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: April 14, 2003
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	

CVM's Critique of Bayer's and AHI's Joint Proposed Findings of Fact

Pursuant to the Administrative Law Judges April 10, 2002, Scheduling Order, the Center for Veterinary Medicine ("CVM" or "the Center") respectfully submits the following critique of Bayer's and AHI's Joint Proposed Findings of Fact:

2. *Campylobacter* are very fragile organisms which can normally only reproduce in the intestinal tract of a host animal. [G-457 P.3; Newell (B-1908) P.22 L.4-6]

CVM CRITIQUE: This proposed finding is misleading as it is taken out of context of the witnesses' testimony, which is included below. The proposed finding is misleading in that it implies that the witness intended to state that what is seen in the laboratory is also what occurs in nature, when a reading of the testimony shows otherwise.

> "*Campylobacters* are generally considered fragile organisms within the laboratory environment, losing viability quickly in normal atmospheric conditions and readily susceptible to the antimicrobial action of sunlight and desiccation. However, in the external environment *Campylobacters* can be robust surviving extended periods especially in moist, cool conditions (Obiri-Danso et al., 2001) (Easton, 1996). Survival in meat, especially poultry meat, and milk contaminated during production, is well recognized and has been [extensively studied (Jacobs-Reitsma, 2000)]." [Newell, p. 22]

3. *Campylobacter* require a reduced oxygen environment to grow. [Meng (G-1466) P.2 L.10, P.2, L.40-43]

CVM CRITIQUE: This proposed finding is misleading and contrary to the cited testimony. The cited testimony of Meng states that "*Campylobacter* do not typically grow well in a normal oxygen atmosphere, and need to be cultured in an oxygen-reduced environment". (emphasis added). The second citation referring to this testimony (P. 2, L. 40-43) reads "... isolation and culturing of *Campylobacter* were always done under a micro-aerobic atmosphere..." This quotation refers to what was done for laboratory analysis, not meant to serve as a general reference to organisms in the environment.

4. *Campylobacters* are susceptible to stresses such as heat and atmospheric oxygen. [Newell (B-1908) P.22 L.5-6; G-457 P.3; B-205 P.1]

CVM CRITIQUE: This proposed finding is a variation on proposed finding of fact 3 above and includes the same citation to Newell's testimony (B-1908 p. 22 L. 5-6). It is misleading by ignoring the context of the testimony, which refers to laboratory effects, not necessarily reflecting what occurs in nature where the bacterium is not present in an artificial laboratory medium. For example, *Campylobacter* was shown to survive heat necessary to melt butter, after which it caused an outbreak of campylobacteriosis (G-444, P. 144), indicating that it can clearly tolerate some measure of heating.

13. Farm-workers play an interesting role in the epidemiology of flock colonization. Case-control studies have demonstrated farm staff as a risk factor and external contamination of a flock by catchers has been demonstrated. [Tompkin (A-204) P.45 L.13-15]

CVM CRITIQUE: This proposed finding does not give enough information about what "interesting" means, nor does it cite to any case control studies. Without more information, CVM is unable to properly respond; however, CVM notes there is no indication of how many case control studies have looked at this issue, no mention of the odds-ratio associated with the various risk factors found nor mention of whether this proposed finding even addresses *Campylobacter* rather than other organisms.

15. Few *Campylobacters* from environmental sources have been investigated but fluoroquinolone-resistant organisms have been recovered from wild birds including sparrows. [Patterson (B-1910) P.10 L.11-13; Newell (B-1908) P.17 L.10-11]

CVM CRITIQUE: This proposed finding of fact is misleading because it is taken out of context and does not include important information. While it is true that fluoroquinolone-resistant *Campylobacter* have been isolated from sparrows, the investigators attribute this finding to sparrows' exposure to animals treated with fluoroquinolones.

Patterson cites Sorum & L'Abee-Lund (2002) for the fact that fluoroquinolone -resistant *Campylobacter* has been isolated from sparrows. In their paper (p.49), Sorum and L'Abee-Lund state the following:

> In Japan, *C. jejuni* has been isolated from sparrows and some of these strains were quinolone resistant. The sparrows were thought to have acquired these strains from contact with animals or animal feed in industrialized production of chicken, pigs and cattle. The frequent use of quinolones to treat these animals may have been the reason for the transfer of quinolone-resistant strains to sparrows. It was also considered that sparrows carrying quinolone-resistant *C. jejuni* could subsequently be an infection source of quinolone-resistant *Campylobacters* to the meat industry (Chuma, T., Hashimoto, S., Okamoto, K., 2000. Detection of thermophilic *Campylobacter* from sparrows by multiplex PCR; the role of sparrows as a source of contamination of broilers with *Campylobacter*. J. Vet. Med. Sci. 62, 1291-1295).

19. Evidence shows that turkeys are preferentially colonized by *Campylobacter coli* compared to *Campylobacter jejuni* . [Gonder (A-201) P.12 L.17-23; G-727; Newell (B-1908) P.4 L.7-8]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Gonder's WDT and Exhibit G-727 indicate the predominance of *C. coli* recovered from retail turkey. No data is presented on sampling live turkeys. Dr. Newell's WDT indicates that:

> There is also some suggestion that turkeys may be preferentially colonized by *C. coli* rather than *C. jejuni* (Zhao et al., 2001) (Nielsen & Nielsen, 1999) though this is not confirmed by other studies (Wallace, et al., 1998) and may be reflection of regional differences and contact with animals, such as pigs, with *C. coli* infections (R. Meinsermann, personal communication).

None of the cited testimony indicates that turkeys are preferentially colonized by *Campylobacter.*

20. Studies suggest that *Campylobacter* colonization in broilers and turkeys may have significant host specific differences. [Newell (B-1908) P.4 L.11-12]

CVM CRITIQUE: Regarding this proposed finding of fact, there are no cited studies in the evidentiary record or elsewhere confirming that there are host specific differences influencing colonization by *Campylobacter* species.

29. *Campylobacter*, including fluoroquinolone-resistant *Campylobacter* are frequently isolated in surface and ground waters, including drinking water supplies. [Patterson (B-1910) P.4 L.9-10]

CVM CRITIQUE: This statement of opinion is without factual basis on the record. The record provides no evidence to verify that fluoroquinolone-resistant *Campylobacter* has been isolated frequently from surface and ground waters, including drinking water supplies, nor what the sources of *Campylobacter* into the water was (i.e., runoff from

agricultural land that had chicken litter used to fertilize crops). Further, Wegener's WDT p. 9 L 1-7 states that water is not a natural reservoir for *Campylobacter*.

30. Studies suggest there is little or no carry-over or persistence of *Campylobacter* from one flock to the subsequent flock, and that the majority of flocks are infected by strains from external sources. [Newell (B-1908) P.8 L.17 – P.9 L.8; Tompkin (A-204) P.44 L.20-22]

CVM CRITIQUE: This proposed finding of fact does not accurately represent what is cited in the written direct testimony of Newell (B-1908), in that the cited section of testimony says nothing about carry-over between flocks, but only about the introduction of *Campylobacter* into a flock from external sources. The testimony of Bayer witness Tomkin (A-204) states that carry-over is unlikely, but provides no supporting scientific study. CVM witness Jacobs-Reitsma provides evidence that flock-to-flock carryover does occur (G-1459, P.3, L. 24-26). In addition, this proposed fact is contradicted in Exhibit G-428, in which litter is shown to harbor *Campylobacter* which can go on to infect subsequent flocks placed on the same litter.

31. There are no reports of *Campylobacters* being isolated from fresh bedding or feed. This is not surprising as these organisms are very susceptible to desiccation. [Newell (B-1908) P.7 L.4-6 citing B-673, (Luechtefeld et al., 1981) (Doyle & Roman, 1982)]

CVM CRITIQUE: This proposed finding of fact is contradicted by Bayer witness Newell (B-1908, P.7 L.1-3) where it is stated that, "Potential horizontal sources for poultry include services in the broiler house (feed, water, air, staff) and an environment contaminated by wild life, domestic animals and previous flocks.

32. There is little or no persistence of *Campylobacter* strains within the poultry house and that the majority of flocks are infected by strains from external sources. [Newell (B-1908) P.8 L.15-16]

CVM CRITIQUE: This proposed finding of fact is contradicted by Exhibits G-428 and G-686, which show that *Campylobacter* can be recovered from litter and persist to infect subsequent flocks.

35. All of the quinolones physically interact with DNA gyrAse, an enzyme essential for bacterial replication, and prevent it from functioning normally. [Barrett (G-1453) P.2 L.7-9]

CVM CRITIQUE: This proposed finding of fact does not accurately represent the cited testimony, wherein the witness states that this "appears to be" the case. We agree with the statement by Barrett, since this phenomenon has not been demonstrated for all fluoroquinolones.

40. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. [Newell (B-1908) P.15 L.12-13]

CVM CRITIQUE: This proposed finding is without factual basis on the record. The record provides no evidence to verify that fluoroquinolone-resistant *Campylobacter* emerges in the absence of quinolone exposure. This proposed fact is contrary to numerous studies in the record showing that the use of fluoroquinolones in the treatment of domestic flocks is the only identified condition for the emergence of fluoroquinolone-resistant *Campylobacter* (G-403, G-404, G-405, G-1421, B-868, A-190, B-432, inter alia).

CVM acknowledges that naturally occurring mutations result in low levels of fluoroquinolone-resistant *Campylobacter* in poultry but without the selection pressure of a fluoroquinolone drug, this does not result in colonization of fluoroquinolone-resistant *Campylobacter* in the birds. Further, CVM acknowledges that fluoroquinolone-resistant *Campylobacter* can be found in birds exposed to fluoroquinolone-resistant *Campylobacter* from other birds treated with a fluoroquinolone, but CVM maintains that such exposure to a fluoroquinolone-resistant *Campylobacter* would not occur without the use of fluoroquinolones in the other flock.

41. Treatment is not the only source of fluoroquinolone-resistant *Campylobacters* in poultry. Gaunt and Piddock, in 1993/4, before enrofloxacin was licensed for use in the UK, undertook a small survey of retail domestic and foreign produced poultry products. ciprofloxacin-resistant *Campylobacters* were found in one of 64 UK-produced chickens. This indicates that resistant *Campylobacter* can be acquired by broiler flocks, other than by treatment. [Newell (B-1908) P.16 L.24 – P.17 L.6 citing B-609 and Gaunt and Piddock (1996)]

CVM CRITIQUE: This proposed finding is contradicted by numerous other studies examining many more isolates of *Campylobacter*, which clearly demonstrate that fluoroquinolone resistance emergence is a consequence of quinolone exposure (B-842, B-868). We believe that it would be an error to extrapolate from the finding by Piddock of a single isolate the proposed finding of fact. The finding of a single isolate, the resistance of which has not been confirmed by re-testing with other methods, can not be relied upon to formulate a universal proposition.

43. Fluoroquinolone-resistant *Campylobacter* (*C. jejuni* and *C. coli*) existed in chickens and turkeys in the United States prior to 1995. [CVM Response to Bayer's Interrogatory 81]

CVM CRITIQUE: This proposed finding is misleading because it takes CVM's response to Bayer's Interrogatory Number 81 out of context. CVM's entire response to Bayer's Interrogatory Number 81 is, "The existence of *Campylobacter* mutants resistant to fluoroquinolones, albeit low in prevalence, is a natural phenomenon that can be expected to occur once in approximately 5 x 10^8 cells [1 in 50 million] (Gootz 1991), regardless of host species."

50. Antibiotic residues such as fluoroquinolones or tetracycline in sewage treatment plants may select for resistance in bacterial strains entering or residing within the sewage treatment plants. [Patterson (B-1910) P.12 L.22 – P.13 L.1]

CVM CRITIQUE: This proposed finding is based on an opinion that is not supported by scientific studies on the record of this hearing showing that fluoroquinolone resistance has emerged in *Campylobacter*, or any other bacterium, as the result of selection by antibiotic residues in sewage treatment plants.

51. Exposure to the array of drug residues present in sewage treatment plants may select for resistant strains at the expense of more susceptible organisms. [Patterson (B-1910) P.13 L.2-3, citing to B-1807]

CVM CRITIQUE: The cited WDT and exhibit do not support this proposed finding. The cited WDT lines do not address sewage treatment plants and B-1807 does not address drug residues at sewage treatment plants, nor does it mention *Campylobacter*.

52. Because sewage treatment plants discharge into waters used for recreation and drinking water sources, they likely constitute a major source of resistant bacteria, including fluoroquinolone-resistant *Campylobacter*, to human populations, both in the United States and abroad. [Patterson (B-1910) P.13 L.12-14; Burkhart (B-1900) P.4, L.4-9]

CVM CRITIQUE: There is no citation to the record on the issue of sewage treatment plant discharges into recreational or drinking water sources to support Mr. Patterson's cited WDT.

53. Poultry production (including farm runoff) or processing facilities cannot be a dominant source of fluoroquinolone-resistant *Campylobacter* into sewage treatment plants, given the widespread geographical occurrence of antibiotic-resistant pathogens influent to (and effluent from) major municipal sewage treatment plants and that the vast majority of major municipal sewage treatment plants are outside of the geographically localized poultry raising and processing regions within the U.S. [Patterson (B-1910) P.13 L.15-19]

CVM CRITIQUE: This proposed finding is an opinion of the witness that is not supported by reference to factual evidence on the record. There is no evidence cited that provides the location of sewage treatment plants or poultry growout farms that would be necessary to support such an opinion.

60. The prevalence of susceptible *Campylobacter* far exceeds that of fluoroquinolone-resistant *Campylobacter* in the poultry population. (Prucha (A-203) P.14 L.3-4)

CVM CRITIQUE: This proposed finding of fact is an opinion without factual basis in the record. CVM does not know what "far exceeds" means in Mr. Prucha's WDT, and because no quantification or other basis for this statement was given in Mr. Prucha's WDT, the proposed finding is unsupported by credible record reference.

62. In 2002, based on pooled samples of 5 individual birds, McDermott conducted an experimental lab study on the use of fluoroquinolones in chickens. Birds were treated with sarafloxacin at 40 ppm for 5 days. Within 24 hours of treatment, 100% of *C. jejuni* isolates were resistant to ciprofloxacin. However, three weeks after ending treatment, 72% of the isolates tested still displayed high-level ciprofloxacin MICs (32 mg/l or higher) while 28% were again susceptible isolates (cipro MICs of 0.125 mg/l). Hence, there exists a limited persistence of fluoroquinolone resistance after the discontinuation of the fluoroquinolone. [B-868]

CVM CRITIQUE: This proposed finding is misleading because it is a misrepresentation of the study results, as it fails to report all of the findings and seeks to generalize the sarafloxacin results to Baytril and all fluoroquinolones. A cursory reading of the report will show that the effect of Baytril was also examined. In this experiment, the high-level resistance persisted in 100% of the isolates recovered after the discontinuation of Baytril, and lasted throughout the experiment. The final sentence in the proposed finding is a generalization based on what was observed following sarafloxacin use only, not Baytril or fluoroquinolones in general. In addition, Bayer's proposed finding contains an incorrect date. Although Dr. McDermott published his study in 2002, the study was conducted in 2001. Further, Bayer's assertion that the study was based on pooled samples of five individual birds is misleading as set out in the study B-868, p. 2). "In both studies, 50 freshly voided fecal samples (25 each from the treated and control groups) were collected on each sampling day. The 25 samples were combined into five composite samples of five individual samples each. This resulted in a total of 35 composite samples from the sarafloxacin-treated birds and 30 composite samples from the enrofloxacin-treated birds. These composites were cultured for *C. jejuni*."

63. McDermott acknowledges in his 2002 article that the results of his study were essentially the same as those found by Jacobs-Reitsma in 1994. [McDermott (G-1465) P.4 L.11-12; B-868]

CVM CRITIQUE: The proposed finding is contrary to the cited testimony, which simply states that "our results support the findings of Jacobs-Reitsma". It is misleading to restate this quote as "essentially the same as those found by Jacobs-Reitsma". The experimental design, testing methods and resulting data were very different. Further, Dr. Jacobs-Reitsma did not use sarafloxacin in her experiment; therefore, this portion of the finding of fact could only have been referring to Dr. Jacobs-Reitsma's finding that 100% of the isolates from enrofloxacin treated birds continued to display resistance through the end of the study.

64. Although Jacobs-Reitsma's method did not quantify the magnitude of change in resistance in the study and the McDermott study was able to do so, the results of the McDermott study are the same as the results of the Jacobs-Reitsma study: in both experiments fluoroquinolone treatment did not eliminate *Campylobacter* from the intestinal tract of chickens, but rather, rapidly selected for fluoroquinolone-resistant isolates. [McDermott (G-1465) P.4 L.15-23; B-868]

CVM CRITIQUE: This proposed finding of fact is misleading because it mischaracterizes both studies (Jacobs-Reitsma and McDermott). The results of the two respective experiments cannot be the same, as the measured endpoints were not the same. The implications of both studies are mutually supporting – that is, that the use of fluoroquinolones according to label indications does not eliminate *Campylobacter* from the intestinal tract of chickens, but rather, rapidly selects for fluoroquinolone-resistant isolates.

65. In 2001, Luo conducted an experimental lab study on the use of fluoroquinolones in chickens. Birds were treated with enrofloxacin at 25 ppm and 40 ppm for five days. Within three days after treatment, 100% of *C. jejuni* isolates were resistant to fluoroquinolones. However, at 8 days after treatment, only 50% of the population treated at 25 ppm were fluoroquinolone-resistant, and only 33% of the population treated at 25 ppm were fluoroquinolone-resistant after 12 and 15 days after treatment. [A-190]

CVM CRITIQUE: This proposed finding of fact is contradicted by Exhibit G-1800 (see p. 3) and by written communication (B-946) between the study director Dr. Q. Zhang and Bayer, in which Dr. Zhang states that the dose of 40 ppm was a typographical error and should have read 50 ppm. G-1800 is a publication in a peer reviewed journal of the article describing the 2001 study by Luo. The peer reviewed article contains a chart (Figure 2) that appears to indicate that the percentage of *C. jejuni* isolates from chickens treated with 25 ppm enrofloxacin was more than 60% at day 8 (chart appears to indicate between 60 – 80%) and approximately 60% at day 12. Also note that 100% of *C. jejuni* isolates from chickens treated with an approved dose of 50 ppm enrofloxacin remained resistant at days 8 and 12.

66. Although use of fluoroquinolones will select for fluoroquinolone-resistant *Campylobacter*, current evidence most relevant to actual usage conditions (i.e. 25 ppm), demonstrates that fluoroquinolone-resistant *Campylobacter* do not persist and that fluoroquinolone-susceptible *Campylobacter* recolonize the boiler gut, particularly at the 25 ppm dose. [B-868; A-190]

CVM CRITIQUE: This proposed finding of fact is contradicted by TerHune WDT P.5 L.16-P.6 L.1, B-868, A-190 and G-1800. The FDA approved dose range for Baytril is 25-50 ppm. There is nothing in the evidence to verify the claim by Bayer witnesses that a dose of 25 ppm is most relevant to actual usage conditions. In addition, the statement that "fluoroquinolone-resistant *Campylobacter* do not persist" is contradicted by what is reported in the cited exhibits. B-868 showed that resistant *Campylobacter* emerging following Baytril treatment persisted to the end of the experiment in 100% of isolates tested. Exhibit A-190 and G-1800likewise showed that resistant *Campylobacter* emerging following Baytril treatment persisted throughout the course of the experiment in 100% of isolates from animals treated at 50 ppm. Resistant strains also persisted in animals treated at 25 ppm, although at lower levels over time (see B-868; A-190 and G-1800).

67. In 1992, Jacobs-Reitsma studied the susceptibility of 116 strains of *Campylobacter* and found 13% of the *Campylobacter* isolates from non-treated laying hens from The Netherlands showed complete cross-resistance to the quinolones tested. [Jacobs-Reitsma (G-1459) P.6 L.26-40; B-36]

CVM CRITIQUE: The proposed finding is misleading because it is phrased to make the reader believe the 116 isolates studies were all from non-treated laying hens. In actuality, Dr. Jacobs-Reitsma studied a total of 116 *C. jejuni* strains – 31 from broilers, 30 from turkey flocks, and 55 from laying hens.

68. The presence of fluoroquinolone-resistant *Campylobacter* in untreated flocks demonstrates that there are potential selective pressures in poultry other than enrofloxacin usage. [B-36 P.2-3; G-62 1-2; Hanninen (G-1458) P.4, ¶ 3; Jacobs-Reitsma (G-1459) P.6 L.36-37; Newell (B-1908) P.17 L.1-6]

CVM CRITIQUE: The declaration that "the presence of fluoroquinolone-resistant *Campylobacter* in untreated flocks demonstrates that there are potential selective pressures in poultry other than enrofloxacin usage" is without foundation or support in the cited WDT. There is no support that anything other than fluoroquinolone use selects for fluoroquinolone resistance in bacteria. In fact, Newell agrees that "*Campylobacter* resistance to fluoroquinolones occurs naturally as a point mutation in the *gyrA* gene and is selected by the presence of fluoroquinolones." (B-1908, P. 12, L. 21-22). Additionally, there is no ¶ 3 on P.4 of Hanninen's WDT and Jacobs-Reitsma does not suggest that there are other potential selective pressures in poultry other than enrofloxacin use. The cited portion of her testimony simply reports results of her study. Likewise, the two exhibits cited by Bayer, B-36, P.2-3 and G-62, P.1-2, do not support this proposed finding. B-36, P.2-3 does not support the opinion that there may be other selection pressures other than enrofloxacin; possible reasons for the observed resistance were not discussed in this paper. G-62, P.1-2, does not present an opinion on the selective pressure of enrofloxacin. Note, too, that Hanninen does state that Bernston found 4.5% of the strains were resistant to enrofloxacin, but she also states "possible reasons for the resistance were not discussed in that paper" Hanninen WDT P.4, ¶ 5.

69. In the United Kingdom, Piddock (1995) investigated strains from 64 retail chicken carcasses prior to the licensing of enrofloxacin in 1993/4 and found 2.7% resistance. [Newell (B-1908) P.14 L.15-17]

CVM CRITIQUE: This proposed finding is not justified by the paper cited. The referenced passage in the Newell WDT cites to "Piddock (1995)" and claims "2.7% resistance" in 64 retail chicken carcasses "prior to the licensing of enrofloxacin in 1993/4". Bayer witness Newell included the 2.7%, but the paper she referenced for it did not. Because 2.7% of 64 would correspond to a non-integer number of carcasses (1.68976 carcasses) it is worth checking this Bayer cite. Although Bayer did not reveal the source paper in the citation listed for the requested finding, recourse to the Newell WDT "References" list, at exhibit page 73, lines 22-23 identifies the only such Piddock reference as Bayer Exhibit B-609.

Oddly enough, that Bayer Exhibit B-609 also does not provide the 2.7% figure, but it does reveal that the "investigation" was actually a small study, mentioned in passing in the 1995 paper as "personal observations" of 114 chicken carcasses, 64 of which were from the UK. Thirty-seven of those carcasses contained *Campylobacter* and one of the 37 domestic chicken carcasses that was *Campylobacter* -positive was said to have been ciprofloxacin resistant. One in 37 is approximately 2.7%, so this ratio seems to be the basis of the percentage sought by the proposed finding.

But, as stipulated by the parties here (Stipulation 65), enrofloxacin was registered in the United Kingdom in 1993. And these samples are described in the Piddock paper as having been collected in "1993/4 before the U.K. licensing of enrofloxacin". Neither the testimony of Newell, nor the cited paper provides any data to resolve this discrepancy, which prevents the requested finding.

70. Chlorine and organic acids may exert selective pressures for gyr-A mutations in enteric bacteria. [Silley (B-1913); Attachment 1 P.53 ¶ 1 and P.52 ¶ 3; B-983]

CVM CRITIQUE: This proposed finding of fact is not supported by the cited references or otherwise in the record. For example, Bayer witness Silley (B-1913, P. 53, ¶ 1) cites Alekshun and Levy to support this claim. However, in the cited work, those authors are referring to a metabolic response mediated by the *E. coli* mar operon, not the *Campylobacter gyrA* gene. The attempt to equate two unrelated genetic systems in two unrelated bacterial genera is invalid. The subsequent citation to Miché & Balandreau P. 53, ¶ 1) who "demonstrated that hypochlorite, routinely added to drinking water in poultry houses and used in chiller tanks, was responsible for an increase in the frequency of nalidixic acid-resistant mutants of *Burkholderia vietnamiensis*" is an inaccurate representation of their study. This organism is not an enteric bacterium. In addition, contrary to the Silley testimony, these authors made no reference in that paper to the use of hypochlorite in "drinking water in poultry houses and used in chiller tanks". That paper (B-983) describes the effect of hypochlorite as used as a surface sterilant on rice grains. Lastly, the citation to Sanchez (B-1531) is misapplied, as this report does not include any attempts to examine the ability of chlorine or organic acids to select for *gyrA* mutations.

71. Baytril 3.23% Concentrate Antimicrobial Solution (hereinafter "Baytril") is not used to treat *Campylobacter* in poultry, Baytril is used only to treat *E. coli* infections and fowl cholera, both life threatening diseases. [Glisson (B-1903) at P.5 L.21 – P.6 L.1; Smith (B-1914) P.18 L.8-9]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Glisson's WDT states that enrofloxacin is effective for treating *E. coli* infections in chickens and *E. coli* and *Pasteurella multocida* infections in turkeys. Dr. Smith's WDT indicates that *E. coli* infection is the target condition for enrofloxacin.

78. Baytril is administered via drinking water and FDA acknowledges water medication as a safe and effective means to administer therapeutic animal drugs. [Joint Stipulation 18]

CVM CRITIQUE: This proposed finding is not supported by Joint Stipulation 18. First, the stipulation addresses the drinking water delivery system as being safe; Bayer's proposed finding states that water medication is safe. Second, the stipulation addresses water delivery to administer therapeutic drugs to commercially grown broiler chickens and turkeys; Bayer's proposed finding addresses therapeutic animal drugs in general, with no reference to the species of animals to which the drug is to be administered. The proposed finding is not supported by the stated reference.

79. The vast majority of broilers in the United States who are treated with enrofloxacin are treated at a dose of 25 ppm for three days. [Hofacre (A-202) P.20 L.22 – P.21 L.1, P.23 L.7-11; Glisson (B-1903) P.5 L.10-12; Smith (B-1914) P.27 L.4-7]

CVM CRITIQUE: This proposed finding is contrary to the cited testimonies. Drs. Hoffacre and Smith state that the first day/loading dose will be higher than 25 ppm.

80. Many turkeys in the United States are treated with enrofloxacin at a dose of 25 ppm, although the labeled dosage is 25-50 ppm. [Gonder (A-201) P.27 L.6-9; Wages (B-1917) P.18 L.12]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Wages WDT indicates that the typical dosage for turkeys is <u>50</u> ppm not 25 ppm.

88. An important tenet of epidemiologic analysis is to identify, control for, and correct for confounding variables. "Confounding is the distortion of an exposure-disease association by the effect of some third factor (a 'confounder'). A third factor may be a confounder and distort the exposure-disease association if it is: associated with the outcome independent of the exposure – that is, even in the nonexposed group. (In other words, it must be an independent "risk factor."); or associated with the exposure but not a consequence of it." [Feldman (B-1902) P.8 L.1-7, citing B-1902 Attachment 1 (Gregg 2002)]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibit. As explained in B-1902 Attachment 1, P.120, 147-148 (Gregg P.130, 157-158), as well as in the quoted passage in Feldman WDT P.8 L.8-24, in order for a factor to be a confounder, <u>both</u> criteria stated in the proposed finding must be met. Therefore, the proposed finding is fundamentally erroneous because it uses the disjunctive "or" rather than the conjunctive "and" in its definition of the concept of "confounder."

91. Host factors such as immunity, age, gender, and behaviors (such as eating undercooked meats) are some of the many host factors that affect a person's likelihood of exposure to *Campylobacter* and which have been demonstrated to effect the incidence of campylobacteriosis in epidemiologic studies. [Feldman (B-1902) P.9 L.4-7]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any epidemiologic study that has demonstrated that the specified host factors "effect (sic) the incidence of campylobacteriosis."

92. Acquired immunity is a potentially important host factor in *Campylobacter* epidemiologic investigations. [Feldman (B-1902) P.9 L.8-9]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. In fact, Feldman WDT P.9 L.11-12, L.16-17 admits that the hypothesis in the proposed finding "has never been fully explored" and "remains not fully evaluated."

