribution

would exceed his illness threshold and then chicken consumption would be associated with some cases of campylobacteriosis, WDT B-1901: P85.

Clearly, Cox's flawed benefits model depends heavily on the errors discussed above, namely the choice of a biologically implausible dose-response curve and the failure to incorporate good estimates of the mean and variability of the dose distribution. These errors produce a model that could not be better designed to (falsely) produce a large prediction of human health impact from the removal of enrofloxacin.

2. Bayer's Risk-Benefit Analysis of Enrofloxacin is Biased

Finally, Bayer contends that the risks of enrofloxacin use must be weighed against the supposed benefits to humans. Bayer Br. P89. But in addition to calculating the supposed benefits incorrectly, Bayer has exhibited extreme bias in its logic of what constitutes a complete risk benefit analysis. Although Bayer considers the alleged reduction in cases of salmonellosis among the benefits of continued enrofloxacin use in poultry (Bayer Br. P88-89), Bayer does not model the risk of FQ resistance in salmonellosis patients. FQ resistance in *Salmonella* develops more slowly than FQ resistance in *Campylobacter,* because resistance in *Salmonella* requires a multi-step genetic mutation, WDT G-1463: P3, L22-32, whereas resistance in *Campylobacter* only requires a one-step genetic mutation, CVM Br. P13. Bayer chose not to have Cox model the risks associated with FQ-resistant *Salmonella,* despite Bayer's claims that his model is predictive. If Bayer's claims were correct, such a model should have been possible.

Moreover, any benefit associated with the use of Baytril must be discounted by the availability of other alternatives to Baytril and to changes in the slaughter process which would reduce contamination of carcasses with fecal matter. See Commissioner's DES decision, 44 Fed. Reg. 54852, 54886 (1979) ("One factor that the manufacturing parties seem to ignore is the availability of alternatives to DES. If a claimed benefit from the use of DES is also available

from a potential substitute, it is appropriate as a matter of common sense and logic to discount that benefit in determining whether the benefits of DES outweigh its risks."). The evidence presented at hearing indicate that there are alternatives to Baytril. WDT G-1478: P18, L34-46. Further, the evidence shows that changes in evisceration processes could reduce pathogen contamination. AHI argues that "[t]here is evidence of a reduction in enteric pathogen contamination as a result of manual evisceration rather than mechanical. [Gonder (A-201) P.12, L.4-5]." AHI Br. P34. When properly evaluated, there is no doubt that the risks to humans of Baytril use in poultry far exceed any benefit of Baytril use in poultry to humans, and in fact, there is no credible evidence of any benefit to human health of Baytril use in poultry.

V. There is a Reasonable Basis From Which Serious Questions About the Safety of Baytril Use in Turkeys May Be Inferred

Bayer claims that CVM did not meet its burden to present evidence about turkeys from which serious questions about the safety of Baytril use in turkeys may be inferred, leaving the substance of this argument for AHI's initial brief. This issue is fully addressed in CVM's reply to AHI's initial brief.

VI. Conclusion

The evidentiary record of this hearing provides a reasonable basis from which serious questions about the safety of Baytril use in poultry can be inferred. CVM has met its burden to adduce this evidence and what it shows, shifting to Bayer the burden to demonstrate that the use of Baytril under the approved conditions of use in poultry has been shown to be safe. Bayer has not met its burden in this case. CVM respectfully requests that the Administrative Law Judge

find that Baytril use in poultry is not shown to be safe for use under the approved conditions of use and order the withdrawal of the NADA for Baytril use in poultry.

Respectfully submitted:

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Enrofloxacin Hearing
Docket No: 00N-1571

CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of the foregoing Center for Veterinary Medicine's Reply to Bayer's Post Hearing Brief was hand delivered this 15th day of August, 2003, to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
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Rockville, MD 20852

I also certify that a copy of the Center for Veterinary Medicine's Reply Brief was hand delivered and e-mailed this 15th day of August, 2003, to:

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I also certify that a copy of the Center for Veterinary Medicine's Reply Brief was mailed and e-mailed this 15th day of August, 2003, to:

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