95. Environmental factors such as "seasonality" and "place" are two of the many environmental factors that affect a person's likelihood of exposure to *Campylobacter* and which have been demonstrated to effect the incidence of campylobacteriosis in epidemiologic studies. [Feldman (B-1902) P.10 L.11-14]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any epidemiologic study that has demonstrated that the specified environmental factors "effect (sic) the incidence of campylobacteriosis."

96. Time patterns or "seasonality" is important in infectious disease epidemiologic evaluations. [Feldman (B-1902) P.10 L.15-16]

CVM CRITIQUE: This proposed finding is contradicted by Feldman WDT P.10 L.16-17 (citing Gregg P.97). As stated in this portion of the testimony, "time patterns" or "seasonality" may be important in epidemiologic studies of infectious diseases; their importance varies by disease.

97. Geographic location is another important variable to examine in epidemiologic investigations. This is particularly important in *Campylobacter* cases since an infection acquired outside the country may be by a strain of bacteria with different virulence from those acquired in the United States. [Feldman (B-1902) P.16 L.7-10]

CVM CRITIQUE: The second sentence of this proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the second sentence of the proposed finding.

100. A cohort study is a follow-up study in which enrollment of the study group is based on exposure characteristics or membership in a particular group. The occurrence of disease or outcome is determined and the rate or frequency in the Cohort group is compared

among other exposure groups. [Feldman (B-1902) P.13 L.5-8, citing B-1902 Attachment 1 (Gregg 2002)]

CVM CRITIQUE: The second sentence of this proposed finding mischaracterizes the cited exhibit. As explained in the cited exhibit, B-1902 Attachment 1, P.108 (Gregg P.118), the "frequency of those occurrences is compared among exposure groups." In other words, the cohort is the entire study group; outcomes are compared among different exposure groups within the cohort.

110. The most important natural reservoirs of *Campylobacter* include the intestinal tract of humans, and of warm-blooded wild and domesticated animals (dogs and cats), rodents (field mice, foxes, rabbits, badgers), deer, pets, swine, cattle, sheep, and birds including wild starlings, gulls, sparrows, and geese. [Patterson (B-1910) P.3 L.22 – P.4 L.3; Newell (B-1908) P.9 L.18-21, P.19 L.18-20; Feldman (B-1902) P.15 L.5-10; Nachamkin (G-1470) P.4 L.608; Wegener (G-1483) P.8 L.15-17]

CVM CRITIQUE: The proposed finding of fact is contradicted by Wegener WDT P.8 L.15-17. This portion of Dr. Wegener's WDT provides only that 2-4% of dogs and cats harbor *C. jejuni*, calling into question Bayer's proposed finding with respect to domesticated animals (dogs and cats) and pets being included in the most important natural reservoirs of *Campylobacter*.

114. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. [Patterson (B-1910) P.4 L.4-6; Newell (B-1908) P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1]

CVM CRITIQUE: This proposed finding of fact is not supported by the citation to CVM's Response to Interrogatory 1. CVM's response to Bayer's Interrogatory Number 1 does not address *Campylobacter* in water at all, it does say *Campylobacter* is ubiquitous and can exist in the intestinal flora of various food-producing animals, but it says nothing about *Campylobacter* in water. In addition, the cited portion of Dr. Newell's WDT states that "between 16-82% of surface water samples are contaminated with recoverable *Campylobacters*" citing Thomas, et al., 1999, a reference not contained on the Docket or on the evidentiary record of their proceeding. The subsequent statements by Newell that "Surface water contamination may be from a variety of sources including human sewage (Koenraad et al., 1995) and water-fowl (Luechtefeld et al., 1980; Pacha et al., 1988)" is a case of selective citation. The Koenraad citation, on which Newell is a co-author, also showed that effluent from poultry houses was an important source of this water contamination, and later that "not all environmental *Campylobacters* may be pathogenic for man." Note, too, the proposed finding does not concern itself with *C. jejuni*, the most common source of human *Campylobacter* infections (see Robach WDT, P.5 L.41-42). In sum, this proposed finding of fact is contrary to the cited exhibits when taken in context and cited in full.

115. *Campylobacter*, including fluoroquinolone-resistant *Campylobacter*, are frequently isolated in surface and ground waters, including drinking water supplies. *Campylobacter*

jejuni and *Campylobacter coli* have been reported present as cohorts in both source water and in municipal drinking water treatment plants. [Patterson (B-1910) P.4 L.8-12]

CVM CRITIQUE: This proposed finding is based on a statement of opinion without factual basis on the record. The record provides no evidence to verify that fluoroquinolone-resistant *Campylobacter* has been frequently isolated from surface waters, ground waters or drinking water supplies, other than the witness's unsupported assertions.

CVM CRITIQUE: Agree.

119. Campylobacteriosis outbreaks in the United States have been caused by a variety of non-poultry foods, including beef, fruit, and other foods, but the most common single food is unpasteurized milk. [Tauxe (G-1475) P.6 L.27-29]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Tauxe's WDT states that outbreaks have been caused by a variety of foods including poultry, not that outbreaks have been caused by non-poultry foods.

123. The putative sources of human *Campylobacter* infections are direct animal contacts, food, water, environment, and human contacts. [Wegener (G-1483) P.10 L.38-39]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Wegener's WDT does not specifically indicate the sources of human *Campylobacter* infections, instead states the sources of human infection in general. When Dr. Wegener does discuss *Campylobacter* specifically in the cited paragraph, he concludes that "broiler chicken is the single most important reservoir of human *Campylobacter* infections, and that broiler products are the single most important sources of human campylobacteriosis in the industrialized world." [Wegener G-1483 P.11 L.5-7]

126. Epidemiological investigations in the United States and in other developed nations to determine risk factors for sporadic *Campylobacter* infections consistently indicate that a dominant source of infection is transmission from pets and other animals. [Angulo (G-1452) Attachment 3 P.82]

CVM CRITIQUE: This proposed finding of fact is misleading because the statement is taken out of context of the cited exhibit. Angulo WDT (G-1452) Attachment 3 P.82 actually states that epidemiological investigations have "consistently indicated several dominant sources of [*Campylobacter*] infection" and lists "contact with and consumption of poultry" before mentioning "transmission from pets and other animals" and "consumption of raw milk."

127. Epidemiological investigations in the United States and in other developed nations to determine risk factors for sporadic *Campylobacter* infections consistently indicate that a dominant source of infection is consumption of raw milk. [Angulo (G-1452) Attachment 3 P.82]

CVM CRITIQUE: This proposed finding of fact is misleading because the statement is taken out of context of the cited exhibit. Angulo WDT (G-1452) Attachment 3 P.82 actually states that epidemiological investigations have "consistently indicated several dominant sources of [*Campylobacter*] infection" and lists "contact with and consumption of poultry" before mentioning "transmission from pets and other animals" and "consumption of raw milk."

129. Transmission of campylobacteriosis from ill food handlers occurs. [Angulo (G-1452) P.9 L.28-29]

CVM CRITIQUE: This proposed finding of fact is misleading and mischaracterizes the cited testimony. First, the cited testimony states that such transmission "occurs occasionally but is not common." Second, the actual statement made in the testimony appears in a paragraph on the sources implicated specifically in outbreaks rather than in sporadic infections.

131. The sources and routes of transmission of campylobacteriosis, and the relative contribution of all these potential sources, remain unclear. [Newell (B-1908) P.21 L.19-20]

CVM CRITIQUE: This proposed finding of fact is unintelligible, as there is no indication of what is meant by "all these potential source". In addition, potential sources are, by definition, not scientifically verified sources, and thus can not constitute factual information.

133. The fact that most studies have focused on chicken combined with a variety of other factors, which may vary from study to study, might contribute to the frequent detection of poultry as a risk factor for *Campylobacter* infection. [Wegener (G-1483) P.15 L.28-30]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The finding does not include the comparison made in the cited statement. Dr. Wegener's WDT indicates the frequent detection of poultry as a risk factor compared to other risk factors for *Campylobacter* infections. The cited sentence continues on to note the strong scientific support that documents that poultry, notably chicken, is an important risk factor for human campylobacteriosis. [Wegener (G-1483) P.15 L.28-33]

135. Ascribing most nonforeign-travel-related *Campylobacter* infections in humans to the handling and consumption of raw or undercooked poultry is problematic and/or unfounded in light of convincing recent molecular and other evidence that non-poultry sources have been significantly underestimated. Among the sources most seriously underestimated are drinking water and recreational contact waters. [Patterson (B-1910) P.5 L.15-19]

CVM CRITIQUE: This opinion of the witness is not supported by the weight of current scientific evidence, including Patterson's own WDT. Patterson's testimony concerns

itself mostly with outbreaks, not sporadic campylobacteriosis. Many witnesses have testified that most campylobacteriosis in the United States is sporadic in nature and not part of an outbreak (see Tauxe WDT P.6 L.14-16; Feldman WDT P.15 L.1; Kist WDT P.3 L.7; Robach WDT P.5 L.17; and Tompkin WDT P.14 L.13). Also, as explained more fully in critique of Bayer's proposed finding of fact 152, water is not the predominant source of human *Campylobacter* infections.

136. It remains impossible to determine the contribution of poultry as a source of human campylobacteriosis because representative populations from structured surveys have not yet been undertaken. However, it seems likely that the role of poultry has been overestimated, on the basis of these studies, as contributing disproportionally to human campylobacteriosis. The importance of other potential sources, such as sheep, cattle and pets, and environmental contamination is now increasingly recognized. [Newell (B-1908) P.36 L.18-24]

CVM CRITIQUE: This proposed finding of fact is a statement of opinion not a statement of fact and the cited testimony is contrary to the reference cited by Newell (Tam et al., Clinical Infectious Diseases 2002:34, P. 719-720). In fact, the Tam reference is a correspondence and does not mention sheep, cattle or "environmental contamination" as purported by the cited testimony (B-1908, P. 36, L. 18-24). In addition, immediately following the Tam letter is a response from the author of the original article which states "Although numerous case-control studies of *Campylobacter*-infected persons, including the studies cited by the authors, have documented a variety of potential sources, when one reviews the literature in its totality, the evidence is rather overwhelming that poultry consumption and preparation is implicated in most infections in humans [3]." (Allos, Clinical Infectious Diseases 2002:34, P. 720-721) Furthermore, the statement that "representative populations from structured surveys have not been undertaken" is incomprehensible; how can populations be undertaken? A survey can measure the burden of disease, but an analytic study utilizing one or more comparison groups, such as a case-control study, is necessary to determine whether a particular exposure is a risk factor for a disease (and to quantify the relationship between exposure and disease). Numerous case-control studies on the Docket have demonstrated that poultry consumption is a risk factor for campylobacteriosis, including the largest U.S. *Campylobacter* case-control study, described in Exhibits G- 1452 (pages 9-11), G-228, and G-1488 (also filed under G-1452, Attachment 3); the results of several studies are reviewed in Exhibit G-1644 (also filed under G-444).

137. The assumption that poultry is a major source of fluoroquinolone-resistant *Campylobacters* is now questioned, and alternative sources are being actively sought. [Newell (B-1908) P.40 L.20-22; Feldman (B-1902) P.35 L.1 – P.36 L.11]

CVM CRITIQUE: This proposed finding of fact is an opinion and contradicted by numerous testimonies and their included exhibits (McDermott G-1465; White G-1484; Meng G-1466; Newell P. 16, L. 16) showing that live poultry and poultry-derived retail meats are the only environmental niches where fluoroquinolone-resistant *Campylobacter* are routinely found. Alternative sources of fluoroquinolone-resistant *Campylobacter*

have been actively sought but none have been found. This is shown by the lack of any data demonstrating any such data anywhere in the record.

139. Effler recognizes that his questionnaire was skewed toward chicken; "Finally, because it is a well-recognized source of *C. jejuni*, the histories pertaining to poultry were intentionally very detailed. Resources did not permit obtaining such comprehensive information on all other food items included in the questionnaire and it is possible that associations between illness and other food items were missed as a result." [Effler (G-185) P.4; Feldman (B-1902) P.26 L.11-17]

CVM CRITIQUE: This proposed finding is misleading and mischaracterizes the cited exhibit. Nowhere in Effler (G-185) is the study questionnaire characterized as "skewed." In fact, in the paragraph from which the quoted portion of the proposed finding was extracted, the Effler study concludes:

> Two other studies, however, both from New Zealand, have also found an association between *Campylobacter* illness and commercially prepared chicken. In our opinion, the agreement of these separate studies conducted by different investigators and across countries, greatly reduces the likelihood that the association is spurious.

140. Epidemiological investigations in the United States and in other developed nations to determine risk factors for sporadic *Campylobacter* infections consistently indicate that a dominant source of infection is consumption of contaminated drinking water. [Angulo (G-1452) Attachment 3 P.82]

CVM CRITIQUE: This proposed finding of fact is misleading because the statement is taken out of context of the cited exhibit. Angulo WDT (G-1452) Attachment 3 P.82 actually states that epidemiological investigations have "consistently indicated several dominant sources of [*Campylobacter*] infection" and lists "contact with and consumption of poultry" before mentioning other factors including "contaminated drinking water."

142. Emerging recognition of the significance of bacterial pathogens in drinking and recreational contact waters has become increasingly important during the past two decades. These include newly recognized pathogens from fecal sources, such as *Campylobacter* spp. [Patterson (B-1910) P.3 L.12-14]

CVM CRITIQUE: Of the four exhibits cited to support Patterson's WDT P.3 L.12-13, only one is in the evidentiary record and it does not support this proposed finding. In fact, B-515 (Mead) does not deal with waterborne transmission of pathogens; it is an article on food-related illness and death from known pathogens in the United States.

145. *Campylobacter* spp., particularly *C. jejuni*, are gastroenteric pathogens of environmental concern. [Patterson (B-1910) P.3 L.20-21]

CVM CRITIQUE: It is unclear what is meant by "environmental" in this proposed finding of fact as well as in Mr. Patterson's WDT cited for support of this proposed finding of fact. Since Mr. Patterson fails to cite to any factual support for this statement in his WDT, the record does not help CVM discern the meaning of the word "environmental" and CVM therefore believes this proposed finding is too vague.

146. *Campylobacter* can survive for several weeks to months in aqueous environments at low temperatures. For example, *Campylobacter jejuni* inoculated into autoclaved mountain stream water remained viable for 33 days at 4o C. [Patterson (B-1910) P.3 L.16-19; Newell (B-1908) P.3 L.14-15, P.7 L.8-11]

CVM CRITIQUE: While CVM agrees with this proposed finding of fact, it is important to point out that these water borne isolates may not be pathogenic to humans, as noted in an exhibit on which Newell is a co-author (G-344).

152. The U.S. population is routinely exposed to the pathogen *Campylobacter* via waterborne routes, and there is, at minimum, parity in the incidences of campylobacteriosis in the U.S. between all foodborne routes and the waterborne route. [Patterson (B-1910) P.7 L.20-22]

CVM CRITIQUE: CVM strongly disagrees with this proposed finding of fact. This proposed finding of fact is without factual basis in the record. First, Mr. Patterson bases his testimony on findings from waterborne outbreaks despite the fact that many witnesses (both CVM and Bayer witnesses) have testified that the majority of human illness is caused by sporadic cases not as a part of an outbreak (see Tauxe WDT P.6 L.14-16; Feldman WDT P.15 L.1; Kist WDT P.3 L.7; Robach WDT P.5 L.17; and Tompkin WDT P.14 L.13). Second, Mr. Patterson bases his estimate of foodborne *Campylobacter* infections diagnosed per year at 60,000 (see B-1910 P.26 L.14-15), rather than on the estimated number of food-borne related *Campylobacter* cases in the United States each year of 1,963,141 (B-515). Yet, Mr. Patterson bases his figure of 500,000 water-borne related *Campylobacter* cases in the U.S. each year on estimates not actual reported cases. (B-1910 P.27 L.9-11). Further, the articles cited to support Mr. Patterson's contention that waterborne cases of campylobacteriosis are estimated at 500,000 actually states that waterborne instances of campylobacteriosis are estimated as 320,000 (B-927 P.9).

153. The predominant routes of fluoroquinolone-resistant *Campylobacter* to humans are other than associated with poultry. [Patterson (B-1910) P.8 L.3-4]

CVM CRITIQUE: This statement of opinion is without factual basis on the record. Further, as found by the many epidemiological studies looking at risk factors of acquiring campylobacteriosis, poultry consumption is consistently found to be the main risk factor (see G-182, G-1686, G-185, G-602, B-412, G-299, G-334, G-307, B-561, G-268, G-474 and G-337). Further, Bayer's witness, Mr. Prucha has testified that about one half of all *Campylobacter* cases in the mid 1990's were attributed to meat and poultry and the number of *Campylobacter* cases attributed to meat and poultry are rising (Prucha WDT P.4 L.4-7). That WDT, coupled with other WDT stating the prevalence of

Campylobacter found in non poultry meat is low (Meng WDT P.3 L.216-217; P.24-29), show poultry to be a major source of the *Campylobacter*. Finally, giving Mr. Patterson's WDT with respect to the number of waterborne cases of *Campylobacter* its appropriate weight (see CVM's critique of Bayer's proposed finding of fact 152), CVM believes there is nothing on the evidentiary record to support Bayer's proposed finding of fact 153, and, in fact, there is much on the record that contradicts this proposed finding.

154. *Campylobacter* are found in high concentrations in raw sewage, and they occur in fecally contaminated surface and ground waters. [Patterson (B-1910) P.9 L.18-19]

CVM CRITIQUE: CVM is unable to agree with this proposed finding because the two references cited to support this statement are not available to review to see whether Mr. Patterson's characterization of "high concentrations" is correct. Further the very term "high concentration" is vague.

157. Recent studies have implicated free-living birds and aquatic sources as the origin of near-universal colonization of commercial poultry flocks by *Campylobacter* (Piddock, et al., 2000). Wild birds have also been implicated in one *C. jejuni* waterborne community-wide disease outbreak (Sacks, et al. 1986) and one boarding school campylobacteriosis outbreak (Palmer, et al., 1983). In Japan, fluoroquinolone-resistant *C. jejuni* have been cultured from sparrows (Sorum and L'Abee-Lund, 2002). [Patterson (B-1910) P.10 L.7-12, citing to, inter alia, B-50, B-1800]

CVM CRITIQUE: This proposed finding of fact is misleading because the first and third sentences in this proposed finding of fact mischaracterize the cited references, which in fact do not support the proposed finding. Piddock, et al., (B-50) does not address free-living birds and aquatic sources as the origin of colonization of commercial poultry flocks. B-50 is an abstract entitled "Implications for Human Health." Sacks, et al., (B-1800) implicated birds (grackles, sparrows, doves) who perched on top of an open-top settling tank as source of *Campylobacter* responsible for an outbreak of water-bornE campylobacteriosis in a town in Florida. Although *C. jejuni* were isolated from the birds, no *Campylobacter* were isolated from water samples, and the strains isolated from birds did not match the human isolates obtained from ill patients. While Sorum and L'Abee-Lund (2002) is not on the docket or the evidentiary record, CVM researched this citation provided by Patterson as support for his statement that fluoroquinolone-resistant *Campylobacter jejuni* have been cultured from sparrows and note that the authors attributed the finding to sparrows' contact with production animals treated with fluoroquinolones.

158. Multiple antibiotic resistant (including fluoroquinolone-resistant) fecal bacteria have been isolated from wild deer and geese in suburban Morris County, NJ. All isolates were resistant to ciprofloxacin. [Patterson (B-1910) P.10 L.5-7]

CVM CRITIQUE: The proposed finding of fact misrepresents the cited reference in support thereof. CVM reviewed the cited reference, although it is not on the docket, and

found that Torrents and de la Cruz (2002) looked at resistance in fecal *E. coli* and *enterococci*, not *Campylobacter*.

159. Data indicate that free-ranging wild birds play a major role of in the dissemination of fluoroquinolone-resistant *Campylobacter*, including via fecal contamination of surface waters. [Patterson (B-1910) P.10 L.12-14, citing to, inter alia, B-50, B-1774, B-1800 and Sorum and L'Abee-Lund, 2002]

CVM CRITIQUE: See CVM Critique of Bayer's proposed finding of fact 157.

161. Biofilms in drinking water pipe distribution networks may harbor *Campylobacter*, from which the *Campylobacter* are then reintroduced into the distributed water. Biofilms may provide an organic substrate, a low dissolved oxygen environment, and protection from residual disinfectant. Residence within the biofilm was reported to approximately double the survival time of *Campylobacter jejuni* at 4°C. [Patterson (B-1910) P.19 L.9-13, Newell (B-1908) P.7 L.8-11]

CVM CRITIQUE: The proposed finding of fact mischaracterizes the reference cited in support thereof. Bushwell et al, 1998 (G-84) is cited as the reference for the residence time of *Campylobacter jejuni* in biofilm. However, this experiment was conducted using a biofilm model and it was not direct sampling from drinking water pipes. There is no indication of the survival time of *Campylobacter jejuni* in a natural biofilm.

162. Water has been established as a major source of campylobacteriosis in both outbreaks and in sporadic cases. [Patterson (B-1910) P.27 L.8-11]

CVM CRITIQUE: See CVM's critique to Bayer's proposed finding of fact #152.

163. Waterborne *Campylobacter* infections in the U.S. are indicated to exceed all other sources. [Patterson (B-1910) P.28 L.1-2]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact #152.

164. There is evidence that the waterborne route is the predominant route for transmission of *Campylobacter* infections. [Patterson (B-1910) P.6 L.8-9]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact #152.

165. There is evidence that the waterborne route is the predominant route for transmission of fluoroquinolone-resistant *Campylobacter* infections at least to the extent that such infections are environmentally derived (i.e., not related to direct patient-to-patient transmission of fluoroquinolone-resistant *Campylobacter*). [Patterson (B-1910) P.6 L.9-11]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact #152.

166. One epidemiological observation intriguing to epidemiologists searching for the sources of infection is the observed seasonal peak of human campylobacteriosis in all countries with longitudinal surveillance data. [Newell (G-1908) P.3 L.22-23, P.25 L.23 – P.26 L.1]

CVM CRITIQUE: This proposed finding of fact is without support. There is no verifiable data showing that epidemiologists are intrigued by the seasonal peak of campylobacteriosis.

168. Fluoroquinolone resistance in *Campylobacter* peaks in the winter and declines in the summer. [Feldman (B-1902) P.11 L.9-10]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

170. None of the poultry peaks obviously precede, or terminate before, the human peaks in each country, as would be expected if these were the sources of human infection. [Newell (G-1908) P.26 L.12-14]

CVM CRITIQUE: This proposed finding appears to be an opinion. The witness' purported cite "Newell et al., 1999" does not exist in our list of references and no exhibit reference is provided to support this opinion. The seasonality of *Campylobacter*, and the ecology of the organism, is not completely understood. For this reason, what "would be expected" is mere speculation, which cannot justify a finding of fact.

171. The poultry and human seasonality peak data could be interpreted to suggest that the peak in the shedding of human *Campylobacters* into the environment could be the cause of the poultry flock peak. [Newell (G-1908) P.26 L.14-16]

CVM CRITIQUE: This speculation cannot support a finding. The phrase "could be interpreted to suggest" is inherently subjective and implies the opposite possibility.

172. There may be a common source of *Campylobacter* for both the humans and poultry flocks. [Newell (G-1908) P.26 L.20]

CVM CRITIQUE: This proposed finding of fact is unsupported. That humans and poultry flocks have been infected with *Campylobacter* from a common source is not supported by any molecular or medical epidemiology in the evidentiary record, and appears to be the opinion of the witness cited. That this is only opinion is demonstrated by the testimony of the Bayer witness which states (P. 26, L. 20) that 20, "As yet these sources are unknown but may be the common source at these times for both the humans and poultry flocks."

173. The fact that fluoroquinolone resistance in *Campylobacter* peaks in the winter and declines in the summer, indicates that there may be different sources in different seasons. [Feldman (B-1902) P.11 L.9-10]

CVM CRITIQUE: The first part of this proposed finding ("The fact . . . summer") appears to be an unjustified statement of opinion not a statement of fact. The second part of this proposed finding ("indicates . . . seasons") also appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding: (1) does not identify any source of support for the hypothesis suggested by the first part of the proposed finding; (2) does not identify any source of support for the hypothesis suggested by the second part of the proposed finding; and (3) does not identify any source of support for linking the two unsupported hypotheses.

174. Seasonality must be accounted for while examining many enteric pathogens because it is not unusual for the prevalence of the infecting organism and the incidence of the disease to vary over the course of a year in a cyclical pattern. If a case-control study examines too narrow of a window in time, the results may be skewed too high or too low. In either event, the prevalence and incidence found in a short-duration case-control study can not be properly used as a basis for annual prevalence or incidence rates. [Feldman (B-1902) P.30 L.13-18]

CVM CRITIQUE: The first sentence of this proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. The remaining sentences of this proposed finding are contradicted by Attachment 1 (Gregg, Field Epidemiology) of Feldman WDT B-1902 (B-1902 is the testimony cited in support of this proposed finding).

> Gregg on incident cases versus prevalent cases
>
> Cases may be either incident cases or prevalent cases. Incident cases or health events are changes in the status of an individual—from well to ill, from uninfected to infected, from alive to dead. Prevalent cases represent the existing status of an individual—well, ill, uninfected, infected, alive, deceased. Incident cases are determined by following individuals over time and counting those who change their status . . . [P]revalent cases are determined by taking a measurement on individuals usually at one point in time. (B-1902 Attachment 1 P.69)
>
> Gregg on incidence versus prevalence
>
> All incidence rates involve counts of incident cases over a defined time period in a defined population...Prevalence rates reflect the proportion of the population that has an existing condition (prevalent cases)...Prevalence is a function of both incidence (risk) and duration of illness, so measures of association based on prevalent cases reflect both the exposure's effect on

incidence and its effect on duration or survival. (B-1902 Attachment 1 P.71, P.74, and P.134)

Gregg on cohort study and incidence/risk

In a prospective cohort study, enrollment takes place before the occurrence of disease. In fact, any potential subject who is found to have the disease at enrollment will be excluded. Thus each subsequently identified case is an incident case. Incidence may be quantified as the number of cases over the sum of time that person was followed (incidence rate), or as the number of cases over the number of persons being followed (attack rate or risk)." (B-1902 Attachment 1 P.111)

Gregg on case-control study and incidence/risk

One of the most important advantages of the cohort design is that you can directly measure the disease risk (attack rate) of disease. . . . The case-control study, with a set number of cases and an arbitrary number of controls, does not permit calculation of disease risk for a given exposure group. In most case-control studies, because you do not know the true size of the exposed and unexposed groups, you do not have a denominator with which to calculate an attack rate or risk. (Gregg B-1902 Attachment 1 P.117 and P. 133)

This indicates that, despite the contention in the proposed finding regarding "the revalence and incidence found in a short-duration case-control study," in most case-control studies, one can calculate neither incidence (risk) nor prevalence (a function of risk).

175. Naturally-occurring epidemiological experiments give no clear indication that poultry is a major source of human campylobacteriosis. [Newell (B-1908) P.24 L.17-19]

CVM CRITIQUE: This proposed finding of fact is contrary to the record. Numerous epidemiological experiments have linked chicken handling and consumption to human campylobacteriosis (G-444, Chapter 6). [Molbak WDT P.12 L.1-19] [Wegener WDT P14; P.16 L.33; P.17 L.2; P.18-20]

176. Data from the 1999 Belgian dioxin scare, which precipitated a sharp decrease in chicken consumption in Belgium show that no unusual drop in campylobacteriosis rates occurred in 1999 compared to the same months in other years. [Cox (B-1901) P.36]

CVM CRITIQUE: First, there is no reference to the 1999 Belgian dioxin scare on page 36 of B-1901. Page 37 and Appendix A include the proposed finding. This proposed finding is contradicted by the Vellinga and Van Loock citation in Cox (B-1901, Appendix A). When the 1999 Belgian dioxin scare data are appropriately analyzed by

Vellinga and Van Loock a drop in campylobacteriosis case rates is observed following the ban and reduced poultry production.

177. Data from the 1999 Belgian dioxin scare, which precipitated a sharp decrease in chicken consumption in Belgium show a large change in chicken consumption was followed by no unusual changes in campylobacteriosis rates, suggesting that chicken consumption is not a detectable cause of campylobacteriosis. [Cox (B-1901) P.36; Newell (B-1908) P.23 L.18-21]

CVM CRITIQUE: This proposed finding is contradicted by the Vellinga and Van Loock citation in Cox (B-1901, Appendix A). When the 1999 Belgian dioxin scare data are appropriately analyzed by Vellinga and Van Loock, a drop in campylobacteriosis case rates is observed following the ban and reduced poultry production.

178. Data showing that poultry is not a major source of campylobacteriosis is consistent with evidence from England, where there was increased consumption of poultry meat during the foot and mouth disease (FMD) outbreak (and a reduction in the consumption of lamb, pork and beef) but no detectable increase in campylobacteriosis. [Cox (B-1901) P.37, citing Newell testimony (B-1908) P.24 L.10-14]

CVM CRITIQUE: This proposed finding is misleading in that the statement is taken out of context. The campylobacteriosis case rates following the FMD outbreak are not adjusted in any way for changes in consumer behavior. Newell [B-1908, P.24 L.2-12] in describing an unexplained drop in campylobacteriosis cases in Iceland noted that there were changes in biosecurity on poultry farms and concomitant changes in public perception. She reiterates authors who the concluded that "a number of factors were potentially involved in this decrease..." In line 11 she notes that during the 2000 FMD outbreak there was public perception of a risk from FMD. It is likely that under conditions of general concern for the safety of the food supply, more care was taken in the production and preparation of the chicken than would be taken under typical circumstances.

191. Food samples often contain only small numbers of *Campylobacter*, and the bacterial cells may also be seriously injured during processing such as freezing, cooling, heating, and sanitizing. [Meng (G-1466) P.2 L.2-4]

CVM CRITIQUE: This proposed finding of fact is contradicted by G-444, P.147, which notes that "the quantity of *Campylobacter* organisms on the surface of a fresh chicken carcass has been estimated to be 10^3 to 10^6 per chicken. Ingestion of a drop of raw chicken juice could easily provide the infectious dose of 500 organisms." Bayer's proposed finding takes Dr. Meng's statement out of the context in which it was offered; that is, to explain why enrichment broth is sometimes used to culture *Campylobacter* from retail meat and direct plating is used for culturing stool samples. Dr. Meng's WDT states, "The methods used to isolate and identify *Campylobacter* from food are derived from those originally designed for clinical samples. Fecal samples often contain large numbers of viable *Campylobacter*; therefore, the isolation of *Campylobacter* is possible

by placing the fecal material directly onto an artificial growth medium. Food samples, however, often contain only small numbers of *Campylobacter*, and the bacterial cells may also be seriously injured during processing such as freezing, cooling, heating and sanitizing. Liquid enrichment media such as Bolton Broth (Oxoid, Ogdenburg, NY) have been developed to detect small numbers of the organisms by promoting the recovery of sub-lethally damaged cells" Meng WDT P.1 L.44- P.2 L.7.

193. *Campylobacter* are not typically found in muscle tissue of poultry, but instead only on the surface of the birds. [B-196].

CVM CRITIQUE: Bayer's proposed finding mischaracterizes the finding of Exhibit B-196. *Campylobacter* was found in approximately 3% of samples. Three percent does not equate to "not typically found," rather it was found, albeit in low incidence. Further, the retail meat studies cited by CVM witnesses Drs. White and Meng provide substantial evidence that muscle tissue is contaminated, (White WDT P.3-4; Meng WDT P.2-4; B-387; G-589; G-1528) and not that *Campylobacter* is only found on the surface of the bird.

194. Double strength Bolton's Broth was used to enrich for *Campylobacters* in retail meat samples from the study reported in exhibit G-727. [G-727]

CVM CRITIQUE: This proposed finding of fact misrepresents the cited testimony. Double-strength Bolton Broth was added to a equal amount of sample so as to dilute the Bolton Broth in half. Thus, the enrichment was carried out in regular strength Bolton Broth.

197. From 1997-2001 the percentage of *Campylobacter* isolates resistant to erythromycin (MIC > 8) has decreased from 8% (17/217) in 1997 to 1% (5/324) in 2000. [G-749]

CVM CRITIQUE: CVM notes that the erythromycin breakpoint used was ≥8μg/mL rather that >8μg/mL stated in the proposed finding of fact.

198. CVM does not have any facts or data demonstrating any increase in overall *Campylobacter* loads in live chickens or in live turkeys after fluoroquinolones were approved for use in chickens and turkeys. [CVM Response to Bayer's Interrogatory 23]

CVM CRITIQUE: This proposed finding of fact is without support in the record, and is misleading. CVM points out that its answer to Bayer's Interrogatory 23 indicated it interpreted the interrogatory to be asking about the absolute number of *Campylobacter* organisms on the live bird.

199. CVM does not have any facts or data demonstrating any increase in fluoroquinolone-resistant *Campylobacter* loads in live chickens or in live turkeys after fluoroquinolones were approved for use in chickens and turkeys. [CVM Response to Bayer's Interrogatory 25]

CVM CRITIQUE: This true statement does not justify any finding in the absence of data on such tests.

200. CVM does not have any facts or data demonstrating any increase in fluoroquinolone-resistant *Campylobacter* loads in retail chicken products or in retail turkey products after fluoroquinolones were approved for use in chickens and turkeys. [CVM Response to Bayer's Interrogatory 24]

CVM CRITIQUE: This proposed finding is without support in the record and is misleading. This proposed finding completely misrepresents CVM's response to Bayer's Interrogatory 24. In its response to that interrogatory, CVM made clear that its answer referred to live birds. Bayer's attempt to transform this answer into a proposed finding concerning retail poultry products is misleading and inappropriate.

201. CVM does not have any facts or data demonstrating any increase in fluoroquinolone-resistant *Campylobacter* in or on cooked chicken meat or cooked turkey meat ready for consumption after fluoroquinolones were approved for use in chickens and turkeys. [CVM Response to Bayer's Interrogatory 26]

CVM CRITIQUE: CVM notes that Bayer cites to an inappropriate record reference to support its proposed finding of fact; however, CVM refers the ALJ to Interrogatory 27 and CVM's answer thereto.

203. Four studies conducted by FDA to measure consumer knowledge and food handling practices demonstrate that progress is being made toward educating consumers and reducing risk from food borne microbiological pathogens. The FDA conducted a random digit-dial survey of a nationally representative sample of American consumers in 1988, 1993, 1998, and 2001 (Fein, Levy and Lando, 2002). The trends for both cross contamination measures and eating potentially risky foods were very similar. No improvement occurred between 1988 and 1993, and for one measure (washing hands after touching raw meat or chicken), the safety of the behavior became worse. Between 1993 and 1998, significant improvement on all of the measures of cross contamination was found, as was also the case on four of the six measures of eating potentially risky food. Then, between 1998 and 2001, most of the measures of cross contamination showed an additional but small improvement, which is an achievement after such a dramatic initial change. [Tompkin (A-204) P.10 L.4-18].

CVM CRITIQUE: CVM points out that this proposed finding of fact conveniently omits a sentence in which Bayer witness Tompkin acknowledges poultry as a source of *Campylobacter*. That sentence, which in Tompkin's WDT appears after the first sentence in the proposed finding states, "Clearly, continued emphasis on educating food handlers will be a critical element to achieve further reductions in foodborne illness (e.g., salmonellosis, campylobacteriosis that my result from raw meat or poultry). [Tompkin WDT P.10 L.6-8]

205. In studies conducted by FDA, consumption of raw shellfish (3.2%) and undercooked hamburger (43%) were more common in Connecticut than the other four states. Raw milk consumption was more common among people who lived on a farm (8.6%) compared with people who lived in a city or urban area (1.1%). Preference for undercooked hamburger was more common among men (35%), young adults (18 to 25 years, 33%), people with college education (38%), and among people with household income of more than $100,000/year (49%). African-Americans were less likely to prefer undercooked hamburger compared to other racial groups (10% versus 30%). Men washed their hands less often than women (89% versus 97%). Young adults compared to older adults were less likely to wash their hands after handling raw chicken (88% versus 95%). [Tompkin (A-204) P.12 L.4-13]

CVM CRITIQUE: CVM notes that FDA did not conduct this study.

229. Although FoodNet data provide detailed information regarding *Campylobacter* infections, the data do not reflect the entire US population." [Molbak (G-1468) P.5 L.17-21]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The proposed finding does not contain the limitations of the FoodNet data as expressed by Dr. Molbak's WDT. Dr. Molbak's WDT indicates that "although FoodNet data provided the most detailed information available for infections, the data do not reflect the entire United States population".

230. Data collected for the Human NARMS program do not represent the general United States population and the program contains no means to correct its estimates for inherent sampling biases to make them representative of the general population. [DeGroot (A-200) P.17 L.23-24 – P.18 L.1-2]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of Dr. Frederick Angulo (G-1452), Chief of the FoodNet/NARMS Unit at the Centers for Disease Control and Prevention. Exhibit G-1452 states the following: "Several NARMS activities, including susceptibility testing of human *Campylobacter*, are conducted exclusively in FoodNet sites. ... FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States. ... These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness." [Angulo (G-1452) P.3, L.45 – P.4, L.34]

245. Any *Campylobacter* isolation, speciation and susceptibility testing protocol relying on nalidixic acid susceptibility as a criterion to identify *C. jejuni* or *C. coli* would have excluded all quinolone-resistant isolates from surveillance for these two species and therefore underreport resistance in *C. jejuni* and *C. coli*. [Barrett (G-1453) P.3 L.31-36]

CVM CRITIQUE: This proposed finding of fact, that screening by nalidixic acid susceptibility would have excluded all quinolone-resistant isolates, cannot be accepted as

written. It is true or false depending on the surveillance years in question. [Tollefson WDT P.19 L.22-27]

246. Any *Campylobacter* isolation, speciation and susceptibility testing protocol that relied on susceptibility to nalidixic acid as one of the primary criteria to differentiate between the thermophilic *Campylobacters* (with *C. jejuni* and *C. coli* considered to be susceptible) would result in an underestimate of fluoroquinolone resistance, because some of the isolates discarded for not being *Campylobacter jejuni/coli* (because they were not susceptible to nalidixic acid) could in fact be resistant *Campylobacter jejuni/coli*, meaning they were resistant to both nalidixic acid and to fluoroquinolones. [Barrett (G-1453) P.3 L.1-3; Tollefson (G-1478) P.9 L.36-46]

CVM CRITIQUE: This proposed finding of fact, that screening by nalidixic acid susceptibility would have excluded all quinolone-resistant isolates, cannot be accepted as written. It is true or false depending on the surveillance years in question. [Tollefson WDT P.9 L.22-27 and P.19 L.22-36]

247. There is no NCCLS or other generally accepted "standard" method of isolating *Campylobacters* from human, food or environmental sources. [Silley (B-1913) P.5 L.20-21]

CVM CRITIQUE: This proposed finding of fact appears to misrepresent the actual situation by implying that NCCLS is involved in formally approving bacterial culture methodologies, which it is not. FDA publishes the Bacteriological Analytical Manual (BAM), which outlines a method for isolating *Campylobacters* from foods. This is accepted as a standard method for culturing *Campylobacter* from food samples (G-1464. P. 4, L18).

248. Media for isolating *Campylobacters* from faeces, food and water have different attributes and, therefore are not optimal for recovering the representative diversity of *Campylobacter* species present in the original sample. There is no consensus concerning the best media and methods to isolate representative species of *Campylobacters* from the sample. [Silley (B-1913) P.5 L.22 – P.6 L.3]

CVM CRITIQUE: This proposal requests two separate findings. The first incorporates an incorrect assumption. Because the "media for isolating *Campylobacter*" is different depending on the sample being cultured (as is the case in most microbiological culture protocols), it does not follow that they are "therefore not optimal." To the contrary, the media differ precisely because they have been optimized for culturing different samples. Regarding the second proposed fact, CVM agrees there is no such consensus, and notes that consensus is not required.

249. Antimicrobials in selective media developed for *Campylobacters* have been chosen on the basis of those to which test strains are resistant and those most effective in inhibiting competitive flora. At least seventeen different single antimicrobials have been used (cephalothin, cephazolin, cefsulodin, cephalexin, cefoperazone, trimethoprim, polymyxin

B, colistin, vancomycin, teicoplanin, rifampicin, novobiocin, bacitracin, cycloheximide, actidione, amphotericin, nystatin) either singly or more often in combination, including five different cephalosporins. [Silley (B-1913) P.6 L.8-14]

CVM CRITIQUE: The proposed finding is unsupported. The Bayer witness testimony cited to support this proposed finding of fact does not provide any reference to the scientific literature or the Docket, and therefore cannot be verified as factual.

250. Incorporation of antimicrobials into selective media has the greatest significance with regard to introducing bias into the isolation procedure. [Silley (B-1913) P.6 L.15-17]

CVM CRITIQUE: This appears to be opinion of the Bayer witness and is without supporting experimental data either in the Docket or in other scientific literature.

252. Unlike *Salmonella* culture media, *Campylobacter* culture media have no indicator system to identify putative colonies. As a result, colonies are randomly chosen by lab technicians. [Silley (B-1913) P.35 4 – P.36, ¶ 1, Attachment 1]

CVM CRITIQUE: This proposed finding of fact is unsupported on several levels, the first being that it grossly misrepresents the basic practice of bacteriology. As written, this proffered fact incorrectly implies that, without indicator systems built into the culture medium, lab technicians are randomly picking from a miscellany of colonies. It ignores the culture processes used to isolate *Campylobacter* (B-544, B-547, B-1096), which inhibit the growth of nearly all non-*Campylobacters* and result in easily recognizable growth, from which species confirmation is subsequently made. There is no cited support for the term: "putative colony."

253. Studies have been reported where more than one strain of *Campylobacter* spp. has been found on 67% of infected carcasses and up to six strains on a single carcass. Studies such as these show that *Campylobacter* isolation techniques do not necessarily accurately isolate the species of *Campylobacter* present in a given sample, causing significant doubt on the inferences that may be drawn from such techniques, including inferences about the reservoir of the organism, and whether it has caused the disease. [Silley (B-1913) P.7 L.19 – P.8 L.2]

CVM CRITIQUE: The proposed finding is unsupported that studies have shown "more than one strain of *Campylobacter* spp. has been found on 67% of infected carcasses and up to six strains on a single carcass." As can be seen from the testimony of Silley, a single study reported this based on one sample set. The remaining section of this proposed finding of fact is fundamentally unintelligible. There is no grammatical meaning to "accurately isolate." Since this proposed finding of fact invokes multiple disciplines (epidemiology, bacteriology, ecology, among others) without distinction or tribute, it is lacking support in multiple specialties. The language "significant doubt on inferences" highlights that this is of the nature of an opinion, even though the object of this opinion can not be determined.

254. Filtration methods permit isolation without use of antimicrobial-containing media. [B-205 P.2]

CVM CRITIQUE: This proposed finding of fact appears to be the opinion of the author of exhibit B-205. It is contrary to standard practices as alluded to by the testimony of Bayer witness Silley who notes that "almost all methods incorporate antibiotics into the isolation media to inhibit growth of other bacteria within the sample." (B-1913, P. 14, L. 7-8).

255. The development of filtration techniques represents a significant advance over the use of selective media, and this method is now recommended for primary isolation of *Campylobacters*. [B-205 P.2]

CVM CRITIQUE: This proposed finding of fact is contradicted by the WDT of Silley, and appears to be the opinion of the author of exhibit B-205. It is contrary to standard practices as indicated to by the testimony of Bayer witness Silley who notes that "almost all methods incorporate antibiotics into the isolation media to inhibit growth of other bacteria within the sample." (B-1913, P. 14, L. 7-8).

256. Method of recovery can influence the subtypes of strains observed. Enrichment preferentially selects some strains. [G-457 P.4]

CVM CRITIQUE: This proposed finding is misleading, as it confuses appropriate growth promotion with preferential selection. See critique for proposed finding of fact 257.

257. Culture methods for *Campylobacter* obtained from human stool samples are different than those used to isolate *Campylobacter* from retail food products. [Meng (G-1466) P.1 L.44 – P.2 L.9]

CVM CRITIQUE: This proposed finding of fact is contradicted in the Docket. As Meng states, "Liquid enrichment media such as Bolton Broth have been developed to detect small numbers of the organisms by promoting the recovery of sub-lethally damaged cells." He does not state that the enrichment step is only performed when culturing retail food products. Enrichment is used in some clinical laboratories to culture *Campylobacter* in fecal sample. This fact is admitted by Bayer witness Silley (B-1913, P. 7, L. 12-14) where he states that "This introduces serious doubt as to whether enrichment culture techniques are isolating those organisms responsible for infection ..."

260. Human and animal fecal samples frequently contain more than one species of *Campylobacter* and/or more than one strain of the same species of *Campylobacter*. Culture methodologies employing antimicrobials are known to effect both the species, strain types, and antimicrobial susceptibilities of organisms isolated in such cases. [Silley (B-1913) Attachment 1 P.33; ¶ 3 – P.36 ¶ 1; Newell (B-1908) P.33 L.17-24]

CVM CRITIQUE: This proposed finding requests two separate findings. The first does not accurately reflect what the cited studies report. The statement that, "Human and animal fecal samples frequently contain more than one species of *Campylobacter* and/or more than one strain of the same species of *Campylobacter*" is attributed to three studies. The first study (Lawson, 1999) cited by Silley (B-1913) reported more than one species of *Campylobacter* in 3.6% of 529 infections. In these cases, the mixed infections were caused by *C. jejuni* and *C. coli* only. The other cited studies (Richardson, 2001; Ruberg, 1998) showed that in no more than 7-8% of infections, was more than one species of *Campylobacter* was found. This is not a frequent event. In fact, the title of the Ruberg study was, "The simultaneous detection of different *Campylobacter* strains during human infection is rare."

262. The pre-enrichment step in carcass washes and retail product sampling can allow revived *Campylobacter* cells to multiply. Rapidly growing cells will have opportunity to overgrow slow growing cells, with resulting sample biasing. [Silley (B-1913) P.36 Attachment 1 3; B-1062]

CVM CRITIQUE: The second part of the proposed finding misrepresents the limitations of bacteriology by suggesting that differences in strain growth rates and the resulting "bias" are unique to *Campylobacter*. This is a limitation of the science and applies to all organisms. More fit organisms always outgrow less fit counterparts in any environment. The notion that certain strains will outgrow others is to be expected in any environment, natural or artificial, and occurs with all microorganisms.

263. Enrichment culture in the presence of antimicrobials biases the recovery of *Campylobacters* originally present on the enriched sample. [Silley (B-1913) P.37, Attachment 1 ¶ 1]

CVM CRITIQUE: The proposed finding is unsupported. The use of antimicrobials in enrichment cultures is to selectively enrich for the growth of the organism of interest. If it can be called "bias," it is an example of intentional "bias," the purpose of which is to segregate that organism from other interfering populations.

264. The selection of single colonies suspected to be pure clones of *Campylobacter* from enrichment agar plates can be misleading because *Campylobacter* readily forms biofilms that cause strains of species and/or different species of *Campylobacter* to aggregate. This can result in both incorrect identification of species and incorrect interpretation of anti-microbial susceptibility tests run on these isolates. This is estimated to occur roughly 10% of the time. [Silley (B-1913) P.37 Attachment 1 ¶ 1; B-1213]

CVM CRITIQUE: The proposed finding as to this phenomenon, and its interpretation, appears to be unique to a single USDA testing laboratory, which reports it to occur about 10% of the time. There is no supporting scientific data to show that this is observed outside that one laboratory.

265. An approved method for *Campylobacter* susceptibility testing for isolates of animal origin was not available until May 2002 when NCCLS published M31-A2. [Silley (B-1913) P.11; Joint Stipulation 29]

CVM CRITIQUE: The proposed finding is unsupported or it is a materially misleading truncation of the actual joint stipulation which reads:

> A NCCLS approved method for animal-origin *Campylobacter* susceptibility testing was not available until May 2002 when NCCLS published M31-A2, "Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals." [Emphasis added here to reveal the misleading nature of the omission.]

CVM deliberately added the wording "NCCLS approved" so as to be completely accurate. There are other best practices organizations around the world that are independent of NCCLS, which have approved methods (B-886). Thus the proposed finding of fact would misrepresent this fact by omitting the words "NCCLS approved" from the stipulation.

266. Antimicrobial susceptibility testing on isolates that are not pure cultures are invalid. [Silley (B-1913) P.37 Attachment 1 ¶1]

CVM CRITIQUE: This proposed finding is self-contradictory and unsupported. If the isolate consists of multiple different bacteria, it is not an isolate by definition. It will be an isolate only after being isolated from the other organisms.

267. Sublethally damaged *Campylobacter* cells are often more sensitive to the selective antimicrobial agents used in traditional culture approaches than cells which are cultured from normal biological niche. [Silley (B-1913) P.38 Attachment 1 ¶ 2]

CVM CRITIQUE This proposed finding is not supported in the evidentiary record. Silley cites material not present on the Docket, thus the reliability of this cannot be determined, particularly the claim that cells are "often more sensitive."

268. When submitting MIC data to FDA with regard to antimicrobial safety studies it is conditional that MIC's must be generated in isolates that have not been exposed to antimicrobials for at least three months prior to isolation. It is therefore difficult to place significant scientific weight on MIC data from isolates exposed to several antimicrobials during the isolation process. [Silley (B-1913) P.38 Attachment 1 ¶ 3]

CVM CRITIQUE: This proposed finding of fact appears to be the unfounded opinion of the Bayer witness. Being the regulatory agency referred to in this claim, we can find no evidence within the FDA that this is an accurate statement, and Bayer and Silley cite noting in support of it.

270. Studies have compared the same *Campylobacter* source samples by filtration isolation versus antimicrobial enrichment isolation and shown that the latter result in *Campylobacters* with reduced antimicrobial susceptibilities. This work also demonstrates genetic biasing via changes in RAPD profiles of the isolates. [Silley (B-1913) P.41 Attachment 1]

CVM CRITIQUE: The proposed finding is based upon an opinion based upon an unverifiable cite "Lee (2002)" not referenced to any exhibit of record.

271. Disk diffusion studies with *Campylobacter* result in little or no inter-laboratory or intra-laboratory reproducibility. [Silley (B-1913) P.42 Attachment 1 ¶ 1]

CVM CRITIQUE: The proposed finding is a misrepresentation. No multi-laboratory studies using disk diffusion, nor the data derived from them are cited or available in the evidentiary or scientific record to verify this claim.

272. The E-test is fundamentally a disk diffusion test. [Silley (B-1913) P.43 Attachment 1 ¶ 2]

CVM CRITIQUE: This proposed finding is contrary to testimony in this record. Differences between these two tests are evident in the testimony of Walker at P.3 L.38 - P.4 L.23.

273. Studies demonstrate that the E-test MIC's for the quinolones tended to be at least one dilution step higher (for resistant isolates) or lower (for susceptible isolates) than that from the agar dilution method. [Silley (B-1913) at P.43 Attachment 1 ¶ 1; Walker (G-1481) P.9]

CVM CRITIQUE: This proposal should not be accepted as a fact because, as is often the case, different studies have produced different results. CVM agrees that these were the results in one study (G-763) but not in others (A-168). Saying "studies demonstrate" is misleading in that there is only one available example. Thus, CVM disagrees that a single select study should be generalized into a universal, and offered as a fact.

274. MIC data generated using non-validated methodologies without standardized Quality Assurance procedures cannot be considered definitive. This applies to all NARMS generated antimicrobial susceptibility data as well as the studies of G-589, B-59 & B-22. [Silley (B-1913) P.45 Attachment 1 ¶ 8]

CVM CRITIQUE: This proposed finding of fact is contradicted by data available in the evidentiary record. This proposed fact seeks to discredit the use of the Etest for measuring fluoroquinolone susceptibility in *Campylobacter* (this method is used by the NARMS and in G-589), thereby calling into question the derived data. Comparative studies using the reference agar dilution method have all shown that the Etest is a reliable method for detecting resistance in *Campylobacter* (G-763, A-168). In addition, the

proposed finding does not and can not apply to "all NARMS generated ... data" as most is generated with NCCLS-approved validated methods.

276. In *E. coli*, efflux pumps can be activated by a variety of compounds, including other antimicrobials, typically resulting in changes in fluoroquinolone MIC. [McDermott (G-1465) P.5]

CVM CRITIQUE: Bayer's proposed finding is misleading because it misrepresents Dr. McDermott's testimony. Dr. McDermott qualified this statement by saying "In *E. coli*, for example, efflux pumps can be activated by a variety of compounds, including other antimicrobials, typically resulting in small changes in fluoroquinolone MICs." (emphasis added). [McDermott WDT P.5 L.39-41]

278. White, et al., found that they had to incubate samples at 42° C (107.6° F) in order to recover *Campylobacter* from samples taken during their retail survey. [White (G-1352) Protocol Amendment, P.34]

CVM CRITIQUE: Bayer's proposed finding is contradicted by G-1352 P.34. White, et al., found that they could not culture *Campylobacter* incubated at 35°C and when they incubated *Campylobacter* at 42° they could culture it. That does not necessarily support Bayer's finding that they had to incubate samples at 42°C. There is no information on what could or could not have been cultured at any temperature between 35° - 42°C and therefore Bayer's proposed finding is without support in the cited exhibit.

282. NARMS susceptibility testing of human *Campylobacter* isolates is conducted exclusively in FoodNet sites. [Angulo (G-1452) P.3 L.46-47, Tollefson (G-1478) P.6 L.37-40]

CVM CRITIQUE: This proposed finding is contrary to the cited testimonies. Dr. Angulo's testimony states that the state health departments sent *Campylobacter* isolates to the CDC for susceptibility testing (G-1452, P.3 L.38-40). Dr. Tollefson's testimony states that human isolate testing is conducted at the CDC's National Center for Infectious Diseases Foodborne Disease Laboratory in Atlanta (G-1478, P.6 L.35-37).

292. The Human NARMS sample collection protocol calls for participating public health laboratories to submit only the first *Campylobacter* isolate received in each laboratory each week to CDC for susceptibility testing. [Tollefson (G-1478) P.7 L.32-34; Angulo (G-1452) P.7 L.26-30; G-1679 P.28]

CVM CRITIQUE: This proposed finding is contrary to the cited testimonies because the proposed finding inserts the word "**only**." Dr. Tollefson's testimony at this citation states " . . . select and forward the first *Campylobacter jejuni* or *Campylobacter coli* isolates received in each laboratory each week to CDC for susceptibility testing." The participating sites are not required to do so. Dr. Angulo's cited testimony states "The National Antimicrobial Resistance Monitoring System (NARMS) began antimicrobial susceptibility testing of human *Campylobacter* isolates in 1997 when laboratories in California, Connecticut, Georgia, Minnesota and Oregon selected and began forwarding

Campylobacter isolates each week to the CDC. Laboratories were added in Maryland and New York in 1998, in Tennessee in 1999 and in Colorado in 2000." Neither cited testimony states that the sites ***only*** send the first isolate nor are they required to send ***only the first isolate***.

299. Rates of campylobacteriosis and fluoroquinolone-resistant *Campylobacter* are extremely variable among FoodNet sites. [Molbak (G-1468) P.4 L.38-44; P.6, Table 1; P.8 L.17-18; P.9, Table 3]

CVM CRITIQUE: This proposed finding mischaracterizes the testimony by inserting the word "extremely" to exaggerate the variation in rates.

300. Human NARMS fails to distinguish isolates from patients with known factors for ciprofloxacin resistance such as foreign travel and prior fluoroquinolone use. [DeGroot (A-200) P.19 L.16-17]

CVM CRITIQUE: This proposed finding is misleading because it incorrectly implies that, in order for the NARMS surveillance program to be useful, it must have collected such risk factor data. To the contrary, Dr. Frederick Angulo's testimony (G-1452), P.8 L.23 – P.9, L.13, presents the multivariate logistic regression analyses conducted on the NARMS data that, when controlling for the variables available through NARMS public health surveillance, showed an increase between 1997 and 2001 in ciprofloxacin-resistant *C. jejuni* isolates from humans. NARMS public health surveillance (as part of FoodNet) was the platform for the largest case-control study of sporadic *Campylobacter* infections in the United States. The data from this case-control study have been analyzed to determine the risk factors for becoming infected with *Campylobacter* and ciprofloxacin-resistant *Campylobacter*. [Angulo (G-1452), P.9 L.46 – P.10, L.12.]

301. Ciprofloxacin resistance rates in particular, are affected by such factors as prior antimicrobial use and foreign travel. [DeGroot (A-200) P.19 L.21-23, citing B-50 and G-589]

CVM CRITIQUE: This proposed finding is not supported by the cited Exhibit B-50. In fact, B-50 is not even related to the issue of the proposed finding, i.e., resistance, prior antimicrobial use, and foreign travel.

302. The Human NARMS program does not consistently characterize isolates with respect to either age or gender, important determinants of campylobacteriosis risk [http://www.cdc.gov/foodnet/annual/2000/2000_summary.htm] for which significant associations with resistance can also be reasonably hypothesized. [DeGroot (A-200) P.19 L.23 – P.20 L.1-2]

CVM CRITIQUE: This statement appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source that supports an assertion about the consistency with which NARMS characterizes the age and gender of isolates. Moreover, the proposed finding's own

words show that its conclusion regarding significant associations between age / gender and resistance is merely "hypothesized," and the proposed finding offers no source of support for its hypothesis.

303. Ciprofloxacin resistance estimates generated from the Human NARMS *Campylobacter* sample selection protocol are erroneously elevated due to seasonal variation. [DeGroot (A-200) P.20 L.14-15]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Moreover, this proposed finding is contradicted later in the testimony of DeGroot (A-200), P.22 L.8 – P.24 L.6, which characterizes as "small" the effect revealed in DeGroot's own calculation of the potential impact of seasonal variation on the ciprofloxacin resistance estimates for one of the NARMS sites.

304. Even though campylobacteriosis is the second most commonly identified bacterial cause of diarrhea in the U.S., the NARMS *Campylobacter* sampling protocol limits *Campylobacter* resistance submissions to 52 or 53 per participating site per year. [DeGroot (A-200) P.20 L.18-21]

CVM CRITIQUE: This proposed finding is unsupported and contradicted by the cited testimony. The cited testimony refers to "CDC, 2000a" in support of its assertion regarding the frequency with which campylobacteriosis is identified. The references for DeGroot (A-200) list "CDC (2000a)" as "B-1782." B-1782 is titled "Participant Blinding and Gastrointestinal Illness in a Randomized, Controlled Trial of an In-Home Drinking Water Intervention" and is unrelated to campylobacteriosis frequency. The references for DeGroot (A-200) also provide the web address "www.cdc.gov/foodnet/annual.htm; FoodNet/annual/2000/pdf" for "CDC (2000a)." The 2000 FoodNet Annual Report found at the www.cdc.gov/foodnet/annuals.htm website reports, at P.6-7, that *Campylobacter* is the most frequently laboratory confirmed bacterial infection identified in the FoodNet sites.

305. Non- *Campylobacter* pathogens monitored by NARMS have a broader sampling protocol than that for *Campylobacter*, taking every 5th or 10th specimen, for example, rather than the first specimen of the week. [DeGroot (A-200) P.20 L.21-22. See also Tollefson (G-1478) P.7 L.23-34]

CVM CRITIQUE: The proposed finding is misleading in that, although the NARMS sampling protocols for enteric pathogens other than *Campylobacter* may be different from that of *Campylobacter*, they are not necessarily "broader."

306. Participating state health departments submitted more *Shigella* and more *Escherichia coli* isolates to NARMS than *Campylobacter* isolates during 2000, even though these other diarrheal agents are not identified nearly as commonly as *Campylobacter*. [DeGroot (A-200) P.20 L.24 – P.21 L.1-2]

CVM CRITIQUE: This statement is unsupported by the cited testimony. The cited testimony refers to "CDC, 2000a" in support of its assertion regarding the relative frequency with which *Campylobacter* isolates are submitted to NARMS. The references for DeGroot (A-200) list "CDC (2000a)" as "B-1782." B-1782 is titled "Participant Blinding and Gastrointestinal Illness in a Randomized, Controlled Trial of an In-Home Drinking Water Intervention" and is unrelated to *Campylobacter* submission to NARMS. The references for DeGroot (A-200) also provide the web address "www.cdc.gov/foodnet/annual.htm; FoodNet/annual/2000/pdf for "CDC (2000a)." The 2000 FoodNet Annual Report found at the www.cdc.gov/foodnet/annuals.htm website does not report the number of isolates submitted in NARMS.

307. The Human NARMS protocol systematically collects a higher proportion of isolates available from winter, when campylobacteriosis incidence is lower, than from summer, when campylobacteriosis incidence is higher. [DeGroot (A-200) P.21 L.10-13]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

308. Ciprofloxacin resistance among isolated *Campylobacter jejuni* is higher in the winter than it is in the summer. [DeGroot (A-200) P.21 L.13-14; Feldman (B-1902) P.11 L.9-10]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

309. Yearly resistance estimates reported by the Human NARMS program are higher than the general level of ciprofloxacin resistance. [DeGroot (A-200) P.21 L.14-15]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

310. In 2000 the Minnesota Department of Health website reported 11% overall incidence of *Campylobacter* resistance from all cases at www.health.state.mn.us/divs/dpc/ades/surveillance/table2000.pdf while at the same time Minnesota's year 2000 NARMS-submitted samples were 25% resistant. [DeGroot (A-200) P.16 L.21 – P.17 L.2; P.21 L.15 – P.25 L.6; P.45 L.8 – P.47 L.6 G-749, P.13]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The table in DeGroot (A-200) P.46 representing DeGroot's assessment shows that *Campylobacter*

resistance to ciprofloxacin for all *Campylobacter* cases (i.e., not limited to *Campylobacter jejuni* cases only) is not 25% but rather 24%.

311. Year-to-year comparisons of apparent prevalence of ciprofloxacin resistance among *Campylobacter* reported by Human NARMS are confounded with effects attributable to changes in the U.S. population and its exposure to factors known to increase risks of ciprofloxacin-resistant *Campylobacter* infection such as foreign travel or recent prior use of a fluoroquinolone. [DeGroot (A-200) P.25 L.18-22]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. Moreover, the proposed finding is contradicted by DeGroot (A-200) P.25 L.15-18 which states:

> As previously mentioned, foreign travel among residents of the FoodNet catchment area increased by 60% from 1998 to 2000. Similarly, antibiotic use among the same population rose by 10% (12.0% (112/12755) to 13.2% (184/13113) from 1998 to 2000.

First, 112/12755 is not 12.0% but 0.9% and 184/13113 is not 13.2% but 1.4%. More importantly, these numbers do not represent antibiotic use, according to the FoodNet Atlas of Exposures, the cite provided by DeGroot (A-200), P.24 L.20-22 and P.26 L.18-22. [According to the FoodNet Atlas of Exposures, those numbers actually relate to foreign travel in 1998-1999 and 2000.] In addition, any increase in "antibiotic use" does not necessarily imply that fluoroquinolone use has increased, especially "recent prior use of a fluoroquinolone," as suggested by the proposed finding.

312. Foreign travel among residents of the FoodNet catchment area increased by 60% from 1998 to 2000. [DeGroot (A-200) P.25 L.16-17]

CVM CRITIQUE: This statement is misleading in that it fails to acknowledge that, according to DeGroot (A-200) P.24 L.20-22, and the FoodNet Atlas of Exposures cited therein, foreign travel was uncommon (less than 1.0% and 1.5% of the population surveyed in 1998-1999 and 2000, respectively). Consequently, any change over time would result in a fairly large percent change even if the difference is not meaningful.

313. Antibiotic use among residents of the FoodNet catchment area rose by 10% (12.0% (112/12755) to 13.2% (184/13113) from 1998 to 2000. [DeGroot (A-200) P.25 L.17-18]

CVM CRITIQUE: The proposed finding is contradicted by DeGroot (A-200). First, 112/12755 is not 12.0% but 0.9% and 184/13113 is not 13.2% but 1.4%. More importantly, these numbers do not represent antibiotic use, according to the FoodNet Atlas of Exposures, the cite provided by DeGroot (A-200), P.24 L.20-22 and P.26 L.18-22.

314. NARMS estimates not corrected for the confounders foreign travel and prior fluoroquinolone use cannot be meaningfully compared to the general population. [DeGroot (A-200) P.25 L.22-23]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. Moreover, the proposed finding is contradicted by DeGroot (A-200). The numbers that appear to be relied on here [see DeGroot (A-200) P.25 L.15-18] are: inaccurate (the arithmetic is wrong); irrelevant (the numbers purporting to represent antibiotic use do not, according to the cite provided in the testimony); nonspecific (an increase in "antibiotic use" does not necessarily imply that fluoroquinolone use has increased, especially "recent prior use of a fluoroquinolone"); or misleading (the low frequency of foreign travel was obscured).

315. Human NARMS Selection is biased by inconsistent diagnostic protocols employed by attending physicians. [DeGroot (A-200) P.27 L.5-24]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. In the cited testimony, DeGroot (A-200) P.25 L.12-18, states that there is an increase in the numbers of AIDS cases in the United States, that doctors are more likely to order stool samples for patients with HIV or AIDS, and that those two factors increase resistance estimates in NARMS. First, it is unclear what the cited sources are for the two factors. The sources cited to support the two factors ("CDC 2000a" and "Hennessy," respectively) are not listed on the reference pages in DeGroot (A-200) and are not associated with any exhibit number to the docket; neither source is provided with a title. Second, the cited testimony fails to explain how a patient with HIV or AIDS is more likely to have a fluoroquinolone-resistant *Campylobacter* infection; without this link, the purported existence of the two factors mentioned above is meaningless in terms of NARMS estimates of fluoroquinolone-resistant *Campylobacter* infections.

316. There is no statistical difference in the prevalence ratio estimate of fluoroquinolone resistance comparing 1997 NARMS data to 1998, 1999, 2000 and 2001 NARMS data when Connecticut data was removed from the analysis conducted by CDC. [Molbak (G-1468) P.9 Table 4]

CVM CRITIQUE: This proposed finding is the same as finding 338. his proposed finding is misleading because it mischaracterizes the exhibit cited in support thereof. The proposed finding does not indicate that in Dr. Molbak's WDT [Exhibit (G-1468], P.9 Table 4 is based on 2001 preliminary data.

318. NARMS only tests a very small fraction of *Campylobacter* cases in the FoodNet catchment areas. [Burkhart (B-1900) P.44 L.2-3]

CVM CRITIQUE: This proposed finding is misleading to the extent that it implies that NARMS is missing cases within the FoodNet catchment area that it should have captured. As explained in the lines immediately following the testimony cited in support of the proposed finding [Burkhart (B-1900) P.44 L.6-

8], *Campylobacter* is under-reported in any public health system, including those that participate in FoodNet. However, FoodNet and NARMS were designed to capture only laboratory-confirmed (i.e., reported) cases of *Campylobacter* infection, not all cases of *Campylobacter* infection regardless of whether they were reported or unreported to public health officials through public health surveillance [see Burkhart (B-1900) P.41 L.15-16)]. Moreover, the sample of *Campylobacter* cases in NARMS is considered to be generally representative of the United States population. As Dr. Angulo [Angulo (G-1452), P.3 L.45 - P.4 L.34] explains:

Several NARMS activities, including susceptibility testing of human *Campylobacter*, are conducted exclusively in FoodNet sites. ... FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States. ... These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness.

319. There is no statistical difference in the 13.6% resistance reported by NARMS in 1997 compared to the 17.6% reported in 1999. [DeGroot (A-200) P.50 L.12-14]

CVM CRITIQUE: This proposed finding is unsupported by the cited testimony and also contradicted by the witness whose testimony is cited here as support for the proposed finding. First, the cited testimony does not offer a percentage of resistance reported by NARMS in 1997. Second, DeGroot's testimony recognizes the need to account for changes in the number of NARMS sites when examining the trend in NARMS fluoroquinolone resistance data. "[T]he 17.6% resulting from submission from seven sites in 1999 is not directly comparable to the 13.4% resulting from submissions from five sites in 1997." Moreover, DeGroot recognizes the need for logistic regression analysis to account for such variation in the data. [DeGroot (A-200) P.52 L.3-4] The testimony of CVM witness Dr. Frederick Angulo provides a logistic regression analysis that controls for NARMS site and for patient age. That analysis, which can be found at Angulo (G-1452) Attachment 2 P.77, reveals a statistically significant difference in the proportion of fluoroquinolone-resistant *Campylobacter* in 1999 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.1, 95% Cl: 1.2, 3.9). [DeGroot (A-200) P.51 L.12-14].

320. There is no statistical difference in the 13.3% resistance reported by NARMS in 1998 compared to the preliminary 2001 figure of 18%. [DeGroot (A-200) P.50 L.14-16]

CVM CRITIQUE: This proposed finding is unsupported by the cited testimony and also contradicted by the witness whose testimony is cited here as support for the proposed finding. First, the cited testimony does not offer a 13.3% resistance reported by NARMS in 1998. Second, DeGroot's testimony recognizes the need to account for changes in the number of NARMS sites when examining the trend in NARMS fluoroquinolone resistance data. [DeGroot (A-200) P.51 L.12-14]. Moreover, DeGroot recognizes the need for logistic regression analysis to account for such variation in the data. [DeGroot

(A-200) P.52 L.3-4] The testimony of CVM witness Dr. Frederick Angulo provides a logistic regression analysis that controls for NARMS site and for patient age, which can be found at Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77. That analysis, which includes the data from all available years (as opposed to omitting all of the data from 1997), reveals a statistically significant difference in the proportion of fluoroquinolone-resistant *Campylobacter* in 2001 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.5, 95% CI: 1.4, 4.4).

321. No explanation of Human NARMS ciprofloxacin resistance estimates, used as part of the basis for the NOOH by CVM, is complete without a measure of sampling protocol compliance failure and data integrity violation. [DeGroot (A-200) P.52 L.10-12]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. There is no valid analysis on the record to suggest protocol compliance failures or data integrity violations; therefore, the proposed finding is meaningless.

322. Both the preliminary and final Logistic Regression Model used to analyze the NARMS data include information on age categorization. [DeGroot (A-200) P.54 L.12-13]

CVM CRITIQUE: This proposed finding is ambiguous because it does not state whose analysis (i.e., CVM witness or Bayer witness, for example) it is referring to.

323. A logistic regression model created by DeGroot, with the data made available to Bayer by CDC, clearly shows that reported yearly resistance varied not as the result of a generalized phenomena, but rather as the result of various effects operating within specific states in specific years. [DeGroot (A-200) P.54 L.2-4]

CVM CRITIQUE: This proposed finding is flatly contradicted by the witness whose testimony is cited here as support for the proposed finding. A logistic regression model created by DeGroot to describe resistance levels did, in fact, reveal a generalized phenomenon to explain the increase in resistance levels over time. DeGroot's logistic regression model revealed that "associations between reported ciprofloxacin resistance levels and year and state from [which] isolates were submitted achieve generally accepted significance levels using indicator variables for year and state." [DeGroot (A-200) P.53 L.15-17]

324. Resistance documented in Connecticut for the 1999 and 2001 NARMS collections were roughly twice as high as reported in the baseline year of 1997. [DeGroot (A-200) P.54 L.5-7]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony and is contradicted by other testimony of the witness. The cited testimony does not offer what percentages of resistance are being used to generate the result stated in the proposed finding. Another portion of DeGroot's testimony [DeGroot (A-200) P.52 Table] provides a percentage for 1997 and 1999 (but not for 2001); however, a comparison between 1997

and 1999 using the numbers in the DeGroot Table does not reveal a two-fold difference in resistance.

325. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. [DeGroot (A-200) P.54 L.17-20]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The multivariate logistic regression model used by CDC to analyze the NARMS data compared data from each successive year (1998, 1999, 2000, and 2001) with data from the baseline year (1997), looking for "a direction of movement," i.e., trend, in the proportion of fluoroquinolone-resistant *Campylobacter* isolates between any of the following time periods: 1998 compared with 1997; 1999 compared with 1997; 2000 compared with 1997; and 2001 compared with 1997.

327. In conducting the Logistic Regression Model to analyze the NARMS data, CDC failed to explore how the independent variables and outcome measured vary with respect to passage of time; this analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. [DeGroot (A-200) P.54 L.21 – P.55 L.4]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony and is also contradicted by Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77. First, the model selected by CDC to analyze the NARMS data receives praise in the cited testimony, which states that "such techniques [i.e., comparing yearly outcomes to a baseline year using sets of indicator variables, as was done in the NARMS analysis] are attractive because they do not impose assumptions on how independent variables .. . and the outcome .. . vary with respect to the passage of time." Second, selection of this model did not preclude an examination of trend. In fact, the analysis presented in Dr. Angulo's testimony reveals a statistically significant trend, i.e., increase, in the proportion of fluoroquinolone-resistant *Campylobacter* in 2001 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.5, 95% CI: 1.4, 4.4). [Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77]

328. CDC fails to report on the ecological factors associated with varying ciprofloxacin resistance in different states and different years. [DeGroot (A-200) P.55 L.11-12]

CVM CRITIQUE: This proposed finding is vague in that it is unclear (and the cited testimony does not specify) what "ecological factors" are being referred to and, therefore, the statement cannot serve as a finding of fact.

329. The Human NARMS data provide no insight into national ciprofloxacin resistance trends among *Campylobacter* causing diarrhea in U.S. residents. [DeGroot (A-200) P.55 L.6-7]

CVM CRITIQUE: This proposed finding is contrary to the weight of the evidence, specifically as described in the testimonies of Dr. Tollefson and Dr. Angulo. As Dr. Tollefson explains, NARMS was established to:

track changes in susceptibilities among enteric pathogens in both animals and humans. NARMS was specifically designed as an on-going monitoring system in both animal and human populations for the purpose of examining the impact of drug use in food-producing animals on human health . ... We designed the system to allow us to track changes over time in both populations [animals and humans] .... [Tollefson (G-1478, P.14 L.26-43]

As Dr. Angulo explains:

Several NARMS activities, including susceptibility testing of human *Campylobacter,* are conducted exclusively in FoodNet sites . .. . FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States . ... These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness. [Angulo (G-1452), P.3 L.45 - P.4 L.34]

Dr. Angulo concludes that NARMS data:

demonstrate that a high proportion (approximately one-fifth) of human *Campylobacter* isolates in the United States are resistant to ciprofloxacin. Furthermore, when using a multivariate model to account for the marked regional variation and increasing population size in NARMS, the proportion of human *Campylobacter* in the United States resistant to ciprofloxacin is two and a half times higher in 2001 than it was in 1997; the trend of an increasing prevalence of ciprofloxacin resistance among human *Campylobacter* isolates is statistically significant, is relatively consistent from year-to-year, and is not due solely to an increasing prevalence observed in a single site. [Angulo (G-1452), P.9 L.1-7]

330. CDC does not enforce the stated protocols for Human NARMS *Campylobacter* collection, resulting in haphazard specimen submission and potential data corruption. [DeGroot (A-200) P.30 L.1 – P.33 L.17]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. There is no valid analysis on the record to suggest protocol compliance failures or data integrity violations; therefore the proposed finding is meaningless.

331. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, the human NARMS *Campylobacter* sampling methodology was described by Dr. Fred Angulo, Chief of the CDC NARMS Activity, as "artificial" and not population based as is the methodology for all of the other bacteria in the human NARMS program (i.e., the *Campylobacter* sampling methodology is distinctly different than that for all of the other organisms in the NARMS programs). [Carnevale (A-199) P.11 L.14-19]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

332. The consequences of CDC's "artificial" *Campylobacter* sampling methodology are significant, as it causes a marked over-representation of fluoroquinolone resistant *Campylobacter* isolates in the NARMS program. It has been shown that the incidence of human *Campylobacter*iosis is highest during summer months while rates of resistance to fluoroquinolones are highest during the winter months. (For example, see A-71). Therefore, CDC's "artificial" program of selecting only the first isolate each week from the participating laboratories causes the level of fluoroquinolone resistance to be over-represented in the CDC program. [Carnevale (A-199) P.11 L.22 – P.12 L.2]

CVM CRITIQUE: This proposed finding is flatly contradicted by the testimony of AHI witness DeGroot (A-200). The testimony of DeGroot (A-200), P.22 L.8 - P.24 L.6, characterizes as "small" the effect revealed in DeGroot's calculation of the potential impact of seasonal variation on the ciprofloxacin resistance estimates from one of the NARMS sites.

333. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, Dr. Fred Angulo, Chief of the CDC NARMS Activity stated, "Now your question is to the extent that the prevalence we [CDC] identify is representative of the country, and I agree completely there are limitations in the generalization of our prevalence nationally." [Carnevale (A-199) P.13 L.12-15]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and"..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

334. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, Dr. Fred Angulo, Chief of the CDC NARMS Activity stated, " For *Campylobacter*, as you heard described, we [CDC] do not have a population based sampling methodology." [Carnevale (A-199) P.13 L.16-17]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and"..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

335. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, Dr. Fred Angulo, Chief of the CDC NARMS Activity stated, " We [CDC] agree completely, that there's a limitation in our sampling scheme of *Campylobacter*. That's why we're moving towards trying to develop a population based collection of *Campylobacter* isolates." [Carnevale (A-199) P.13 L.18-20]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and"..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

336. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, Dr. Fred Angulo, Chief of the CDC NARMS Activity stated, " So, and then *Campylobacter* is not population based, as was pointed out. So, I think that for all pathogens except *Campylobacter* we have a representative sample of culture confirmed cases at the state level." [Carnevale (A-199) P.13 L.21-24]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting.

Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and"..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

337. At the 2002 NARMS Annual Scientific Meeting held November 19 - 22, in Hilton Head Island, SC, Dr. Fred Angulo, Chief of the CDC NARMS Activity stated, "I agree. Its [*Campylobacter* resistance numbers] not a prevalence. It [*Campylobacter* resistance numbers] is not an estimate of the national prevalence because we [CDC] have artificially created this once a week sample." [Carnevale (A-199) P.13 L.24-28]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony or any other evidence in the record. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the purported tape recording made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

338. There was no statistical difference in the prevalence ratio estimate of flouroquinolone resistance comparing 1997 NARMS data to 1998, 1999, 2000 and 2001 NARMS data when Connecticut data was removed from the analysis conducted by CDC. [Molbak (G-1468) P. 9 Table 4]

CVM CRITIQUE: This proposed finding is the same as finding 316 and it is misleading because it mischaracterizes the exhibit cited in support thereof. The proposed finding does not indicate that in Dr. Molbak's WDT [Exhibit (G-1468)], P.9 Table 4 is based on 2001 preliminary.

340. Bayer could not duplicate the Logistic Regression Model analysis since the data received contained numerous missing data on age. [Burkhart (B-1900) P. 43 L. 13-15]

CVM CRITIQUE: This proposed finding is unsupported by any evidence in the record. It has not been established in the evidentiary record (or elsewhere) that the data referred to in the proposed finding were missing age variables and, therefore, the reason for Bayer's inability to conduct a logistic regression analysis may be the result of any number of other reasons besides the one offered here.

341. NARMS only tests a very small fraction of *Campylobacter* cases in the FoodNet catchment areas. [Burkhart (B-1900) P. 44 L. 2-3]

CVM CRITIQUE: This proposed finding is a duplicate of 318. The response to 318 is repeated here for convenience. This proposed finding is misleading to the extent that it implies that NARMS is missing cases within the FoodNet catchment area that it should have captured. As explained in the lines immediately following the testimony cited in support of the proposed finding [Burkhart (B-1900) P.44 L.6-8], *Campylobacter* is under-reported in any public health system, including those that participate in FoodNet. However, FoodNet and NARMS were designed to capture only laboratory-confirmed (i.e., reported) cases of *Campylobacter* infection, not all cases of *Campylobacter* infection regardless of whether they were reported or unreported to public health officials through public health surveillance [see Burkhart (B-1900) P.41 L.15-16)]. Moreover, the sample of *Campylobacter* cases in NARMS is considered to be generally representative of the United States population. As Dr. Angulo [Angulo (G-1452), P.3 L.45 - P.4 L.34] explains:

> Several NARMS activities, including susceptibility testing of human *Campylobacter,* are conducted exclusively in FoodNet sites . .. . FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States . . .. These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness.

342. There is no statistical difference in the 13.6% resistance reported by NARMS in 1997 compared to the 17.6% reported in 1999. [DeGroot (A-200) P. 50 L. 12-14]

CVM CRITIQUE: This proposed finding is a duplicate of 319. The response to 319 is repeated here for convenience. This proposed finding is unsupported by the cited testimony and also contradicted by the witness whose testimony is cited here as support for the proposed finding. First, the cited testimony does not offer a percentage of resistance reported by NARMS in 1997. Second, DeGroot's testimony recognizes the need to account for changes in the number of NARMS sites when examining the trend in NARMS fluoroquinolone resistance data. "[T]he 17.6% resulting from submission from seven sites in 1999 is not directly comparable to the 13.4% resulting from submissions from five sites in 1997." [DeGroot (A-200) P.51 L.12-14]. Moreover, DeGroot recognizes the need for logistic regression analysis to account for such variation in the data. [DeGroot (A-200) P.52 L.3-4] The testimony of CVM witness Dr. Frederick Angulo provides a logistic regression analysis that controls for NARMS site and for patient age. That analysis, which can be found at Angulo (G-1452) Attachment 2 P.77, reveals a statistically significant difference in the proportion of fluoroquinolone-resistant *Campylobacter* in 1999 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.1, 95% CI: 1.2, 3.9).

343. There is no statistical difference in the 13.3 % resistance reported by NARMS in 1998 compared to the preliminary 2001 figure of 18%. [DeGroot (A-200) P. 50 L. 14-16]

CVM CRITIQUE: This proposed finding is a duplicate of 320. The response to 320 is repeated here for convenience. This proposed finding is contrary to the cited testimony and also contradicted by other testimony given by the witness whose testimony is cited here as support for the proposed finding. First, the cited testimony does not offer a 13.3% resistance reported by NARMS in 1998. Second, DeGroot's testimony recognizes the need to account for changes in the number of NARMS sites when examining the trend in NARMS fluoroquinolone resistance data. [DeGroot (A-200) P.51 L.12-14]. Moreover, DeGroot recognizes the need for logistic regression analysis to account for such variation in the data. [DeGroot (A-200) P.52 L.3-4] The testimony of CVM witness Dr. Frederick Angulo provides a logistic regression analysis that controls for NARMS site and for patient age, which can be found at Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77. That analysis, which includes the data from all available years (as opposed to omitting all of the data from 1997), reveals a statistically significant difference in the proportion of fluoroquinolone-resistant *Campylobacter* in 2001 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.5, 95% CI: 1.4, 4.4).

344. No explanation of Human NARMS ciprofloxacin resistance estimates, used as part of the basis for the NOOH by CVM, is complete without a measure of sampling protocol compliance failure and data integrity violation. [DeGroot (A-200) P. 52 L. 10-12]

CVM CRITIQUE: This proposed finding is a duplicate of 321. The response to 321 is repeated here for convenience. This proposed finding appears to be an unjustified statement of opinion not a statement of fact. There is no valid analysis on the record to suggest protocol compliance failures or data integrity violations; therefore, the proposed finding is meaningless.

345. Both the preliminary and final Logistic Regression Model used to analyze the NARMS data include information on age categorization. [DeGroot (A-200) P. 54 L. 12-13]

CVM CRITIQUE: This proposed finding is a duplicate of 322. The response to 322 is repeated here for convenience. This proposed finding is ambiguous because it does not state whose analysis (i.e., CVM witness or Bayer witness, for example) it is referring to.

346. A logistic regression model created by DeGroot, with the data made available to Bayer by CDC, clearly shows that reported yearly resistance varied not as the result of a generalized phenomena, but rather as the result of various effects operating within specific states in specific years. [DeGroot (A-200) P. 54 L. 2-4]

CVM CRITIQUE: This proposed finding is a duplicate of 323. The response to 323 is repeated here for convenience. This proposed finding is flatly contradicted by the witness whose testimony is cited here as support for the proposed finding. A logistic regression model created by DeGroot to describe resistance levels did, in fact, reveal a generalized phenomenon to explain the increase in resistance levels over time. DeGroot's

logistic regression model revealed that "associations between reported ciprofloxacin resistance levels and year and state from [which] isolates were submitted achieve generally accepted significance levels using indicator variables for year and state." [DeGroot (A-200) P.53 L.15-17]

347. Resistance documented in Connecticut for the 1999 and 2001 NARMS collections were roughly twice as high as reported in the baseline year of 1997. [DeGroot (A-200) P. 54 L. 5-7]

CVM CRITIQUE: This proposed finding is a duplicate of 324. The response to 324 is repeated here for convenience: This proposed finding is not supported by the cited testimony and is contradicted by other testimony of the witness. The cited testimony does not offer what percentages of resistance are being used to generate the result stated in the proposed finding. Another portion of DeGroot's testimony [DeGroot (A-200) P.52 Table] provides a percentage for 1997 and 1999 (but not for 2001); however, a comparison between 1997 and 1999 using the numbers in the DeGroot Table does not reveal a two-fold difference in resistance.

348. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. [DeGroot (A-200) P. 54 L. 17-20]

CVM CRITIQUE: This proposed finding is a duplicate of 325. The response to 325 is repeated here for convenience. This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The multivariate logistic regression model used by CDC to analyze the NARMS data compared data from each successive year (1998, 1999, 2000, and 2001) with data from the baseline year (1997), looking for "a direction of movement," i.e., trend, in the proportion of fluoroquinolone-resistant *Campylobacter* isolates between any of the following time periods: 1998 compared with 1997; 1999 compared with 1997; 2000 compared with 1997; and 2001 compared with 1997.

350. In conducting the Logistic Regression Model to analyze the NARMS data, CDC failed to explore how the independent variables and outcome measured vary with respect to passage of time; this analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. [DeGroot (A-200) P. 54 L. 21- P. 55 L. 4]

CVM CRITIQUE: This proposed finding is a duplicate of 327. The response to 327 is repeated here for convenience. This proposed finding is contrary to the cited testimony and is also contradicted by Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77. First, the model selected by CDC to analyze the NARMS data receives praise in the cited testimony, which states that "such techniques [i.e., comparing yearly outcomes to a baseline year using sets of indicator variables, as was done in the NARMS analysis] are attractive because they do not impose assumptions on how independent variables .. . and the outcome .. . vary with respect to the passage of time." Second, selection of this model did not preclude an examination of trend. In fact, the analysis presented in Dr. Angulo's

testimony reveals a statistically significant trend, i.e., increase, in the proportion of fluoroquinolone-resistant *Campylobacter* in 2001 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.5, 95% CI: 1.4, 4.4). [Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77]

351. CDC fails to report on the ecological factors associated with varying ciprofloxacin resistance in different states and different years. [DeGroot (A-200) P. 55 L. 11-12]

CVM CRITIQUE: This proposed finding is a duplicate of 328. The response to 328 is repeated here for convenience. This proposed finding is vague in that it is unclear (and the cited testimony does not specify) what "ecological factors" are being referred to and, therefore, the statement cannot serve as a finding of fact.

352. The Human NARMS data provide no insight into national ciprofloxacin resistance trends among *Campylobacter* causing diarrhea in U.S. residents. [DeGroot (A-200) P. 55 L. 6-7]

CVM CRITIQUE: This proposed finding is a duplicate of 329. The response to 329 is repeated here for convenience. This proposed finding is contrary to the weight of the evidence, specifically as described in the testimonies of Dr. Tollefson and Dr. Angulo. As Dr. Tollefson explains, NARMS was established to:

> track changes in susceptibilities among enteric pathogens in both animals and humans. NARMS was specifically designed as an on-going monitoring system in both animal and human populations for the purpose of examining the impact of drug use in food-producing animals on human health . . .. We designed the system to allow us to track changes over time in <u>both</u> populations [animals and humans] .... [Tollefson (G-1478, P.14 L.26-43]

As Dr. Angulo explains:

> Several NARMS activities, including susceptibility testing of human *Campylobacter,* are conducted exclusively in FoodNet sites . .. . FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States . . .. These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness. [Angulo (G-1452), P.3 L.45 - P.4 L.34]

Dr. Angulo concludes that NARMS data:

> demonstrate that a high proportion (approximately one-fifth) of human *Campylobacter* isolates in the United States are resistant to ciprofloxacin. Furthermore, when using a multivariate model to account for the marked regional variation and increasing population size in NARMS, the proportion of human *Campylobacter* in the United States resistant to ciprofloxacin is two and a half times higher in 2001 than it was in 1997; the trend of an increasing

prevalence of ciprofloxacin resistance among human *Campylobacter* isolates is statistically significant, is relatively consistent from year-to-year, and is not due solely to an increasing prevalence observed in a single site. [Angulo (G-1452), P.9 L.1-7]

353. Under the National Antimicrobial Resistance Monitoring program, there is not a population based sampling program for the collection of human *Campylobacter* isolates for antibiotic susceptibility testing. [Carnevale (A-199) P. 11 L. 2 – 22; P. 12 L. 17 – P. 13 L. 28; P. 85; P. 87; P. 88]

CVM CRITIQUE: The proposed finding is not supported by the cited testimony, which is the purported tape recording of Dr. Angulo made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the tape recording. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and ". . . " notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

354. Under the National Antimicrobial Resistance Monitoring program, there is not a population based sampling program of human *Campylobacter* isolates for antibiotic susceptibility testing, as there is for all other bacteria monitored in the NARMS program. [Carnevale (A-199) P. 11 – L. 1 – 15; P. 13 L. 22 – 24]

CVM CRITIQUE: The proposed finding is not supported by the cited testimony, which in relevant part is the purported tape recording of Dr. Angulo made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the tape recording. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

355. Since there is not a population based sampling program for the collection of human *Campylobacter* isolates for antibiotic susceptibility testing under the NARMS program, the data generated by it for *Campylobacter* resistance cannot represent the rate of occurrence of *Campylobacter* resistant isolates in the United States or any representative subpopulation. [Carnevale (A-199) P. 12 L. 16 – P. 15 L. 15]

CVM CRITIQUE: This proposed finding is contradicted by the testimonies of DeGroot (A-200) and Angulo (G-1452). Regarding any effect of a one-sample-per-week sampling scheme throughout a given year, the testimony of DeGroot (A-200), P.22 L.8 - P.24 L.6, characterizes as "small" the effect revealed in DeGroot's calculation of the potential impact of seasonal variation on the ciprofloxacin resistance estimates from one of the NARMS sites. Moreover, as Dr. Angulo explains:

> Several NARMS activities, including susceptibility testing of human *Campylobacter,* are conducted exclusively in FoodNet sites . .. . FoodNet has evaluated the comparability of the population residing in the FoodNet surveillance area to the population residing in the United States . .. . These data support the generalizability of FoodNet data to the United States population for the purpose of understanding the epidemiology of foodborne illness. [Angulo (G-1452), P.3 L.45 - P.4 L.34]

Finally, to the extent that the proposed finding relies on the purported tape recording of Dr. Angulo made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting, the proposed finding is unsupported. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the tape recording. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

356. The antimicrobial susceptibility data for human *Campylobacter* isolates generated by the NARMS program do not represent the prevalence of fluoroquinolone resistant *Campylobacter.* [Carnevale (A-199) P. 12 L. 16 – P. 15 – 15; P. 88; P. 89]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of AHI witness DeGroot and is not supported by the cited testimony. The cited testimony provides an evaluation of the one-sample-per-week sampling scheme and the purported statements of Dr. Angulo at the 2002 NARMS Annual Scientific Meeting to make the point offered by the proposed finding. First, regarding any effect of a one-sample-per-week sampling scheme throughout a given year, the testimony of DeGroot (A-200), P.22 L.8 - P.24 L.6, characterizes as "small" the effect revealed in DeGroot's calculation of the potential impact of seasonal variation on the ciprofloxacin resistance estimates from one of the NARMS sites. Second, to the extent that the proposed finding relies on the purported tape recording of Dr. Angulo made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting, the proposed finding is unsupported. The validity of any statement attributed in Dr. Carnevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the tape recording. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete

transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

357. Since a single year's NARMS data on human fluoroquinolone resistant *Campylobacter* is not population based and bears no relationship to the actual prevalence or rate of fluoroquinolone resistant *Campylobacter*, it is scientifically inappropriate and not meaningful to make year to year comparisons of the data. [Carnevale (A-199) P. 12 L. 16 – P. 15 – 15; P. 88; P. 89]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of AHI witness DeGroot and is not supported by the cited testimony. The cited testimony provides an evaluation of the one-sample-per-week sampling scheme and the purported statements of Dr. Angulo at the 2002 NARMS Annual Scientific Meeting to make the point offered by the proposed finding. First, regarding any effect of a one-sample-per-week sampling scheme throughout a given year, the testimony of DeGroot (A-200), P.22 L.8 - P.24 L.6, characterizes as "small" the effect revealed in DeGroot's calculation of the potential impact of seasonal variation on the ciprofloxacin resistance estimates from one of the NARMS sites. Second, to the extent that the proposed finding relies on the purported tape recording of Dr. Angulo made by Dr. Carnevale at the 2002 NARMS Annual Scientific Meeting, the proposed finding is unsupported. The validity of any statement attributed in Dr. Camevale's testimony (A-199) to Dr. Angulo has not been, and cannot be, established. In fact, neither Bayer nor AHI has even provided CVM with a copy of the tape recording. Moreover, the tape recording transcription attached to Dr. Carnevale's testimony (Attachment 3) does not even purport to be a complete transcription of statements attributed to Dr. Angulo. [Carnevale (A-199) Attachment 3 P.85] Further, the transcription contains numerous "inaudible" and "..." notations throughout. In many instances, it is not clear what questions were posed that elicited the purported answers. Therefore, the proposed finding is unsubstantiated and lacking factual basis.

358. The NARMS data on human fluoroquinolone resistant *Campylobacter* has no bearing or relationship to the frequency of occurrence of fluoroquinolone resistant *Campylobacter* in any population. [Carnevale (A-199) P. 15 L. 2 – 15]

CVM CRITIQUE: This proposed finding is a hyperbole, is unsupported by evidence in the record, and is contradicted by the weight of the evidence.

359. NARMS animal isolate testing is conducted at the USDA Agricultural Research Service (ARS), Russell Research Center in Athens, Georgia in Dr. Paula Fedorka-Cray's laboratory. [Tollefson (G-1478) P.7 L.45 – P.8 L.1-2]

CVM CRITIQUE: CVM notes this is only true for the animal arm of NARMS.

361. For NARMS FDA purposes, it is the slaughter plant isolates from the animal arm of NARMS that are analyzed. [Tollefson (G-1478) P.8 L.25-26; DeGroot (A-200) P.3 L.12-13]

CVM CRITIQUE: The proposed finding is not what the cited testimony said. The words "are analyzed" are not from Dr. Tollefson's WDT but rather the wording "provide us with the most valuable information on the animal isolates" ends this sentence.

363. The Poultry NARMS program suffers from methodological flaws and other problems that result in an inaccurate view of the overall prevalence of fluoroquinolone-resistant *Campylobacter* in production poultry. [DeGroot (A-200) P.4 L.1-3]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact.

364. In order to utilize Poultry NARMS data to draw conclusions about the impact of any fluoroquinolone use in poultry on fluoroquinolone resistance levels in poultry *Campylobacter* isolates over time, one would need to know the level of pre-approval resistance. [DeGroot (A-200) P.5 L.5-8]

CVM CRITIQUE: This proposed finding is unsupported by the cited testimony. The cited testimony refers to "Kleinbaum et al., 1982(e)," which in DeGroot's reference list is not provided with an exhibit number and does not appear to be on the record. The reference is titled, "Typology of Observational Study Designs"; NARMS is a laboratory-based monitoring system, not an observational study.

365. No credible pre-approval *Campylobacter* resistance data comparable to the NARMS poultry monitoring data are available that would serve as a baseline to allow for meaningful comparison to the 1998, 1999, 2000 and 2001 Poultry NARMS data. [DeGroot (A-200) P.5 L.18-21]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact.

366. *Campylobacter* isolates stored and recovered later for testing can change susceptibility profiles. [DeGroot (A-200) P.5 L.23 – P.6 L.1]

CVM CRITIQUE: This proposed finding is unsupported by the cited testimony. The cited testimony states that Fedorka-Cray (cited as "Fedorka-Cray 2002, Attached") demonstrates the point offered by the proposed finding. The reference list refers to the attached Fedorka-Cray reference as a September 2002 presentation. However, the attached Fedorka-Cray et al., presentation ((A-200) Attachment 3, P. 79 - P.119) actually contains: (1) a presentation by Fedorka-Cray at P.79 - P. 87; (2) a presentation by Englen (title page on P. 88 also includes a citation to "Englen and Kelley, Lett. Appl. Microbiol. 31:421 (2000)"); and (3) a citation on P. 98 to "Englen and Fedorka-Cray, Letters Appl. Microbiol., 2002, In press"). Fedorka-Cray, P.79 - P. 87 does not even address the

specific issue of storage and later recovery of isolates. An abstract of Fedorka-Cray et al. from the 116th AOAC International Meeting on September 22-26 2002 (Exhibit A-200 Attachment 1) does not address that issue either.

367. As the Poultry NARMS program is designed, its data cannot show effects from fluoroquinolone use in poultry. No valid pre-1995 baseline of poultry *Campylobacter* resistance exists for comparison to post-1995 NARMS results. [DeGroot (A-200) P.6 L.3-5]

CVM CRITIQUE: This statement appears to be an unjustified statement of opinion not a statement of fact. The second sentence does not follow from the first. Moreover, the testimony of DeGroot (A-200) P.3 L.18 - P.4 L.1 states that "[f]rom a theoretical standpoint, the sampling protocol of the Poultry NARMS slaughter component is sound."

368. The yearly Poultry NARMS samples have been inconsistent with respect to poultry class and slaughter establishment type, season and geographic region across all years reported 1998 to 2001. [DeGroot (A-200) P.6 L.13-15]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of CVM witness Dr. Tollefson, which shows that, since the beginning of isolate collection through 2001, isolates were collected throughout all seasons and all poultry slaughter houses were included in the sampling. [Tollefson (G-1478) P.9 L.4 - P.12 Table]

380. If the NARMS data are to be used to measure the potential public health threat, and if multiple classes of birds are to be sampled, then the estimates produced must be adjusted to accurately reflect the different contribution each different class of bird makes to the overall campylobacteriosis risk. [DeGroot (A-200) P.7 L.16-19]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

381. Poultry NARMS does not distinguish isolates by chicken type. Thus it is impossible to adjust estimates for the degree of risk posed to the consuming public by different classes of chickens processed at different slaughter facility types. [DeGroot (A-200) P.7 L.19-22]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

384. NARMS poultry carcass rinse specimens for the year 2000 were only collected from January through October. [Tollefson (G-1478) P.10 L.38; DeGroot (A-200) P.8 L.8-9]

CVM CRITIQUE: The proposed finding is not supported. Dr. Tollefson never makes this statement. DeGroot makes the statement but the references cited in his WDT do not match with the statement.

385. *Campylobacter* carriage in chickens varies with the season and resistance patterns of *Campylobacter* carried by chickens also vary by season. [DeGroot (A-200) P.8 L.9-11]

CVM CRITIQUE: This proposed finding does not appear to be supported by the cited testimony. The cited testimony provides two references: "NACMPI 1999-05" and "CVM, 2001." "NACMPI 1999-05" is not listed in the testimony's reference list and "CVM, 2001," which is the CVM Risk Assessment, does not appear to support the suggested hypothesis.

386. Because seasonality plays a role in *Campylobacter* carriage and resistance rates, yearly estimates presented by Poultry NARMS are confounded with seasonal variation. [DeGroot (A-200) P.8 L.11-13]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding

390. Valid surveillance programs ensure that samples representative of the nation are taken if the data is to be used to extrapolate a national prevalence. [DeGroot (A-200) P.9 L.5-6]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

393. Poultry NARMS inappropriately tries to apply geographically limited data to the entire nation without a rational basis. [DeGroot (A-200) P.9 L.6-8]

CVM CRITIQUE: T his proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Moreover, this proposed finding is contradicted by the testimony of Dr. Tollefson (Exhibit G-1478), which states "all federally-inspected slaughter plants in the United States are included in NARMS so that in testing those isolates we are testing products from the plants that produce the majority of the meat and poultry that is derived from health animals and consumed in the U.S." [G-1478, P.8 L.28-33)]

394. A surveillance system must employ consistent laboratory methods in order to provide estimates that are validly comparable over time. [DeGroot (A-200) P.9 L.11-12]

CVM CRITIQUE: This proposed finding is vague and the testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

395. Poultry NARMS employed non-standardized and varying microbiological isolation and testing methods over the reporting years from 1998 to 2001. [DeGroot (A-200) P.9 L.12-14]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

396. Culture and isolation methods can affect subsequent antimicrobial susceptibility test results from the *Campylobacter* recovered. [DeGroot (A-200) P.10 L.4-5]

CVM CRITIQUE: The proposed finding is unsupported by the cited testimony in that, even assuming the cited testimony may support the notion that different culture methods may result in the recovery of different populations, there is no evidence that culture methods affect susceptibility testing results.

397. Resistance estimates resulting from different microbiological methods cannot be compared without first adjusting for the effects of the different methods. [DeGroot (A-200) P.10 L.5-6]

CVM CRITIQUE: The proposed finding is unsupported by the cited testimony in that, even assuming that the testimony of DeGroot (A-200) P.10 L.4-5 may support the notion that different culture methods may result in the recovery of different populations, there is no evidence that culture methods affect susceptibility testing results.

398. The very process of isolating *Campylobacters* for susceptibility testing can select for fluoroquinolone resistance. [DeGroot (A-200) P.10 L.13-14]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion without factual support. The statement is based on the testimony of Dr. Silley (B-1913), and there are no direct data to support it. Furthermore, the proposed finding is contradicted by Exhibit G-403.

403. The National Antimicrobial Resistance Monitoring System ("NARMS") does not provide data that can be interpreted representing general patterns for the entire United States. [DeGroot (A-200) P.13 L.13-18, citing G-644]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony, which purports to quote from Exhibit G-644. The quoted material in DeGroot (A-200) P.13, L.13-18 that is attributed to G-644 is not found in G-644. The first of the two sentences of the quote contain words that do not appear, and do not contain words that appear, in

the actual text of G-644. The second of the two sentences of the quote does not appear to have come from G-644. Furthermore, the proposed finding is contradicted by G-644 P.4, which says, "The human sampling is fairly representative of the human population."

404. NARMS is not designed to link emergent animal resistance and emergent human resistance. [DeGroot (A-200) P.13 L.13-18, citing G-644]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony, which purports to quote from Exhibit G-644. The cited testimony, as well as Exhibit G-644, discusses a "causal" link; omission of the word "causal" changes the meaning of the sentence.

405. Annual NARMS data on *Campylobacter* antimicrobial resistance patterns cannot be meaningfully compared year to year because of differences in sampling patterns. [DeGroot (A-200) P.13 L.13-18, citing G-644]

CVM CRITIQUE: This proposed fact is misleading in that the cited Exhibit G-644 does not contain the quoted portion attributed to it by DeGroot (A-200) P.13 L.13-18.

406. Use of antimicrobials during culture can confound recovery. [DeGroot (A-200) P.12 L.7-8]

CVM CRITIQUE: The cited testimony for this proposed finding states that an abstract of Fedorka-Cray's September 2002 presentation "*Campylobacter*: An Enigma" demonstrates the point offered by the proposed finding. DeGroot (A-200) P.12 L.9-10 also states that the slides from that presentation are attached to the testimony. The slides purported to be from the "*Campylobacter*: An Enigma" presentation (A-200) Attachment 3, P. 79 - P.11-9) actually contain: (1) a presentation by Fedorka-Cray at P.79 - P. 87; (2) a presentation by Englen (title page on P.88 also includes a citation to "Englen and Kelley, Lett. Appl. Microbiol. 31:421 (2000);"); and (3) a citation on P. 98 to "Englen and Fedorka-Cray, Letters Appl. Microbiol., 2002, In press"). Fedorka-Cray, P.79 - P. 87 is titled "*Campylobacter*: An Enigma; however, there is nothing in those pages that corroborates or even appears to address the hypothesis offered in the proposed finding.

407. Further, mixed populations have been observed and aggregation of some strains not only affects speciation, but antimicrobial testing as well." [DeGroot (A-200) P.12 L.8-9]

CVM CRITIQUE: This proposed finding is contradicted by the witness whose testimony is cited here as support for the proposed finding. DeGroot (A-200) P.12 L.8-10 refers to Fedorka-Cray. Fedorka-Cray P.87 (DeGroot (A-200) Attachment 3) is entitled "Problems with Campy ID" and, in bullet-point fashion, questions whether there is confounding of antimicrobial testing and reveals in one instance that the issues are "under study" and in another instance that the answer "depends," without giving further explanation.

409. *C. upsaliensis* is a recently emerged pathogen in immunosuppressed patients as well as infants. [Silley (B-1913) P.34 ¶ 2 (see Goosens et.al.,1990)]

CVM CRITIQUE: This proposed finding of fact is not supported by the testimony. There is no verifiable scientific information to show that *C. upsaliensis* emerged recently as a pathogen in immunosuppressed patients as well as in infants. The cited reference provides no data to suggest this claim, but only report that this species has been isolated in these two patient populations.

410. *C. upsaliensis* is found in high prevalence (27-55%) in dogs and is 11-19% prevalent in cats. [Silley (B-1913) Attachment 1 P.34 ¶ 2]

CVM CRITIQUE: This proposed finding accurately states the numerical results of the cited studies, in which *C. upsaliensis* was found in high prevalence. To state that it is found in high prevalence suggests a universal phenomenon, which is not verifiable from the limited data available.

415. 1998 NARMS poultry data was collected: from May to September 1998, where the samples were taken for the purpose of isolating *Salmonella* under the FSIS HACCP program and were also used by FSIS to isolate *Campylobacter* for susceptibility testing in the NARMS program; and from October 1998 to December 1998, where FSIS *Campylobacter* cultures were obtained from a FSIS *Campylobacter* chicken monitoring program on various classes of young chickens, spent hens, etc., that originated primarily from the Eastern FSJS lab in Athens, GA. [Carnevale (A-199) P.5 L.11-19; Tollefson (G-1478) P.9-10]

CVM CRITIQUE: Part of this proposed finding is contrary to the cited testimony. According to Tollefson (G-1478) P.10 L.8, isolates were received in 1998 beginning in October.

416. 1999 NARMS poultry data was collected: from January 1999 to December 1999 from FSIS *Campylobacter* cultures obtained from a FSIS *Campylobacter* chicken monitoring program on various classes of young chickens, spent hens, etc., that originated primarily from the Eastern FSIS lab in Athens, GA; from January 1999 to October 1999, where *Campylobacter* isolates from the pilot program for a FSIS *Campylobacter* baseline study were utilized; and from November 1999 to December 1999, where *Campylobacter* isolates from a FSIS baseline study were utilized. [Carnevale (A-199) P.5 L.19-26; Tollefson (G-1478) P.9-10]

CVM CRITIQUE: Part of this proposed finding is not supported by the testimony of Tollefson (G-1478) P.12 Table, which does not indicate that isolates from the January to October 1999 pilot program were tested for or included in animal NARMS.

418. 2001 NARMS poultry data was collected from rinsates sent from HACCP testing in slaughter plants to the USDA Agriculture Research Service (ARS) after FSIS isolation of *Salmonella*. ARS then cultured these rinsates for *Campylobacter* and performed

susceptibility testing on recovered isolates. [Carnevale (A-199) P.6 L.8-11; Tollefson (G-1478) P.10-11]

CVM CRITIQUE: Part of this proposed finding is not supported by the testimony of Tollefson (G-1478) P.11 L.5 through P.12 Table, which indicates that the rinsates came from Eastern lab only.

419. 2002 NARMS poultry data was collected from rinsates sent from HACCP testing in slaughter plants after the USDA Agriculture Research Service (ARS) after FSIS isolation of *Salmonella*. ARS then cultures these rinsates for *Campylobacter* and performs susceptibility testing on recovered isolates. [Carnevale (A-199) P.6 L.12-16; Tollefson (G-1478) P.11]

CVM CRITIQUE: Part of this proposed finding is not supported by the testimony of Tollefson (G-1478) P.11 L.5 through P.12 Table, which indicates that the rinsates came from the Eastern lab only.

423. In 1998, 2001 and again in 2002, the animal NARMS program has used HACCP samples as the source of the *Campylobacter* tested. Analysis of *Campylobacter* isolated from HAACP samples will not allow the true prevalence rate of *Campylobacter* on chicken carcasses or their susceptibility patterns to be determined. [Carnevale (A-199) P.7 L.18-22]

CVM CRITIQUE: The second sentence of this proposed finding appears to be an unjustified statement of opinion not a statement of fact and is not supported by any citation to, or evidence in, the record.

424. HACCP samples are not a representative, random sample because the FSIS sampling program has a higher testing rate of poultry processing facilities with higher bacterial contamination. This biases the results of analysis of the samples toward higher levels of bacteria. [Carnevale (A-199) P.8 L.5-9]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact and is not supported by any citation to, or evidence in, the record.

426. CVM contends that the causal relationship between fluoroquinolone use in poultry and increased cases of fluoroquinolone resistance is inferred because of a temporal relationship. [CVM Answer to Bayer Interrogatory 12]

CVM CRITIQUE: CVM notes that such a temporal relationship observed in a number of countries are a partial basis for inferring a casual relationship; however, CVM also relied on other data and information available.

427. There is no clear evidence that resistance to fluoroquinolones has increased over time, especially post licensing, in poultry *Campylobacters*. Moreover, data indicates that resistant poultry isolates were present even before the licensing of fluoroquinolones for use in poultry. [Newell (B-1908) P.14 L.17-20]

CVM CRITIQUE: The proposed finding is contrary to the testimony of the same witness who testified that emerging fluoroquinolone resistance in poultry *Campylobacters* worldwide has been reported subsequent to the licensing of fluoroquinolones for use in poultry. [Newell P.14 L.11-12] See also [Aarestrup (G-1451) P.4-5 and Figure 1] [Endtz (G-1457) P.7 L11 to P9. L6] [Hanninen (G-1458) P.2 - P.6] [Molbak (G-1468) P.8 L.1-28] [Wegener (G-1483 P.20 L18 to P.23 L.15; P.26 L.33; P.27 L.2]

428. Evidence that veterinary use of fluoroquinolones results in the generation of fluoroquinolone resistance in *Campylobacter*, that such resistance is sustained over time, and that such strains can be transmitted to infect humans, is not convincing. [Newell (B-1908) P.39 L.6-8]

CVM CRITIQUE: The proposed finding is contradicted by the testimony cited in CVM's critique to proposed finding of fact 427.

429. CVM's hazard identification and its whole risk assessment fail to assess any evidence for a causal relation between use of enrofloxacin in chickens and adverse human health consequences. [Cox (B-1901) P.26]

CVM CRITIQUE: This statement of opinion is contrary to testimony in this record. Dr. Cox, on page 27, states "That FQ use in animals selects for FQ-r strains in animal microbes is of course not controversial or unexpected." That these fluoroquinolone-resistant bacteria transfer to humans via contact and consumption of poultry and cause adverse consequences is described in Dr. Kassenborg's paper [G-337]. On page 10, Dr. Kassenborg finds that the population attributable risk for fluoroquinolone-resistant *Campylobacter* infections associated with consumption of chicken or poultry at a commercial establishment is 27% among domestically acquired cases. Evidence concerning the adverse human health consequences is given by Marano, et al., [G-394], which indicates that among cases who had not used anti-diarrheal medications, resistance is linked to an average two days increased duration of illness. Molbak [G-1468 P.20-21] describes an extensive study conducted in Denmark which found increased mortality and morbidity associated with fluoroquinolone resistance.

430. Any "temporal relation" between introduction of enrofloxacin and increase in fluoroquinolone-resistant *Campylobacter* rates only shows that some fluoroquinolone-resistant *Campylobacter* rates increased following introduction of enrofloxacin. This is not evidence of causation between the two. [Cox (B-1901) P.26]

CVM CRITIQUE: This proposed finding mischaracterizes the CVM testimonies and exhibits in that it implies that CVM offers the temporal relation as the only scientific

basis rather than as corroboration of the scientific basis for a causal link between the introduction of enrofloxacin and increase in fluoroquinolone-resistant *Campylobacter* rates. The full basis was laid out in the NOOH [G-0935] where it states "CVM has concluded, based on data from surveillance programs, published literature and other sources, that the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant *Campylobacter* on chicken carcasses, and therefore a significant source of fluoroquinolone-resistant *Campylobacter* infections in humans. CVM's conclusion is supported by data establishing a temporal association between the approval of these drugs for use in poultry in the United States and the increase in resistant *Campylobacter* infections in humans. CVM reiterated this point in response to Bayer's Interrogatory 12.

431. CVM has not applied any generally accepted objective methods for identifying causal relations from the available data to discover whether causation is truly present and or to quantitatively estimate causal effects. [Cox (B-1901) P.27]

CVM CRITIQUE: CVM objects to this proposed finding in that it constitutes a statement of opinion that there are "generally accepted objective methods for identifying causal relations from the available data to discover whether causation is truly present and or to quantitatively estimate causal effects." This is contrary to a body of literature, including articles written by Dr. Sander Greenland and Dr. Judea Pearl. Cox relies on the work of Dr. Greenland, citing him in his WDT and on the work of Dr. Pearl, citing him in B-1252. Drs. Greenland, Pearl and Robins say "As realized by Hume centuries ago and reinforced by many authors since, all causal inference is based on assumptions that cannot be derived from observations alone." [Greenland, S., Pearl, J. and Robins, J. (1999) Causal Diagrams for Epidemiologic Research, Epidemiology. 10:37-48]

432. When generally accepted objective tests for identifying causal relations are performed on the available data, they indicate a complete absence of any significant positive causal relation between enrofloxacin use in chickens and fluoroquinolone-resistant campylobacteriosis rates in humans. [Cox (B-1901) P.27]

CVM CRITIQUE: This proposed finding is not supported by the only page cited, and does not identify the allegedly "generally accepted objective tests" it posits. This statement is contrary to the record, see Kassenborg [G-337]. On page 10, Dr. Kassenborg finds that the population attributable risk for fluoroquinolone-resistant *Campylobacter* infections associated with consumption of chicken or poultry at a commercial establishment is 27% among domestically acquired cases.

433. CVM's contention that the introduction of enrofloxacin in poultry in 1996 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1996 is undermined by the fact that fluoroquinolone resistance in multiple bacteria in multiple countries has increased following the introduction and over-prescription of fluoroquinolones in human medicine, whether or not enrofloxacin has been used in food animals. [Cox (B-1901) P.27, citing B-119]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibit B-119 [which is also G-6]. The introduction states that "Extensive use and misuse of these compounds in both human and veterinary medicine led to the emergence and spread of resistant strains."

434. CVM's contention that the introduction of enrofloxacin in poultry in 1995 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1995 is undermined by the fact that in no case has approval and use of enrofloxacin in other countries been demonstrated objectively to have influenced the existing trend of fluoroquinolone resistance in multiple bacteria in humans after the introduction and over-prescription of fluoroquinolones in human medicine. [Cox (B-1901) P.27]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibit B-119 [which is also G-6]. The conclusion of the section on *Campylobacter* states "Fluoroquinolone-resistant *Campylobacter* species have been isolated from both humans and animals and are clearly linked to fluoroquinolone use in veterinary medicine."

435. CVM's contention that the introduction of enrofloxacin in poultry in 1996 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1996 is undermined by the fact that in no case has approval and use of enrofloxacin in other countries been demonstrated objectively to have had any impact on the speed or magnitude of increase in fluoroquinolone-resistant campylobacteriosis in humans following the introduction of fluoroquinolones in human medicine. [Cox (B-1901) P.27]

CVM CRITIQUE: This proposed finding would contradict the testimony of Smith [G-1473], Endtz [G-1457], as well as the Georgetown risk assessment [Exhibit G-29 and B-147]. Dr. Smith's testimony at paragraphs 32-33 provides a summary of other exhibits which report substantial increases in the prevalence of fluoroquinolone-resistance among human cases of campylobacteriosis following the introduction of fluoroquinolones for use in veterinary medicine in various countries. These include Spain, where resistance rose from 6.8% to 29% in the one year following the introduction of enrofloxacin in 1990 [G-734] and by 1993 the prevalence had risen to 50% [G-491] and the United Kingdom where there was an increase to 12% three years following introduction of the veterinary products [G-632]. Dr. Endtz describes in paragraphs 18-10 the history of increasing fluoroquinolone-resistance in the Netherlands following the introduction of enrofloxacin in 1987. There was no resistance in man or animals prior to that time [G-190]. By 1989, the prevalence of resistance had risen to 11% in humans and 14% among poultry-derived strains. The Georgetown risk assessment Table 2 depicts (increasing) prevalence rates of resistance among human isolates from various countries as a function of years since the corresponding veterinary approval. The testimony of Dr. Endtz (G-1457 P.8-9) notes that in Australia there is human-drug exposure to fluoroquinolone, but not animal-drug use of it; and little fluoroquinolone-resistant *Campylobacter*.

436. CVM's contention that the introduction of enrofloxacin in poultry in 1995 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1995 is undermined by the fact that the increase in fluoroquinolone-resistant campylobacteriosis over time has

been comparable in countries with and without enrofloxacin use in broilers. [Cox (B-1901) P.27, citing B-29]

CVM CRITIQUE: This proposed finding is contrary to its own citation. B-29 is Gaudreau and Gilbert. They analyze fluoroquinolone-resistance in human hospital isolates of *Campylobacter* from Quebec from 1985-86 (0%), 1992-93 (3.5%), and 1995-97(12.7%). B-29 does not mention veterinary medical use of fluoroquinolones. It is a mischaracterization of the problem to stress the use of enrofloxacin in broilers in this instance since enrofloxacin was approved as an egg dip in turkeys in Canada until its removal in 1997. It should be noted that B-29 finds a significant increase between 1995 97.7%) to 1996 (19.6%), but not from 1996 to 1997 (12.7%).

437. CVM's contention that the introduction of enrofloxacin in poultry in 1995 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1995 is undermined by the fact that within each year, changes in *Campylobacter* carriage rates in humans tend to precede changes in *Campylobacter* carriage rates in chickens. This makes it unlikely that the human CP rates are caused primarily by the chicken rates and also provides some evidence for reverse causation (i.e., human *Campylobacter* may help cause chicken *Campylobacter*, perhaps through contaminated water, or perhaps a common environmental source contributes to both). [Cox (B-1901) P.27-28; See also Newell (G-1908) P.26 L.12-20)]

CVM CRITIQUE: This proposed finding is undermined by the finding reported in G-376 and recounted in Smith [G-1473], where in Taiwan fluoroquinolone-resistant *Campylobacter* were found in untreated pediatric patients while at the same time 92% of *C jejuni* and 91% of *C. coli* found on retail chicken were fluoroquinolone-resistant. It is also undermined by the fact that resistance problems that are rampant in the human population, e.g., Vancomycin-resistant *Enterococci* (VRE), are not found in poultry or other animals. Linden, et al., Exhibit B-488, first paragraph says "The incidence of infections due to strains of *enterococcus* resistant to vancomycin and teicoplanin has increased dramatically since 1986" in the United States and they list five references to illustrate the point. Meanwhile, despite the fact that *enterococcus* are ubiquitous, there are no VRE found in animals in the United States, Kruse [B-468, page 5, second paragraph in the left column] says "In studies from the United States where avoparcin has never been approved, and from Sweden where avoparcin has not been used for the past 12 years, no VRE were found in samples from animals when selective techniques were used." It should be noted that the samples from animals were taken nearly 10 years after the human drug (vancomycin) had been approved.

438. A study in Sweden published in 1981, long before fluoroquinolones had been introduced, showed that 39% of *C. jejuni* isolates from chickens were then already resistant to nalidixic acid, as were 11% of human isolates. [Gonder, (A-201 P.14 L.9-11; citing B-1851 (Svedhem 1981)]

CVM CRITIQUE: This proposed finding is contradicted by exhibit G-700 (P.1) which states that nalidixic acid is a quinolone not a fluoroquinolone.

440. There exist temporal patterns that refute the hypothesis that human fluoroquinolone-resistant *Campylobacter* rates are caused by enrofloxacin use in poultry. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Cox's WDT states, on page 29 at the second bullet, that 'when CVM asserts that there is a "temporal pattern" relating enrofloxacin use to human FQ-r CP cases, they are looking at only one small part of the total evidence on temporal patterns. Other parts of the temporal pattern suggest that human FQ-r Cp rates are not caused by enrofloxacin use.' Suggestion is not refutation. Dr. Cox acknowledges that there is evidence of a temporal pattern even though he interprets the evidence differently.

441. Analyzing airsacculitis condemnation data (as a proxy for enrofloxacin use) in Minnesota in relation to human fluoroquinolone-resistant *Campylobacter* rates in Minnesota from 1996-1999 shows that within each year, human fluoroquinolone-resistant *Campylobacter* rates are negatively correlated with recent airsacculitis condemnation rates in chickens. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is without factual basis in the record. Dr. Cox states that he analyzed airsacculitis condemnation data in Minnesota in relation to human fluoroquinolone-resistant *Campylobacter* rates in Minnesota from 1996-1999. Only the supposed results of the analysis are presented in the WDT. There is no citation to other exhibits on the docket where the analysis is described in sufficient detail to assess whether or not a negative correlation with recent airsacculitis is obtained. There is also no discussion about the validity of airsacculitis condemnation data as a proxy for enrofloxacin use. It is not clear how the timing of peak airsacculitis condemnation rates relate to enrofloxacin use since different flocks will be experiencing their colibacillosis at different time intervals relative to their slaughter. It is also not clear how the lag between slaughter, consumption, and illness onset were factored into the analysis. Finally, it is not clear what the food distribution chain is for poultry slaughtered in Minnesota. The Smith article [G-589] looks at resistance in retail meats from Minnesota, the product to which the population was exposed.

442. Analyzing airsacculitis condemnation data (as a proxy for enrofloxacin use) in Minnesota in relation to human fluoroquinolone-resistant *Campylobacter* rates in Minnesota from 1996-1999 shows that within each year, human fluoroquinolone-resistant *Campylobacter* rates are significantly positively correlated with future airsacculitis condemnation rates in chickens, suggesting that use of enrofloxacin in chicken does not cause the human fluoroquinolone-resistant *Campylobacter*. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is without factual basis in the record. Dr. Cox states that he analyzed airsacculitis condemnation data in Minnesota in relation to human fluoroquinolone-resistant *Campylobacter* rates in Minnesota from 1996-1999. Only the supposed results of the analysis are presented in the WDT and there is no

citation to other exhibits on the docket where the analysis is described in sufficient detail to assess whether or not a positive correlation with future airsacculitis is obtained.

Secondly, there is no discussion about the validity of airsacculitis condemnation data as a proxy for enrofloxacin use. It is not clear how the timing of peak airsacculitis condemnation rates relate to enrofloxacin use since different flocks will be experiencing their colibacillosis at different time intervals relative to their slaughter. It is also not clear how the lag between slaughter, consumption, and illness onset were factored into the analysis. Finally, it is not clear what the food distribution chain is for poultry slaughtered in Minnesota. The Smith article [G-589] looks at resistance in retail meats from Minnesota, the product to which the population was exposed.

443 Nonparametric nonlinear regression analysis of the 1996-1999 Minnesota data suggests that there was an increase in the slope of the human fluoroquinolone-resistant *Campylobacter* rate (a change point) in early 1998, years after the introduction of fluoroquinolones in chickens. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is without factual basis in the record. Dr. Cox states that he did this analysis, but only a one-line result is provided.

444. Change points occurring at any time in the interval between 1995 and 2001, such as the one identified in 1998 by a nonparametric nonlinear regression analysis of the 1996-1999 Minnesota data can explain the types of "temporal relations" and "trends" that CVM and its witnesses refer to (e.g., Molbak testimony, G-1468, P.8, paragraph 24). [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is a statement of opinion without factual basis in the record. It is a given that there will be change points in a time series that will represent fluctuation in a "random walk." It is the general drift in the series which is interpreted as trend.

445. The increase in the slope of the human fluoroquinolone-resistant *Campylobacter* rate (a change point) in early 1998 is not related to anything that happened in 1995 or 1996, including enrofloxacin introduction. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is contradicted by the entirety of the NOOH and CVM testimony. based upon the unsupported "change point." Alleged (and unsupported above. Read carefully, this proposed finding is an allegation that thc increase in human fluoroquinolone-resistant *Campylobacter* in 1998 "is not related to anything that happened in 1995 or 1996."; i.e., that some events tin time are not related to anything two years earlier.

446. Interpreting a statistically non-significant increase in prevalence ratio between 1997 and 2001 as evidence for an effect caused by a product introduced in 1995 is not scientifically valid. [Cox (B-1901) P.29, referring to Molbak (G-1468) P.8 L.29-32]

CVM CRITIQUE: This proposed finding is misleading because the statement is incomplete. Cox says "Interpreting a statistically non-significant (Molbak, ibid. line 32, after excluding the outlier, CT) increase in prevalence ratio between 1997 and 2001 as evidence for an effect caused by a product introduced in 1995 would not be justified." The parenthetical statement that was omitted refers to a second way of evaluating the data. The initial analysis results in a highly significant result (95% CI for the prevalence ratio is 1.23-3.19 with a difference test $p < 0.008$) and the point of the second analysis was to indicate that the prevalence ratio estimate was fairly robust with respect to the results in CT, which Cox but not Molbak labels an outlier. The prevalence ratio with CT removed is 0.95-2.73, which means that the initial finding was not totally driven by CT (with 14 %, 30.2%, 8.9% and 19.4% in 1998, 1999, 2000, and 2001, respectively).

447. Fluoroquinolone-resistant campylobacteriosis trends have increased in countries without substantial enrofloxacin use. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony and it is also without support in the record. Cox says on this page "It would be desirable to explain why FQ-r CP trends have also increase in countries without substantial enrofloxacin use and in species that are not prescribed enrofloxacin." Cox does not list any countries where he claims that this has happened or cite to an exhibit with such a list. He implies, but does not actually allege in this cite, that there are any such countries.

448. CVM's contention that the introduction of enrofloxacin in poultry in 1995 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1995 is undermined by the fact fluoroquinolone-resistant campylobacteriosis trends have also increased in countries without substantial enrofloxacin use. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. It appears to be the same proposal as 447 except this one is framed in terms of undermining a CVM contention. It is also without support in the record. Cox says "It would be desirable to explain why FQ-r CP trends have also increase in countries *without* substantial enrofloxacin use and in species that are *not* prescribed enrofloxacin." Cox does not document any countries where he claims that this has happened or cite to an exhibit with such documentation.

449. Fluoroquinolone-resistant campylobacteriosis trends have also increased in species that are not prescribed enrofloxacin. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. It appears to by the same proposal as 447 except that this proposed finding substitutes "species" for "countries" not prescribed enrofloxacin. It is also without support in the record. Cox says "It would be desirable to explain why FQ-r CP trends have also increase in countries *without* substantial enrofloxacin use and in species that are *not* prescribed enrofloxacin." Cox does not document any species where he claims that this has happened or cite to an exhibit with such documentation.

450. CVM's contention that the introduction of enrofloxacin in poultry in 1995 is the probable cause of the increase in fluoroquinolone-resistance in humans after 1995 is undermined by the fact fluoroquinolone-resistant *Campylobacter* trends have also increased in species that are not prescribed enrofloxacin. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. It appears to by the same proposal as 449 except it is framed in terms undermining a contention of CVM. It is also without support in the record. Cox says "It would be desirable to explain why FQ-r CP trends have also increase in countries *without* substantial enrofloxacin use and in species that are *not* prescribed enrofloxacin." Cox does not document any species where he claims that this has happened or cite to an exhibit with such documentation.

451. CVM has never presented, nor is there evidence, any analysis showing that introducing fluoroquinolones into animal use has had any impact whatsoever on trends or the time series of human fluoroquinolone-resistant campylobacteriosis rates. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The closest statement to this one on page 42 of Cox's testimony is "As far as we know, *there has never been any analysis showing that introducing FQ into animal use has had any impact whatsoever on trends* or the time series of human FQ-r CP rates." This is contradicted by the WDT of Aaerestrup G-1451 P.4 and Fig. 1; Wegener G-1483 P.21 and P.26 L.37-39.

452. Without an analysis showing that introducing fluoroquinolones into animal use has had an impact on trends or the time series of human fluoroquinolone-resistant campylobacteriosis rates, there is no sound basis in time series analysis or statistical methodology for inferring that fluoroquinolone use in poultry is a cause of observed fluoroquinolone resistance in human campylobacteriosis cases. [Cox (B-1901) P.42]

CVM CRITIQUE: This proposed finding is a statement of opinion without factual basis in the record. It is dependant upon its presumption in previous proposed findings of fact that there have been no valid demonstrations of trends since the introduction of fluoroquinolones into animal use. The testimony of Molbak [(G-1468) P.8 L.29-32] illustrates a trend in the NARMS data using age and site adjustment from 13.4% in 1997 to 19.4% in 2001; the testimony of Smith [(G-1473) paragraph 16] illustrates a trend in Minnesota data from 1.3% resistance in 1992 to 10.2% resistance to nalidixic acid in 1998.

453. Data on human fluoroquinolone-resistant campylobacteriosis rates from before the introduction of enrofloxacin for poultry use (such as the data reported in of Smith et al., 1999 and in Nachamkin et al., 2002) refute the hypothesis of a change in the time series of human fluoroquinolone-resistant campylobacteriosis rates in 1995 or 1996. [Cox (B-1901) P.42, referring to G-589 (Smith 1999) and G-1517 (Nachamkin 2002); See also DeGroot (A-200) P.55 L.20 – P.59 L.13]

CVM CRITIQUE: This proposed finding is contrary to the testimony of the cited witnesses, Drs. Smith and Nachamkin. It also contradicts the interpretation of the trends

in time adopted in Anderson, et al., [B-147], the Georgetown risk assessment. In the Georgetown risk assessment, Anderson relies on the Smith testimony and data from other countries to estimate the rate of increase in fluoroquinolone-resistance rates in humans by year since the introduction of fluoroquinolones for use in veterinary medicine.

454. Based on data on human fluoroquinolone-resistant campylobacteriosis rates from before the introduction of enrofloxacin for poultry use (such as the data reported in of Smith et al., 1999 and in Nachamkin et al., 2002), it appears that the trend of increasing human fluoroquinolone-resistant campylobacteriosis rates occurred before the introduction of enrofloxacin and continued without change when enrofloxacin was introduced. [Cox (B-1901) P.42, referring to G-589 (Smith 1999) and G-1517 (Nachamkin 2002)]

CVM CRITIQUE: This proposed finding is contrary to the testimony of the cited witnesses, Drs. Smith and Nachamkin. It also contradicts numerous reports from European countries where the same trends were noted after their approvals of veterinary fluoroquinolones, e.g., Endtz [G-190] from the Netherlands and Wegener [G-1483]. On page 23, paragraph 106 of his WDT, Wegener testifies "The increase in *Campylobacter* resistant to quinolones in broiler chicken in Denmark was paralleled by an increase in human infections with *Campylobacter* resistant to quinolones. This is consistent with the pattern observed in many other countries. In Denmark, this increase has occurred later than in many other European countries, but, as in other countries, the onset of the increase has occurred shortly after the licensing of fluoroquinolones for use in food animals including poultry. The different times of the onsets of the increase in levels of resistance in different countries, and the common association with the licensing of quinolones for food animals in the countries, in my opinion, strongly support that veterinary use of quinolones and not the medical use of quinolones is the driving factor behind the increase in animals as well as in humans."

455. In the Nachamkin et al. data, human fluoroquinolone-resistant campylobacteriosis rates were lower in 1996 and 1997 than in 1995, and a significant (but unexplained) increase did not occur until 2000. [Cox (B-1901) P.42, referring to G-1517 (Nachamkin 2002); DeGroot (A-200) P.58 L.5-17; Newell (B-1908) P.42 L.1-5]

CVM CRITIQUE: This proposed finding is misleading. It is given out of context and as such appears critical of the Nachamkin report as though it had stated that the data were a compelling indication of trend. The following sentence in that report says that "Such time series trend data are not compelling because they do not adjust for other changes (e.g., in travel patterns, ...etc. over the same period." Nachamkin's report noted this very thing: "The reasons for such a dramatic increase in FQ resistant jejuni in our population are unknown....Whether this is indicative (sic) of foreign travel patterns by our patients is unknown."

456. Human NARMS data for fluoroquinolone-resistant *Campylobacter* show a large degree of heterogeneity within states. [Cox (B-1901) P.43]

CVM CRITIQUE: This proposed finding as to "heterogeneity within states" is not supported by the only citation supplied. It cannot be evaluated in any event, because no definition for "large degree" is established.

457. Human NARMS data for fluoroquinolone-resistant *Campylobacter* show that there is not an increasing trend of fluoroquinolone-resistant *Campylobacter* in some states. [Cox (B-1901) P.43; DeGroot (A-200) P.50 L.6 – P.54 L.10]

CVM CRITIQUE: This proposed finding that no state has an increasing trend is contradicted by the next proposed finding from [Cox (B-1901) P.43].

459. Although the debate over fluoroquinolone-resistant *Campylobacter* has been shaped largely by data from MN, this data is not representative of the general US population, nor of other states such as NY. [Cox (B-1901) P.43, referring to G-589 (Smith 1999)]

CVM CRITIQUE: This proposed finding is a statement of opinion. There is no support on the record for the conclusion that the debate over FQ-r CP has been shaped largely by data from MN.

460. Using trend data from Europe, one could find a "temporal relationship" (by CVM's criteria) between bans on animal antimicrobials in Europe and subsequent trends of increasing campylobacteriosis and salmonellosis rates in Europe. [Cox (B-1901) P.44]

CVM CRITIQUE: This proposed finding is a statement of opinion without even alleged support on the record. There is no support on the record for the conclusion.

461. CVM's finding of a "temporal relationship" to support its contention that use of fluoroquinolones in poultry causes increased fluoroquinolone-resistant campylobacteriosis in humans is an instance of a well-known logical fallacy (the ex post or false cause fallacy) and is not supported by more detailed data analysis. [Cox (B-1901) P.44]

CVM CRITIQUE: This proposed finding is contrary to testimony presented by CVM, which the proposed finding fails to specify. It is not a fallacy to note the temporal relationship, and the WDT of Aarestrup, Endtz, Hanninen, and Wegener as cited in critique 451 above.

462. CVM has not cited any facts or data indicating that fluoroquinolone use in chickens explains any part of the observed trends or levels of fluoroquinolone-resistant campylobacteriosis in humans in the US. [Cox (B-1901) P.54]

CVM CRITIQUE: This proposed finding is contrary to the record. See, among others, Kassenborg WDT (G-1460) P.8 L1 – P.10 L.19.

463. From 1995 to present, per capita chicken consumption in the United States has increased every year compared to the prior year, and over all has increased 12%. [Cox (B-1901) P.28]

CVM CRITIQUE: This proposed finding is not supported or even mentioned by the page cited.

464. Fluoroquinolone-resistant *Campylobacter* were identified in humans before 1995, before fluoroquinolones were approved for use in any food animal, including poultry. [DeGroot (A-200) P.59 L.14 – P.60 L.11]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit G-191 P.3, which shows that fluoroquinolones were approved for use in food animals, including poultry, in a number of countries prior to 1995.

465. In 1988 Barrett found 5% quinolone resistance in *Campylobacter jejuni* isolated from humans, before fluoroquinolones were approved for use in any food animal, including poultry. [Barrett (G-1453) P.3 L.3-10; G-1609; Cox (B-1901) P.71]

CVM CRITIQUE: The proposed finding is misleading because it is phrased so as to suggest that it is unusual that quinolone resistance appeared before fluoroquinolone approval.

466. Kiehlbach found 12% quinolone resistance in *Campylobacter* isolated from humans from August 1992 to April 1995, before fluoroquinolones were approved for use in any food animal, including poultry. [DeGroot (A-200) P.59 L.18-20, citing B-39]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit G-191 P.3, which shows that fluoroquinolones were approved for use in food animals, including poultry, in a number of countries prior to 1995. Since B-39 does not appear to be limited to domestically acquired cases, the resistance may have originated from poultry treated with a fluoroquinolone.

467. In 1992 Smith found 1.3 % fluoroquinolone resistance in *Campylobacter* isolated from humans, and 6% resistance in isolates from 1995, both before fluoroquinolones were approved for use in any food animal, including poultry. [Cox (B-1901) P.34; See also G-589]

CVM CRITIQUE: This proposed finding is not supported by the cited page and is misleading in that it attempts to suggest that fluoroquinolone resistance in humans was on the rise in the United States prior to approval of fluoroquinolones for use in poultry. But the values reported include foreign travelers. As indicated in G-589, page 4, Table 1 in 1996-1997 (years when travel status was investigated in a study) comparing cases with fluoroquinolone-resistant campylobacteriosis to cases (75% who had foreign travel histories; 36% had traveled to Mexico) with fluoroquinolone-sensitive campylobacteriosis (23% who had foreign travel histories; 12% had traveled to Mexico).

It is highly likely that residents of Minnesota traveled to these foreign countries in 1995. Foreign travel to countries where fluoroquinolones were being used in food animals is a confounder responsible for most of the resistance seen prior to the approvals in the United States. When the effect of this confounding is removed, increasing resistance in domestically-acquired cases is seen to be concurrent with veterinary use of fluoroquinolones.

468. Williams found 3.3% quinolone resistance in *Campylobacter* isolated from humans in 1993, before fluoroquinolones were approved for use in any food animal, including poultry. [DeGroot (A-200) P.59 L.22 – P.60 L.4, citing B-67]

CVM CRITIQUE: The proposed finding is misleading. The cited Exhibit B-67 is an abstract describing an enteritis outbreak in a nursing home in New York in 1993. Cases in this report were outbreak related, limited to a residential facility, and involved elderly individuals (between 86 and 97 years of age); no prior antibiotic treatment history was provided for the cases. As noted by the abstract's author, "The appearance of quinolone resistance in Campylobacter strains maybe related to its increasing use in humans and in the poultry industry."

469. Nachamkin found over 20 % fluoroquinolone resistance in *Campylobacter* isolated from humans in 1995, before enrofloxacin was approved and sarafloxacin was actively marketed for use in any food animal, including poultry. [Cox (B-1901) P.34; See also G-1517]

CVM CRITIQUE: This proposed finding is not supported by the cited page and is misleading in the same way that proposed finding 467 is. It is a repeat of proposed finding 455. It is misleading when taken out of context. In a following sentence, Cox also says that "Such time series trend data are not compelling because they do not adjust for other changes (e.g., in travel patterns, . . . etc.... over the same period." [B-1901 P.42] Nachamkin's report noted this very thing: "The reasons for such a dramatic increase in FQ resistant jejuni in our population are unknown ....Whether this is indicative [of] foreign travel patterns by our patients is unknown." [G-157 P.6]

470. CVM has not used any scientifically accepted methodologies for drawing causal inferences from time series, trend data, and pre-approval/post-approval comparisons to support its contention that use of fluoroquinolones in poultry causes increased fluoroquinolone-resistant campylobacteriosis in humans. [Cox (B-1901) P.44]

CVM CRITIQUE: This proposed finding is not supported by the cited page (which refers to "formal statistical tests") and is contradicted by the testimony of Dr. Smith [G-1473 figure at the top of page 8] and similarly in his article [G-589, page 3 Figure 1] where he shows that both the peaks in the first quarter, indicative of resistance more likely attributed to foreign travel, and the valleys in the third quarter, indicative of resistance more likely to be domestically acquired from chicken, increase from the third quarter of 1995 onward. The first United States approval of a fluoroquinolone for use in poultry was in August, 1995.

471. Applying scientifically accepted methodologies for drawing causal inferences from time series, trend data, and pre-approval/post-approval comparisons to examine CVM's contention that use of fluoroquinolones in poultry causes increased fluoroquinolone-resistant campylobacteriosis in humans demonstrates that a causal inference is not justified. [Cox (B-1901) P.44]

CVM CRITIQUE: This proposal is a statement of opinion not supported in the record. It is contradicted by Drs. Kirk Smith and Kare Molbak. Dr. Kirk Smith [G-1473] testifies to the trend in increasing nalidixic acid resistance, which is indicative of shifts in susceptibility to fluoroquinolone, in Minnesota from 1.3% in 1992 to 10.2% in 1998 [paragraph 16]. By using a case-cases study, he is able to determine that this increase exceeds that which can be ascribed to foreign travel and is coincident with the approval of fluoroquinolones for use in poultry in the United States. This same trend is echoed in the NARMS data and was analyzed carefully by Dr. Molbak. He summarizes his finding of a 61 % resistance rate in 2001 compared to 1997 in his testimony [G-1468] on page 8 paragraphs 23-24. The Minnesota finding is important because it includes data from 1992 before fluoroquinolones were approved for veterinary use. The NARMS data which was collected annually from 1997 onward is important because it covers multiple sites in the United States.

475. A causal analysis (conditional independence tests for causality (e.g., Shipley, 2000)) on the data sets from the CDC 1998 - 1999 *Campylobacter* Case-Control study (Friedman et al., 2000), Smith et al. (1999), and Effler et al. (2001), indicate that there is no detectable causal relation between chicken consumption and fluoroquinolone-resistant campylobacteriosis rates in people. [Cox (B-1901) P.45, referring to G-1644 (Friedman 2000), G-589 (Smith 1999) and G-185 (Effler 2001)]

CVM CRITIQUE: This is not a proposed finding of fact, but is a statement of opinion that the causal analysis in the Cox testimony is valid. There is no support for that opinion on the record. CVM is not in agreement that the analysis is valid. Furthermore, the conclusions of this invalid analysis are contradicted by the cited Friedman, et al., [G-1644] exhibit. On pages 13-14 of G-1644, the authors say that a retrospective survey was conducted in four FoodNet sites in 1997 (this is the pilot case control study) and determined that although foreign travel was identified as a risk factor for fluoroquinolone-resistant infections, the majority of the patients surveyed acquired heir infections in the United States and these infections were not associated with previous fluoroquinolone use. She says "Reports from Europe suggest that the rise in fluoroquinolone-resistant *Campylobacter* isolations in humans is associated with fluoroquinolone use in poultry, which has led to fluoroquinolone-resistant *Campylobacter* strains in poultry which have spread to humans via the food chain." Effler [G-185, page 2, top of right column] reports that it is consumption of chicken prepared by a commercial food establishment that is significantly associated with illness caused by *Campylobacter*. The Effler exhibit never mentions resistance to any antibiotic.

476. CVM has not developed any causal graph models or path analysis models from data that involve fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, including data sets from the CDC 1998 - 1999 *Campylobacter* Case-Control study (G-1644), Smith et al. (G-589), and Effler et al. (G-185). [CVM's Answer to Bayer's Interrogatory 17]

CVM CRITIQUE: This proposed finding is a subjective interpretation of CVM's response to Interrogatory 17. In response to the Interrogatory, CVM listed the information which they used to construct a path backwards from the adverse health outcome to its likely sources. The path was based on scientific plausibility. CVM populated the path with data from FoodNet, NARMS, and the CDC 1998-1999 *Campylobacter* Case-Control study as well as FSIS and ERS. The Bayer interrogatories concerning causal graph models persisted in couching the question in terms of analysis of "data that involve fluoroquinolone use in chickens." Essentially this requires CVM to do the impossible since Bayer is well aware that such data are not available to CVM.

477. Causal graph modeling for the CDC 1998 - 1999 *Campylobacter* Case-Control study data set (G-1644) and the Smith et al. (G-589) case-control data set, refutes the hypothesis that chicken consumption is a likely cause of campylobacteriosis cases or fluoroquinolone-resistant campylobacteriosis cases in humans. [Cox (B-1901) P.47, citing B-1020 and B-1252]

CVM CRITIQUE: This proposal is not a finding of fact, but is a statement of opinion that the causal analysis in the Cox testimony is valid. There is no support for that opinion on the record. The findings of the Cox causal model are contradicted by much evidence. The Smith [G-589] exhibit shows in Figure 1 that both peaks (travel-associated) and valleys (domestically-acquired) fluoroquinolone-resistant campylobacteriosis cases rose starting in fall of 1995 after the introduction of veterinary fluoroquinolones. Exhibit G-1644 does not have results from the 1998-1999 *Campylobacter* Case-Control study, but it does provide support the idea that fluoroquinolone rates increased in Europe and the United States after the introduction of veterinary fluoroquinolones. On pages 13-14 of G-1644, the authors say that a retrospective survey was conducted in four FoodNet sites in 1997 (this is the pilot case control study) and determined that although foreign travel was identified as a risk factor for fluoroquinolone infections, the majority of the patients surveyed acquired their infections in the United States and these infections were not associated with previous FQ use. Friedman says "Reports from Europe suggest that the rise in FQ-r *Campylobacter* isolations in humans is associated with fluoroquinolone use in poultry, which has led to fluoroquinolone-resistant *Campylobacter* strains in poultry which have spread to humans via the food chain." [G-1644 P.14]

479. Application of formal statistical tests for omitted explanatory variables and/or confounders in analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans explains away 100% of the campylobacteriosis and fluoroquinolone-resistant campylobacteriosis risks that CVM attributes to chicken. [Cox (B-1901) P.47]

CVM CRITIQUE: This proposal is not a finding of fact but is a statement of opinion that the analysis in the Cox testimony is valid. There is no support for that opinion on the record. The findings of the Cox causal model are contradicted by an exhibit by Kassenborg [G-337] where at the top of page 10, she finds a population attributable fraction of 27% for eating chicken or turkey at a commercial establishment, among domestically-acquired cases. This finding is based on a multivariable analysis that began with variables that had been identified univariately as being associated with having a resistant infection rather than being a well control. These other variables were: eating in a nonfast food restaurant, taking antacids, and eating nonpoultry meat at home. In this model, eating chicken or turkey at a commercial establishment was the only variable that was independently associated with illness. [G-377 P.9]

480. If any confounder or combination of confounders fully explains away an observed positive relation between chicken consumption and campylobacteriosis risk or fluoroquinolone-resistant campylobacteriosis risk, then banning enrofloxacin could reduce the prevalence of fluoroquinolone-resistant *Campylobacter* in chicken without affecting risk to humans at all. [Cox (B-1901) P.49]

CVM CRITIQUE: This is a statement of opinion. There are potentially many other factors associated with truly causal factors that may appear "to explain away" a positive relation between a truly causal factor and an outcome of interest, but those other factors would not be causal. This is why CVM relied on scientific information in addition numbers in datasets to evaluate the association of fluoroquinolone use in poultry and increasing resistance in human cases. As indicated in the response to Bayer's proposed finding of fact 431, Drs. Greenland, Pearl and Robins state "As realized by Hume centuries ago and reinforced by many authors since, all causal inference is based on assumptions that cannot be derived from observations alone."[Greenland, S., Pearl, J. and Robins, J. (1999) Causal Diagrams for Epidemiologic Research, Epidemiology. 10:37-48]

481. The effects of confounders (non-causal statistical associations) must be removed in order to isolate the true causal relation (probably negative) between fluoroquinolone use in chickens and risk of campylobacteriosis and fluoroquinolone-resistant campylobacteriosis illness-days in people. Until corrected for confounders, data sets from the CDC 1998 - 1999 *Campylobacter* Case-Control study (G-1644), Smith et al. (G-589), and Effler et al. (G-185) cannot be interpreted or used to predict what human health effects will be caused by actions such as withdrawing the NADA for enrofloxacin. [Cox (B-1901) P.49]

CVM CRITIQUE: The second sentence of this proposal is an opinion, not a fact, that the effects of confounders must be removed to get a true picture of relationships is generally recognized as true. The unstated controversy in this proposed "finding" is over what methods of doing so would be acceptable. The 1998-1999 *Campylobacter* Case-Control study has had many analyses which were conducted to remove the effects of confounders. For example, the multivariable analysis of Kassenborg [G-337] mentioned in proposed finding of fact 479 finds eating chicken or turkey at a commercial

establishment to be the sole independent predictor of having fluoroquinolone-resistant campylobacteriosis among domestically-acquired cases. Smith [G-589, page 4, right column] reports that resistance among domestically-acquired cases increased from 0.8% in 1996 to 3.0% in 1998 thereby removing the confounding of foreign travel. Without removing this confounder, the rate of resistance in 1998 is 10.2% as reported in the abstract and on page 3. Effler [G-185, page 3, Table 2] provides the results of an analysis that takes confounders into account in two ways. The study design matched subjects by age and telephone exchange thereby controlling for these factors. Then a reverse stepwise regression was used to remove variables that were not independently associated with being a case from among approximately 15 variables that were univariately associated.

482. When data sets from the CDC 1998 - 1999 *Campylobacter* Case-Control study (G-1644), Smith et al. (G-589), and Effler et al. (G-185) are corrected for confounders, no association between chicken consumption and increased campylobacteriosis risk or fluoroquinolone-resistant campylobacteriosis risk remains. [Cox (B-1901) P.49, citing B-1252]

CVM CRITIQUE: This proposed finding is a statement of opinion that presumes that only the analysis presented in B-1901 could be the correct one. As indicated in the critique of proposed finding of fact 481, the cited data sets were analyzed by methods that corrected for confounders, and contrary to the proposed finding, associations between chicken consumption and increased campylobacteriosis risk or fluoroquinolone-resistant campylobacteriosis risk did remain.

483. Attributable fraction calculations do not in general identify, adjust for, or remove the effects of confounders or other risk factors. [Cox (B-1901) P.49, P.62]

CVM CRITIQUE: This proposed finding is a statement of opinion. It is contradicted by the Kassenborg exhibit [G-337] where, at the end of page 9 and the top of page 10, she finds a population attributable fraction of 27% for eating chicken or turkey at a commercial establishment, among domestically-acquired cases. This attributable fraction is based on the multivariable analysis finding that this was the only risk independently associated risk factor.

484. Causal graph modeling allows the effects of confounders to be modeled and the direct causal contribution of chicken consumption to campylobacteriosis risk to be isolated. Applying this technique shows that removing the effects of confounding removes the entire association between chicken consumption and human campylobacteriosis risk. [Cox (B-1901) P.49, citing B-1020 and B-1252]

CVM CRITIQUE: This proposal is not a finding but is a statement of opinion. It presumes that the causal graph modeling is one correctly. The findings of the proposed analysis are contradicted by Friedman [G-1488], Table 4, page 23 which shows that the highest odds ratio in the multivariable analysis is for chicken eaten at a restaurant, with

an associated attributable fraction of 24%. This is in addition to the contradictory evidence cited in the response to proposed finding of fact 481.

485. CVM's estimation of a non-zero risk between chicken consumption and human campylobacteriosis is based entirely on failure to properly correct for confounders. [Cox (B-1901) P.49]

CVM CRITIQUE: This proposed finding is contradicted by Friedman [G-1488] and Effler et al., [G-185]. As described in response to proposed finding of fact 481, their data sets were analyzed by methods that corrected for confounders, and contrary to the proposed finding, associations between chicken consumption and increased campylobacteriosis risk or fluoroquinolone-resistant campylobacteriosis risk did remain. It might also be noted that the text in B-1901, page 49, mischaracterizes the CVM statement made that there were two potential confounders in the process of estimating the risk for fluoroquinolone-resistant infections from chicken (where fluoroquinolone-resistance was the basis of Bayer's Interrogatory 19 that was being addressed): foreign travel and prior fluoroquinolone use. Cox then proceeds to list a set of factors which might have some effect on ascertainment rates for campylobacteriosis cases, but could not have a differential effect with respect to the susceptibility of the cases, e.g., whether the case belonged to an HMO, whether the case had insurance, and what income the case had.

486. CVM has not applied any generally accepted methods of causal inference for interrupted time series and/or quasi-experimental designs to demonstrate a probable causal relation between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans. [CVM Answer to Bayer Interrogatory 40]

CVM CRITIQUE: This proposed finding is misleading in that it presumes 1) that there are generally accepted methods of causal inference for interrupted times series and 2) that there are time series data on fluoroquinolone use in chickens. The first statement is contradicted by the fact that Cox's WDT [B-1901] consistently refers to a text by Shipley (2000), Cause and Correlation in Biology. A user's guide to path analysis, and causal inference, as reference for the causal inference methods he uses. The fact that this material is barely three years old and is added to a relatively new field argues against there being generally accepted methods.

For the second point, it is clear that the coincidence of two time series, with one interrupted can be instrumental in illustrating associations that might be interpreted as causal. This is easily seen in the two time series for chicken production and campylobacteriosis cases in Belgium following the dioxin scare. [See page 93 of B-1901 displaying the graph taken from Vellinga and Van Loock. These data speak so clearly that no causal analysis is required. However, it is well established that in the United States, the data on fluoroquinolone use are not available to construct the coincident graphs of fluoroquinolone use in animals and fluoroquinolone-resistant rates in humans.

487. In interpreting historical trends and data on associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, CVM did not control for the possibility of spurious regression. [CVM Answer to Bayer Interrogatory 41]

CVM CRITIQUE: This proposed finding is misleading because it implies that CVM could have controlled for spurious regression. Controls for spurious regression are applied to time series. CVM did not perform regressions of rates of fluoroquinolone-resistant *Campylobacter* infections in humans versus amounts of veterinary fluoroquinolones used, which might have been subject to the spurious regression to which the proposed finding alludes.

489. In the absence of controls for spurious time series associations and threats to validity, CVM's inference of a causal relation from the claimed "temporal relationship" between enrofloxacin introduction and increasing fluoroquinolone-resistant campylobacteriosis rates in humans is unwarranted. [Cox (B-1901) P.53]

CVM CRITIQUE: This proposed finding is contradicted by the WDT of Dr. Kirk Smith(G-1473). On page 12, line 22 he indicates that among domestically-acquired cases in Minnesota, the percentage of resistant cases rose from 0.8% in 1996 to 3% in 1998, which was a statistically significant increase ($p<0.002$) by means a Chi-square test for linear trend. The major threat to validity, the effect of foreign travel (recognized by Cox B-1901, page 31, middle of the first full paragraph "People are more likely to acquire fluoroquinolone-resistant Campylobacter during international travel," was removed by restriction, that is, all cases that had traveled were excluded from the analysis. Restriction is a technique used by Cox to remove threats to validity in B-1252 Figure 3a, page 6 where he excludes cases who have visited a farm before investigating other risk factors.

492. Smith et al conducted their retail survey of chicken carcasses during the time of the year that has historically proven to give the highest probability of finding *Campylobacter jejuni* positive carcasses, as pointed by Willis in G-701. [Smith (G-589), Harris (B-387) P.3-4, Willis (G-701) P.3]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibits. Dr. Willis' publication indicates that in his study, the highest recovery rates were obtained during the warmer months of the year (May through October) from broiler carcasses obtained from local supermarkets in North Carolina. The authors state that their findings support seasonal variation of detection rates of *C. jejuni* in broiler carcasses, but neither these authors nor Harris attempt to extrapolate their results to other geographical areas nor to Dr. Smith's retail survey results. None of the references cited support Bayer's proposed finding of fact.

493. Domestically acquired fluoroquinolone-resistant *C. jejuni* isolates from MN residents for the calendar year of 1997 having the same fla-A PCR/RFLP types as fluoroquinolone-resistant *C. jejuni* from chicken products isolated in the Minneapolis/St. Paul area in

September, October, and November of 1997 were not shown to be "clonal" in the study referred to be Smith as exhibit G-589. [Smith (G-1473); G-589]

CVM CRITIQUE: The use of quotation marks around the word "clonal" calls into question how Bayer intends for that word to be interpreted in this proposed finding of fact. See also, CVM critique of Bayer's proposed finding of fact 507.

494. Only "clonal" isolates of *C. jejuni* can support epidemiologic evidence for "causality" in studies where both types of work are performed. [Newell (B-1908) P.31 L.5 – P.32 L.4]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony which does not claim, let alone establish, that "only" clonal isolates can support such evidence.

496. Fla-A PCR/RFLP subtyping is a weakly discriminatory subtyping test, (roughly equivalent to serotyping) as compared to PFGE, MLST, or AFLP subtyping methods. PFGE, MLST, and AFLP are considered to be more discriminatory and better able to establish clonality than fla-A PCR/RFLP subtyping. [Nachamkin (G-1470) P.8 L.29; Barrett (G-1453) P.5 L.27,28; Besser (G-1455) P.9 L.5-8; Endtz (G-1457) P.5; L.8-12 & L.12-15; G-1752; G-176; Newell (B-1908) P.34 L.19 - P.35 L.21]

CVM CRITIQUE: The proposed finding of fact is misleading because it is not an accurate representation of the cited testimony and, in some cases, is contrary to the cited testimony. As examples, we quote verbatim a few of the exhibits referenced by the proposed finding of fact.

Nachamkin (G-1470) does not say what is attributed to him in this proposed finding. His testimony reads, "I believe that RFLP analysis is a good typing method. When two strain have different RFLP types, there is a high probability that the strains are indeed different. However, strains with similar types may or may not be similar, and often need to undergo additional "subtyping" testing. I believe PFGE is an excellent subtyping method because it has an even higher level of discrimination, compared with RFLP." [Nachamkin WDT P.8 L.25-30]

Barrett's testimony (G-1453) is similarly misrepresented. The cited portion of his testimony reads, "Although I believe that PFGE is a more discriminating method for subtyping *C. jejuni* than is *flaA*-RFLP, I do not think that conclusion is universally accepted. I also think that PFGE is slightly superior to *flaA*-RFLP for epidemiologic investigations, but at least some researchers would challenge that conclusion. Even if PFGE is superior, the real question is whether *flaA*-RFLP is adequately discriminating for one to draw any meaningful conclusions from *flaA*-RFLP data. I believe the answer to that is clearly yes. It has proved valid in many investigations of *C. jejuni* outbreaks and applied successfully to efforts to understand and control *Campylobacter* infections in broiler flocks. Dr. Newell cites a number of such references in a recent "state of the art" review of *Campylobacter* subtyping (This study can be found on this Docket as Exhibit G-444, pp.44-61). In her review, Newell finds the greatest potential disadvantage of fla

typing to be the problem of genomic instability. As discussed below, Barrett states, "In the context of the Smith paper, however, I believe that fla typing was an appropriate choice of methods and that instability was not an issue. If instability was an issue, it is far more likely that strains that were originally alike became different than that strains that were originally different became alike, and the connection between the chicken and human isolates may be even stronger than it appears." [Barrett WDT P.6 L.18-23]

Besser's WDT states, "At either end of this classification spectrum, it would not be possible to discover epidemiologic trends. The most useful classification level is one where meaningful relationships can be drawn from the associated epidemiologic analyses...positive epidemiologic associations must stand by their own merits, and are independent of the typing system." As shown, Besser's cited WDT does not support the proposed finding of fact. In actuality, Besser devotes a portion of his written direct testimony highlighting the value of RFLP, and the reasons why more discriminating methods are not necessarily better for epidemiological studies (G-1455, P. 7-9). [Besser WDT P.9 L.5-8]

The portion of Endtz's WDT cited by Bayer does not specifically mention RFLP. The citation cited to by Bayer reads, "The great value of Pulsed-field Gel Electrophoresis (PFGE) has been demonstrated, although there may be some limitations. Some authors have stated that this method may be too sensitive to determine genetic relatedness between strains because of frequent genetic rearrangements in the genome of *Campylobacter* and therefore should not be used as a single method [47-50]. Amplified Fragment Length Polymorphisms (AFLP) and Multi-locus Sequence Typing (MLST) have been proposed in the recent literature as outstanding tools for investigating transmission routes from environment and livestock to humans [44,45]. As shown, the cited references do not support this proposed finding of fact number.

497. The most discriminating molecular subtyping methods such as PFGE, MLST, AFLP, are useful in assessing clonal similarities and "genetic overlap" between animal, human and environmentally sourced organisms including *Campylobacter* sps. [Newell (B-1908) P.34 L.19 – P.35 L.21, P.36 L.5-24; G-1785; G-1629; G-1630]

CVM CRITIQUE: CVM agrees that these methods, among others, are useful; however, Bayer does not define the criteria for "most discriminatory," and as quoted in CVM's critique to Bayer's finding of fact 496, Besser's WDT indicates that the most discriminating method may not always be the better one for appropriate epidemiologic association.

498. Molecular subtyping methods may be useful in supporting or undermining epidemiological findings. [Besser (G-1455) P.6 L.43 – P.7 L.3]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The cited testimony does not state, suggest, or imply that molecular subtyping methods can undermine epidemiological findings. Rather, the cited testimony (see also P.6 L.15-43)

discusses how molecular subtyping methods can serve to strengthen statistical associations found by epidemiologic analyses.

499. All molecular subtyping methods have their greatest utility in supporting or undermining epidemiological findings when isolates obtained are closely linked in time and space with the epidemiological findings. [Tenover (G-1476) P.4 L.27,28 & P.7 L.9-23]

CVM CRITIQUE: Bayer's proposed finding of fact is misleading. CVM points out that Dr. Tenover was referring to outbreak isolates and to bacteria in general, not specifically *Campylobacter*. Without these caveats, Bayer's reliance of Dr. Tenover's WDT to support its proposed finding is misplaced.

501. Molecular subtyping methods are less useful in assessing clonal relationships in isolates disparate in time and space due to genetic drift of the organisms. [Tenover (G-1476) P.8 L.18,19] [Newell (B-1908) P.30 L.6-14]

CVM CRITIQUE: This finding of fact is misleading because it is taken out of context and omits important information. First, it fails to indicate what "less useful" means. Less useful than what? Second, Dr. Tenover's testimony is referring to caveats that should be followed if one is to use his PFGE interpretive criteria for discerning strain relatedness and does not support the proposed finding. Third, Dr. Newell indicates that these techniques are useful and have had proven value in the epidemiological investigation of outbreaks, both in humans and poultry flocks. Her testimony states "The techniques exploit variation at the DNA level in either a single locus (i.e., fla-typing or ribotyping) or in the whole genome (i.e., pulsed field gel electrophoresis [PFGE] or amplified fragment length polymorphism [AFLP] [Newell, et al., 2000] [Wassenaar and Newell, 2000]. All these techniques have their advantages and disadvantages but have had proven value in the epidemiological investigation of outbreaks both in humans and poultry flocks (Manning et al., 2001) (Shreeve et al., 2000) (Saito et al., 2002) (Champion et al., 2002) (Kokotovic & On, 1999) and can extensively discriminate strains within single serotypes (Owen et al.,1995)." [Newell WDT P.28 L.10-18]

502. *Campylobacter* sps of human and animal origins have been shown to be genetically unstable. B-33. [Newell (B-1908) P.29 L.23 – P.30 L.14]

CVM CRITIQUE: The proposed finding is only partially true in that, while there are genetic recombination events that can occur within *Campylobacter* species, it is also true that there are stable *Campylobacter* clones which apparently are not subject to such genotypic variations. This is mentioned in Dr. Newell's testimony on page 31, line 15-20, where she lists a few such currently recognized stable clones of *C. jejuni* and notes that "Because such clones do not appear to be susceptible to genetic instability they may be used to investigate the relationship between such strains in humans and other hosts including chickens." Also, what is intended by the term "genetically unstable" is not explicit.

503. Inter and intragenomic recombination has been shown to occur within the fla A&B loci of *Campylobacter jejuni*. [B-33]

CVM CRITIQUE: This proposed finding of fact is misleading. Though this statement is partially true in that there are genetic recombination events that can occur within *Campylobacter* species, it is also true that there are stable *Campylobacter* clones which apparently are not subject to such genotypic variations. This is mentioned in Dr. Newell's testimony on page 31, line 15-20, where she states that "the only *Campylobacter* strains not apparently subject to such genotype variations are those belonging stable clonal groups. There are only a few such stable clones of *C. jejuni* currently recognized including serotypes 0:6,7 (Manning, et al., 2001), 0:19 (Fujimoto et al., 1997) and 0:41 (Wassenaar et al., 2000). Because such clones do not appear to be susceptible to genetic instability they may be used to investigate the relationship between such strains in humans and other hosts including chickens." Also, what is intended by the term "genetically unstable" is not explicit.

504. The flagellin locus in *C. jejuni* is considered to be unstable. [B-33]

CVM CRITIQUE: This proposed finding of fact is misleading. Though this statement is partially true in that there are genetic recombination events that can occur within *Campylobacter* species, it is also true that there are stable *Campylobacter* clones which apparently are not subject to such genotypic variations. This is mentioned in Dr. Newell's testimony on page 31, line 15-20, where she states that "the only *Campylobacter* strains not apparently subject to such genotype variations are those belonging stable clonal groups. There are only a few such stable clones of *C. jejuni* currently recognized including serotypes 0:6,7 (Manning, et al., 2001), 0:19 (Fujimoto et al., 1997) and 0:41 (Wassenaar et al., 2000). Because such clones do not appear to be susceptible to genetic instability they may be used to investigate the relationship between such strains in humans and other hosts including chickens." Also, what is intended by the term "genetically unstable" is not explicit.

506. Low discriminating molecular subtyping methods are generally less useful for interpretive purposes than high discrimination molecular subtyping methods. [Newell (B-1908) P.35 L.1-12]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of Dr. Besser G-1455, P. 7-9 in which it is shown that more discriminatory power is not necessarily better.

507. The only reference placed in evidence on genetic overlap in the U.S. involving human and poultry isolates in a similar region, over a similar time frame is that of Avery Dickins et. al. [G-1785]

CVM CRITIQUE: This proposed finding of fact is contradicted by the record. Exhibit G-589 compares *C. jejuni* isolates recovered from humans and chickens obtained in 1997 in Minnesota.

508. The M. Avery Dickins et. al. study (G-1785) estimates human/poultry clonal overlap of *Campylobacters* to be 6-8 %. [G-1785]

CVM CRITIQUE: This proposed finding is without a basis in the record. G-1785 does not estimate the human/poultry clonal overlap to be 6 – 8% anywhere in the manuscript.

509. *Campylobacter jejuni* isolates from different sources may share identical fla –A banding patterns. This could result in erroneously concluding that two non-clonal isolates were the same. [Tenover (G-1476) P.4 L.18-20] [Smith (G-1473) P.14 L.20,21]

CVM CRITIQUE: This finding of fact is misleading because it is taken out of context and does not include important information. The sentence attributed to Dr. Tenover actually states "By chance, some epidemiologically unrelated isolates may have similar or indistinguishable genotypes, particularly if there is limited genetic diversity within a species or subtype." He is not referring to *C. jejuni* isolates that may share identical *flaA* banding patterns, but rather gives the example of Staphylococcus aureus. Additionally, he mentions this in the context of bacteria that have a limited genetic diversity. Testimony from Dr. Newell mentions that *Campylobacter* does not have a limited genetic diversity, P.29 L.8-10, "Such studies have shown that the genus *Campylobacter* is very diverse (Meinersmann et al., 2002) and the species *C. jejuni* and *C. coli*, although revealing a clonal framework are only weakly clonal (Dingle, et al., 2001)." The sentence attributed to Dr. Smith is also taken out of context. Although he does state on P.14 L.20-21, that "one of the potential pitfalls of any subtyping method is that identical subtypes do not always indicate a common source", the remainder of the paragraph, lines 21-33, explains the factors that indicate this was not an issue with his study.

510. By chance, epidemiologically unrelated isolates can have similar or indistinguishable genotypes. [Tenover (G-1476) P.4 L.18-20] [Smith (G-1473) P.14 L.20,21]

CVM CRITIQUE: This finding of fact is misleading because it is taken out of context and does not include important information. The sentence attributed to Dr. Tenover actually states "By chance, some epidemiologically unrelated isolates may have similar or indistinguishable genotypes, particularly if there is limited genetic diversity within a species or subtype." Additionally, he mentions that this might occur among bacteria that have a limited genetic diversity. Testimony from Dr. Newell mentions that *Campylobacter* does <u>not</u> have a limited genetic diversity, P.29 L.8-10, "Such studies have shown that the genus *Campylobacter* is very diverse (Meinersmann et al., 2002) and the species *C. jejuni* and *C. coli*, although revealing a clonal framework are only weakly clonal (Dingle, et al., 2001)." The sentence attributed to Dr. Smith is also taken out of context. Although he does state on P.14 L.20-21, that "one of the potential pitfalls of any subtyping method is that identical subtypes do not always indicate a common source." The remainder of the paragraph, lines 21-33, explains the factors that indicate this was not an issue with his study.

511. Fla – A subtyping is considered to be of low to moderate discrimination value and cannot establish clonal relationships from isolates disparate in time and space. [Newell (B-1908) P.30 L.15-18]

CVM CRITIQUE: This proposed finding of fact is taken out of context and omits important information. Dr. Newell testifies that *Campylobacter* does not have a limited genetic diversity, page 29, lines 8-10, "Such studies have shown that the genus *Campylobacter* is very diverse (Meinersmann et al., 2002) and the species *C. jejuni* and *C. coli*, although revealing a clonal framework are only weakly clonal (Dingle, et al., 2001)."

512. PFGE is a superior (more discriminatory) subtyping method to fla-A subtyping. [Nachamkin (G-1470) P.8 L.29]

CVM CRITIQUE: This proposed finding is contradicted by WDT in evidence and CVM disagrees that it should be accepted as a fact because there is not general agreement on this point among experts in the field. While PFGE is an excellent subtyping method and does have a high level of discrimination, more discriminatory power does not necessarily equate with superiority, as pointed out by Besser (G-1455, P. 7-9). In addition, Dr. Nachamkin states (G-1470, page 8, lines 13-16) that "the usefulness of fla typing arises from the fact that this gene is highly variable, and therefore can be used to discriminate between strains. Each fingerprinting method has its strengths and weaknesses, and are best used in combination, or interpreted in light of information taken from epidemiological investigations."

513. Because fluoroquinolone-resistant *Campylobacters* are different from wild type *Campylobacters* by only a single base pair change, they can be considered a smaller subset of the fluoroquinolone-susceptible *Campylobacter* population. [Meng (G-1466) P.4 L.10-14]

CVM CRITIQUE: This statement is without factual basis on the record. The record provides no evidence to verify that fluoroquinolone-resistant *Campylobacter* are a smaller subset of fluoroquinolone susceptible *Campylobacter*. In a poultry flock in which Baytril was used, the susceptible strains may actually represent a "smaller subset" of the resistant isolates ((G-1465). In addition, the cited lines to Dr. Meng actually read "In *Campylobacter*, acquired resistance to fluoroquinolones appears to be due mostly to mutations in genes (*gyrA*) encoding DNA *gyrA*se (Engberg et al., 2001). Cloning and sequencing of the *gyrA* gene showed that mutations in *gyrA* at positions Thr-86, Asp-90, and Ala-70 can be detected in fluoroquinolone-resistant isolates (Charvalos et al., 1996; Ruiz et al., 1998; Wang et al., 1993)."

514. Clonally shared populations of *Campylobacter* in humans and poultry are most likely to be identified in the populations, all things being equal, since these represent the largest fraction in each group. [Newell (B-1908) P.31-36]

CVM CRITIQUE: This statement is without factual basis on the record. The record provides no evidence to verify that fluoroquinolone-resistant *Campylobacter* are a smaller subset of fluoroquinolone-susceptible *Campylobacter.* In a poultry flock in which Baytril was used, the susceptible strains may actually represent a "smaller subset" of the resistant isolates (G-1465).

515. Clonal overlap studies in the U.S.(G-1785) describe smaller clonal overlap populations in human and poultry *Campylobacters* than do studies from Canada (B-553) and other European countries [B-380]

CVM CRITIQUE: Bayer's proposed finding is without adequate reference to the evidentiary record of this hearing. Exhibit G-1785 does not give an estimate of clonal overlap and is therefore not an appropriate point of comparison with any other studies, including B-553.

516. The "concordance" argument of Besser (G-1455; P.11) between the alignment of fluoroquinolone-resistant fla-A types in human cases and poultry products is not biologically plausible because fluoroquinolone-susceptible strains are far more prevalent in MN resident cases and in MSP purchased chicken products than are fluoroquinolone-resistant strains. All things being equal, it would be far more likely to see concordance between the types in higher prevalence than between the types of low prevalence. [Newell (B-1908) P.31-36]

CVM CRITIQUE: This proposed finding is an opinion without factual basis on the record and is not supported by the Newell cite provided as she does not testify about the "concordance" argument put forth by Dr. Besser in any of the pages cited (pages 31-36).

517. There is no evidence that fla-A PCR/RFLP typing was "blinded" in the subtyping analysis performed in the report of exhibit G-589. [Tenover (G-1476) P.4 L.31,32]

CVM CRITIQUE: The cited reference in support of this finding does not indicate that the fla-A PCR/RFLP analysis was or was not done in a "blinded fashion." Further, Dr. Tenover is not referring to G-589 or any other study. Dr. Tenover's actual testimony states "If possible, typing should be performed in a blinded fashion to reduce bias." (emphasis added). Furthermore, he again is referring to conditions that should be followed if one is going to use his PFGE interpretive criteria. He is not referring to the *flaA* PCR/RFLP method used in G-589.

520. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. [Newell (B-1908) P.38 L.17-20] [Smith (G-1473) P.14 L.20-25]

CVM CRITIQUE: The proposed finding of fact, is unsupported by either citation (when the Smith citation is taken in context) and lacks foundation in the evidentiary record.

521. The epidemiologic findings of G-589 are negative for poultry as a source of *Campylobacter* or fluoroquinolone-resistant *Campylobacter*. [G-589]

CVM CRITIQUE: This proposed finding is contradicted by G-589. G-589 states, "Poultry has been documented repeatedly as a major food reservoir of *Campylobacter* for infections in humans and our data suggest that poultry is an important source of quinolone-resistant infections as well." Based on their analysis of the epidemiological evidence, Smith et al., (G-589, P.1) concluded that the data suggest poultry is an important source of quinolone-resistant infections. A basis for this finding was an association found between molecular subtypes of resistant *C. jejuni* strains acquired domestically and those found in chicken products (G-589, P.6).

522. Consumption of poultry meat is not a risk factor for infection with fluoroquinolone-resistant *Campylobacter* in domestically acquired *Campylobacter* cases in the UK. [Newell (B-1908) P.40 L.16-22]

CVM CRITIQUE: The proposed finding is contradicted by a U.K. study reported in Exhibit B-340 (bottom of P.6), in which it is stated that, "history of recent consumption of poultry was elicited from 12 (80%) of cases with ciprofloxacin-resistant *Campylobacter* enteritis and 20 (83%) of controls. The majority of Dr. Newell's testimony and conclusions are drawn from a particular reference cited on page 40 (B-1555), which is identified as the *Campylobacter* Sentinal Surveillance Scheme Collaborators, 2002. Page 563 of cited reference B-1555 by Dr. Newell, under the heading of indigenous *C. jejuni* cases, states that "Amongst the 2783 cases who acquired their *C. jejuni* infection in the UK, 291 (10%) were infected with a ciprofloxacin-resistant strain and 1593 (56%) were infected with a strain sensitive to all antimicrobials." Furthermore, it is stated on page 564 of the same reference that "Cases with a ciprofloxacin- resistant *C. jejuni* infection were more likely to report the consumption of pre-cooked cold meats in the 2 weeks prior to illness than those cases infected with strains sensitive to all antimicrobials." B-1555 also states that "over half (55%) of the *Campylobacter* infections acquired abroad were resistant to ciprofloxacin, compared with 10% of UK-acquired strains [relative risk 5.23; 95% confidence interval (CI) 4.58-5.961. For travel-associated cases, ciprofloxacin-resistant infections were independently associated with travel to Spain [odds ratio (OR) 6.67; 95% CI 3.52-13.381, Portugal (OR 22.40; 95% CI 4.36-1 14.99) or Cyprus (OR 11.74; 95% CI 1.2&108.02),and the consumption of chicken (OR 4.95; 95% CI 2.12-1 1.56) or bottled water (OR 3.70; 95% CI1.69-8.10)." This citation also states on page 564 that "The apparent association between the consumption of chicken and the acquisition of a ciprofloxacin-resistant *C. jejuni* infection amongst foreign travelers might point to the use of enrofloxacin in veterinary medicine and animal husbandry."

523. Data showing a genetic overlap between *Campylobacter* isolated from chicken and *Campylobacter* isolated from humans are consistent with the hypotheses of reverse causation (human effluents contaminate chicken flocks, perhaps via intermediate vectors) and common third causes (both humans and chickens are contaminated by some other environmental source). [Cox (B-1901) P.28, citing Hanninen, G-1458, P.7 11)]

CVM CRITIQUE: This proposed finding is contradicted by evidence on the record. Reverse causation as a hypothesis is clearly refuted by the fact that resistance problems that are rampant in the human population, e.g. Vancomycin resistant Enterococci (VRE), are not found in poultry or other animals. Linden, et.al., Exhibit B-488, first paragraph say "The incidence of infections due to strains of Enterococcus resistant to vancomycin and teicoplanin has increased dramatically since 1986" in the United States and they list five references to illustrate the point. Meanwhile, despite the fact that Enterococcus are ubiquitous, there are no VRE found in animals in the United States, Kruse [B-468, page 5, second paragraph in the left column] says "In studies from the United States where avoparcin has never been approved, and from Sweden where avoparcin has not been used for the past 12 years, no VRE were found in samples from animals when selective techniques were used." It should be noted that the samples from animals were taken nearly 10 years after the human drug (vancomycin) had been approved.

With respect to the hypothesis of common sources, the proposed finding is misleading. At the end of the citation, Hanninen, G-1458, P.7 ¶ 11, says "In my view, these results indicate, as do most typing studies, that chicken and human strains with overlapping sero/genotypes provides additional evidence that some portion of human Campylobacter infections are acquired from chickens."

524. Evidence that chickens share *Campylobacter* subtypes with lambs and other animals (presumably not because one species eats the other) indicates that the common third cause interpretation may be the most plausible hypothesis. [Cox (B-1901) P.28]

CVM CRITIQUE: This finding appears to be a statement of opinion rather than a fact, particularly with the insertion of the phrase "most plausible hypothesis." Equally plausible, and accepted more widely, is the hypothesis that chickens are a reservoir for *Campylobacter* and as expressed by Hanninen (see proposed finding of fact 523) humans acquire infections from chicken

525. CVM's hazard identification step of the CVM/Vose Risk Assessment incorrectly identifies chicken as the predominant source of campylobacteriosis and fluoroquinolone-resistant campylobacteriosis in humans. [Cox (B-1901) P.14]

CVM CRITIQUE: With respect to the assertion that the CVM RA incorrectly identifies chicken as the predominant source of campylobacteriosis, this finding appears to be a statement of opinion rather than a statement of fact. CVM did find chicken to be the predominant source of campylobacteriosis, with an attributable fraction distribution centered at 57% [Bartholomew, G-1454, page 14, line 20]. Other testimony indicates that this is not too high a value. B-147, page 2, adopted the 1988 CDC estimate of 60% as the percent of campylobacteriosis cases associated with consumption of improperly cooked or improperly handled poultry.

With respect to the second part of the finding, chicken as the predominant source of fluoroquinolone-resistant campylobacteriosis in humans chicken, this finding mischaracterizes the CVM RA. The RA does not find chicken as the predominant source

of fluoroquinolone-resistant campylobacteriosis. On page 9 of G-1454, line 7, it clearly states that two other major sources of fluoroquinolone-resistant *Campylobacter* in humans are foreign travel and human use of fluoroquinolone microbials (prior to culture). G-953, pages 121 to 124 or more clearly from the CVM website, www.fda.gov/cvm/antimicrobial/RAFinRisk.xls in the sheet called DATA at lines 63 through 70, column E, it is seen that approximately 50 % of the resistant cases were removed as having gotten their resistance from these non-chicken sources.

526. Correct causal analysis of CDC and other data shows that chicken consumption per se is not a predominant cause of human campylobacteriosis, [Cox (B-1901) P.15, citing Exhibit G-1681); See also G-1488 (Friedman 2003) and G-1489 (Nelson 2003)]

CVM CRITIQUE: This proposed finding is idle speculation because there has been no demonstration in the record what an analysis using those methods described as causal analysis methods throughout G-1901 would show if they were executed correctly. The proposed conclusion that chicken consumption per se is not a predominant cause of campylobacteriosis is pedantic game playing that is contradicted by numerous exhibits, including Friedman exhibit [G-1488], Table 4, page 23 where it shows that the highest odds ratio in the multivariable analysis is for chicken eaten at a restaurant, with an associated attributable fraction of 24%. Dr. Friedman apparently considers chicken eaten at a restaurant to be chicken per se. This is in addition to the contradictory evidence cited in the response to proposed finding of fact 481.

It might be noted that G-1489 discusses the duration of illness in cases with fluoroquinolone-resistant *Campylobacter* and fluoroquinolone-sensitive *Campylobacter* and has little nexus with the topic of causes of campylobacteriosis.

527. Chicken handled or prepared at home is associated with a statistically significant reduction in risk of campylobacteriosis. [Cox (B-1901) P.15, citing G-1644 (Friedman 2000), G-185 (Effler 2001) and B-1252 (Cox 2002); See also G-1488 (Friedman 2003) and G-1489 (Nelson 2003)]

CVM CRITIQUE: CVM agrees that G-1488 and G-185 support this finding. G-1644 and G-1488 provide no information in support of this finding.

529. Not accounting for the finding that chicken handled or prepared at home is associated with a statistically significant reduction in risk of campylobacteriosis in the CVM/Vose Risk Assessment model results in the chicken-attributable fractions and other quantities in the CVM/Vose Risk Assessment model incorrectly describing the chicken-campylobacteriosis relation in the current general US population. [Cox (B-1901) P.15, P.57-64]]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion rather than fact. I t presumes that the only way to determine the chicken-campylobacteriosis relation is to make a substantial number of gradations in the routes of exposure to chicken.

530. Analyzing the recent large case-control data set provided by CDC (The 1998 - 1999 FoodNet *Campylobacter* case-control study data set) shows that, with high statistical confidence, there is no detectable association between chicken consumption and risk of fluoroquinolone-resistant campylobacteriosis in humans. [Cox (B-1901) P.15; citing B-1252]

CVM CRITIQUE: This proposed finding is contradicted by exhibit G-1488 in which Friedman did analyze the 1998 - 1999 FoodNet *Campylobacter* case-control study data using multivariable analysis and found an attributable fraction of 24% for chicken eaten at a restaurant [See Table 4, page 23].

531. The finding that there is no detectable association between chicken consumption and risk of fluoroquinolone-resistant campylobacteriosis in humans has also been confirmed by analyzing the Smith et al. 1999 data set. [Cox (B-1901) P.15; citing B-1252]

CVM CRITIQUE: This proposed finding is contradicted by Kassenborg [G-337]. On page 10, Dr. Kassenborg finds that the population attributable risk for fluoroquinolone-resistant *Campylobacter* infections associated with consumption of chicken or poultry at a commercial establishment is 27% among domestically acquired cases.

It should be noted that the case-control study from Minnesota presented in the Smith exhibit G-589 is a case-case study, that is, it enrolled cases with fluoroquinolone-resistant *Campylobacter* and found two age, residence and date of specimen collection matched cases with fluoroquinolone-sensitive *Campylobacter* for each. In order to detect an association between chicken consumption and risk of fluoroquinolone-resistant *Campylobacter* in with this study design there would have to be a differential in risk associated with chicken consumption between the resistant and susceptible cases. If both sets of cases have very high, but similar, risks associated with chicken consumption, epidemiologic methods for assessing risks will not detect this.

532. A traditional definition of exposure assessment is "the qualitative and/or quantitative evaluation of the degree of intake likely to occur". The traditional risk assessment framework considers that the amount of contamination ingested by individuals (e.g., expressed as a population frequency distribution of CFUs, or colony-forming units, of *Campylobacter* ingested in meals) is crucial for quantifying risk. This reflects the fundamental principle that "the dose makes the poison". [Cox (B-1901) P.16]

CVM CRITIQUE: The proposed finding is contradicted by the WDT of Vose [G-1480] paragraph 49. "I have also noted previously that NRC revised their rather prescriptive approach, which required both exposure and dose-response models and which simply collated data, to one that focuses on the needs of decision-makers. An *explicit* dose-response step need only be included in a microbial or antimicrobial risk assessment, therefore, if its inclusion materially improves the quality of the decision that would be made from it. So far, most microbial risk assessments have been produced to model everything from the initial conditions of the food-producing animal to the moment of final human exposure to the bacteria. The reason for that has mostly been the desire to attempt to model everything possible (thus offering the decision-makers, usually agencies

with a much broader set of possible risk reduction options than the CVM, the widest possible range of decisions), and perhaps a lack of direction from those commissioning risk assessments too. The result has been to produce assessments that model everything, but very poorly, making it difficult to make robust decisions from these models. The second generation of risk assessments now being contemplated consider more focused decision questions."

533. FDA has recognized the key concept of exposure assessment in its own previous definitions for other microbial risk assessments, e.g., in defining exposure assessment as "A component of a risk assessment that characterizes the source and magnitude of human exposure to the pathogen", while equating magnitude of human exposure (i.e., "dose") to "The amount or number of a pathogen that is ingested or interacts with an organism (host)". [Cox (B-1901) P.16]

CVM CRITIQUE: The proposed finding is misleading in that it implies by the use of the words "other microbial risk assessments" that the CVM risk assessment is a microbial risk assessment, failing to recognize that the CVM risk assessment is instead an antimicrobial resistance risk assessment. It is also misleading because it implies that there is no latitude in the suggested definitions to tailor the nature of the exposure assessment to be consistent with the hazard and to meet the needs of the particular risk assessment problem at hand. See the above critique for proposed finding of fact 533. In suggesting that this finding

534. The CVM/Vose Risk Assessment model does not quantify or characterize the amount of exposure of humans to *Campylobacter* or fluoroquinolone-resistant *Campylobacter*. [Cox (B-1901) P.16]

CVM CRITIQUE: The proposed finding is misleading because it takes a very narrow view of characterizing exposure, viewing it only as exposures of individuals to probable microbial loads. The CVM risk assessment took a population view of exposure and quantified the pounds of fluroquinolone-resistant *Campylobacter*-contaminated chicken produced annually to which the population as a whole is exposed. The WDT of Dr. Bartholomew [G-1454, Figure 1, on page 5] illustrates how the model relates exposure, expressed in annual pounds of contaminated chicken consumed by the population, to health outcome.

535. The CVM/Vose Risk Assessment model does not follow the established concepts of exposure assessment. Instead, it seeks to quantify the "total prevalence of *Campylobacter* [and of fluoroquinolone-resistant *Campylobacter*] among broiler carcasses" (G-953, P.4-2 emphasis added). That is, it examines only the proportion of carcasses with some *Campylobacter* contamination present, but does not quantify how much contamination is present. [Cox (B-1901) P.16; citing G-953]

CVM CRITIQUE: The proposed finding is misleading because, as indicated above, in response to proposed finding of fact 535, the proposed finding offers a very restrictive view of the definition of the elements of a risk assessment. he original framers of these definitions most likely never intended that they be used proscriptively, but even if they

had, there is widespread agreement in the risk assessment community that this is no longer the case, as testified to in the Vose WDT [G-1480], paragraph 49.

536. Rosenquist et al. (G-1788) demonstrated the need for quantitative detection methods; "The minor effect [less than 10% reduction] on the number of [*Campylobacter*-] positive carcasses at the end of slaughter [of] ... a relatively large reduction in the number of *Campylobacter* on the chickens, for example, a reduction of 3 log10 CFU/chicken... demonstrates the need for quantitative detection methods. ... The incidence of campylobacteriosis related to consumption of chicken was reduced significantly by reducing the number of *Campylobacter* on the carcasses, even though such a reduction had almost no influence on the fraction of positive chickens." [Cox (B-1901) P.16-17; citing G-1788 (Rosenquist 2002)]

CVM CRITIQUE: The proposed finding is misleading. It conveys the idea that only microbial load and not prevalence of contamination is important in predicting risk of campylobacteriosis. The Rosenquist et al., exhibit, page 9-10 states "The simulations showed a linear relationship between the flock prevalence and the fraction of positive chickens leaving the slaughterhouse, and between the flock prevalence and the incidence of campylobacteriosis." Thus the fraction of positive chickens is also linearly related to incidence of campylobacteriosis. On page 10 they say "The simulation indicated that if the flock prevalence was reduced for example two times then the number of cases associated with consumption of chicken meat would also be reduced approximately two times. This is because there is a one-to-one relationship between these two parameters." [G-1788, p. 9-10]

537. Despite the demonstrated need for quantitative detection methods as delineated in the scientific literature, the CVM/Vose Risk Assessment model does not incorporate quantitative assessment of microbial load, instead using the fraction of *Campylobacter* positive chickens. [Cox (B-1901) P.17]

CVM CRITIQUE: The proposed finding is misleading because the demonstrated need for quantitative detection is an issue apart from whether microbial load quantification is required as part of a risk assessment. In Rosenquist at the bottom of page 10 it is clear that their concern is that better quantitative methods are required in slaughter plants to detect minor changes in contamination control because, with better methods, it will be easier to discern 3 log decreases in load than small shifts in percentage of contaminated carcasses. As illustrated in the response to proposed finding of fact 536, the fraction of positive chickens at end of slaughter suffices to estimate the risk to a population.

538. As demonstrated by Rosenquist et al., the mere the fraction of *Campylobacter* positive chickens is insensitive to changes in microbial loads that greatly affect human health. Hence, in general, human health risks are not proportional to the fraction of *Campylobacter*-positive ("contaminated") chickens, in contrast to the CVM/Vose Risk Assessment model's major assumptions. [Cox (B-1901) P.17; citing G-1788 (Rosenquist 2002)]

CVM CRITIQUE: The proposed finding is contradicted by the cited exhibit, as outlined in proposed finding of fact 536.

539. The linear CVM/Vose Risk Assessment model assumed by CVM should not be expected to produce realistic or accurate answers about the effects of risk management interventions because the change in human health risk is not directly proportional to the prevalence of contamination. For example a reduction of less than 10% in the fraction of positive chickens leaving the slaughterhouse can correspond to more than a 30-fold reduction in human campylobacteriosis cases. The change in human health risk (30-fold) is not directly proportional to the prevalence of contamination (1.1-fold). [Cox (B-1901) P.17; citing G-1788 (Rosenquist 2002)]

CVM CRITIQUE: The proposed finding is contradicted by the cited exhibit, as outlined in proposed finding of fact 536. The proposed finding confuses a strict change of 10% in fraction of positive chickens with the same microbial load with a change of 10% in the fraction of positive chickens as a result of a concomitant 3 log reduction in microbial load. What the cited paper actually said was: "The simulations showed that a relatively large reduction of the number of *Campylobacter* on the chickens, for example, a reduction of 3 $\log_{10}$ CFU/chicken (e.g., from the simulated mean level=level 0 to level -3, Fig. 7A), only lead to a minor reduction (less than 10%) in the fraction of positive chickens leaving the slaughterhouse (Fig. 7A)." [G-1788, p. 10].

540. The fraction of *Campylobacter*-positive chicken (which the term "a qualitative method" refers to) is not an adequate exposure metric from which to predict human health risk. [Cox (B-1901) P.17; citing G-1788 (Rosenquist 2002)]

CVM CRITIQUE: The proposed finding is contradicted by the cited exhibit, as outlined in proposed finding of fact 536, especially in the instance of defining risk to a population.

541. The CVM/Vose Risk Assessment model ignores all dose-response information. Instead, it misapplies attributable fraction calculations to assign blame for most human campylobacteriosis cases to chicken, even though most human campylobacteriosis are actually caused by other factors. [Cox (B-1901) P.18, citing B-1252 (Cox 2002); P.64-70]

CVM CRITIQUE: The proposed finding is contradicted by Friedman [G-1488], as outlined in CVM's critique of proposed finding of fact 484.

542. For other microbial risk assessments, FDA has previously defined risk assessment as a process that "consists of the following steps: hazard identification, exposure assessment, hazard characterization (dose-response), and risk characterization". It defined dose-response assessment as "The determination of the relationship between the magnitude of exposure and the magnitude and/or frequency of adverse effects." Similarly, the Codex Alimentarius Commission states that "For biological or physical agents, a dose-response assessment should be performed if the data are obtainable." [Cox (B-1901) P.18; citing Draft Assessment of the Relative Risk to Public Health from Foodborne Listeria monocytogenes Among Selected Categories of Ready-to-Eat Foods, http://www.foodsafety.gov/~dms/lmriskgl.html]

CVM CRITIQUE: The proposed finding is misleading and repetitive with Bayer's proposed finding of fact 533. Please see CVM's critique of 533.

543. Dose-response data for *Campylobacter* in human volunteers are readily obtainable and have been used to create several published dose-response models. [Cox (B-1901) P.18, citing B-517/G-411 (Medema 1996), B-748/G-629 (Teunis 1999), G-628 (Teunis and Havelaar 2000) and G-1788 (Rosenquist 2002)]

CVM CRITIQUE: The proposed finding is misleading in that it suggests that such several dose-response models created were deemed plausible and useful. This is contradicted by the WDT of Travis: "the models predicted nine orders of magnitude (billion-fold) difference in the dose estimated to infect one percent of the subjects (ID_{01}). However, three of the predicted ID_{01} doses were less than 1.0 CFU, meaning that a dose of 1.0 CFU infects more than one percent of the population." [G-1479], page 18, paragraph 72, lines 30-33.

544. Despite dose-response data for *Campylobacter* in human volunteers being readily obtainable and the existence of several published dose-response models, the CVM/Vose Risk Assessment model did not perform any dose-response assessment. [Cox (B-1901) P.18]

CVM CRITIQUE: The proposed finding is misleading in that it suggests that such several dose-response models based on the Black, et al., [G-67] data were deemed plausible and useful. As indicated in proposed finding of fact 543 above, this is not the case. Additionally, it is misleading because it suggests that the CVM Risk Assessment neglected to account for dose response. This is incorrect. Vose [WDT G-1480, page 7, paragraph 25] shows how the CVM Risk Assessment dealt with dose response, "K is thus the aggregate probability of all possible pathways via which people get exposed, combined with the conditional probability distribution of how many bacteria would be received in the exposure, and the dose-response probability function added up over the entire population." K was defined in the paragraph above as "$K \cong$ mean number of campylobacteriosis cases per pound of infected meat at slaughter plant."

545. Other *Campylobacter* risk assessment models such as B-1260 (Cox and Popken 2002) and G-1788 (Rosenquist 2002) incorporate relevant dose-response information for *Campylobacter*. [Cox (B-1901) P.18]

CVM CRITIQUE: The proposed finding is misleading because the Rosenquist et al., article expressed many reservations about the dose-response aspect of their risk assessment, for example on page 14 they say, under "Limitations" of their risk assessment: "...the dose-response relationship is based on only one study describing the response in young American volunteers to 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. As emphasized previously, the objective of this risk assessment was not to produce a risk estimate, but to provide the Danish risk managers with information of the relative importance of different simulated mitigation strategies in chicken production,

processing and preparation." Clearly Rosenquist, et al., recognize the relationship between the risk management questions asked and the type of risk assessment that is done to answer them.

546. The CVM/Vose Risk Assessment model does not incorporate relevant *Campylobacter* dose-response information. [Cox (B-1901) P.18]

CVM CRITIQUE: The proposed finding is misleading. See CVM's critiques to proposed findings 543, 544, and 545, particularly the Vose testimony citation in response to proposed finding of fact 544.

547. Rather than incorporate relevant *Campylobacter* dose-response information, the CVM/Vose Risk Assessment model relies on the assumptions that probability of campylobacteriosis in a person is directly proportional to the quantity of chicken consumed, and that the chicken-attributable risk of fluoroquinolone-resistant campylobacteriosis is proportional to the quantity of *Campylobacter*-contaminated chicken consumed, regardless of the amount of the contamination. [Cox (B-1901) P.18, P.64-70]

CVM CRITIQUE: The proposed finding is misleading. In the critique to proposed finding of fact 536, we show evidence on the record that probability of campylobacteriosis in the population is proportional to the quantity of *Campylobacter*-contaminated chicken consumed by that population. In the critique to proposed finding of fact 544, we show evidence that CVM did incorporate dose-response information in a manner that was relevant for their particular risk assessment.

548. The assumption that the probability of campylobacteriosis in a person is directly proportional to the quantity of chicken consumed is incorrect. [Cox (B-1901) P.18]

CVM CRITIQUE: The proposed finding is misleading and is a variation of 547 .

549. The assumption that the chicken-attributable risk of fluoroquinolone-resistant campylobacteriosis is proportional to the quantity of *Campylobacter*-contaminated chicken consumed, regardless of the amount of the contamination, is incorrect. [Cox (B-1901) P.18]

CVM CRITIQUE: The proposed finding is misleading and the similar to the previous two, except that FQ-r has been added. The CVM Risk Assessment [G-953, Page 13, final paragraph] made the assumption that there is no difference in survivability between susceptible and resistant *Campylobacter* because there was no information to the contrary at that time. No contrary evidence has been reported to date.

550. Despite CVM's assertion, the parameter Kres does not "establish[ ] an exposure-response relationship between the quantity of chicken contaminated with fluoroquinolone-resistant *Campylobacter* and the number of human cases with fluoroquinolone-resistant *Campylobacter*". [Cox (B-1901) P.54, citing CVM Answer to Bayer Interrogatory 49]

CVM CRITIQUE: The proposed finding appears to be a statement of opinion rather than a statement of fact. The statement itself presents the contradictory evidence.

551. The CVM/Vose Risk Assessment model's "K" ratio cannot correctly be interpreted as a dose-response relation, since neither a quantitative dose metric nor response probability as a function of dose has been quantified. [Cox (B-1901) P.19, P.64-70]

CVM CRITIQUE: The proposed finding appears to be a statement of opinion rather than a statement of fact. It presumes that the only response permitted in dose-response functions are probabilities. T his is contradicted by Rosenquist [G-1788]. The Rosenquist et al., Exhibit, page 9-10 states "The simulations showed a linear relationship between the flock prevalence and the fraction of positive chickens leaving the slaughterhouse, and between the flock prevalence and the incidence of campylobacteriosis." These are examples of dose-response functions where the responses were not probabilities.

553. The CVM/Vose Risk Assessment model seeks to quantify the average exposure of the "average consumer". But this quantity cannot be used to accurately predict risk, either for individuals or for populations. The average exposure level for the average consumer is irrelevant for predicting risk of campylobacteriosis (fluoroquinolone-resistant or not) since, as experimental data indicate, risks are caused primarily by concentrations of CFUs much higher than average in ingested foods. [Cox (B-1901) P.67]

CVM CRITIQUE: The proposed finding is misleading because it mischaracterizes the CVM Risk Assessment as defining risk for an average consumer. This is incorrect; the Risk Assessment defined risk in terms of the population. As provided in response to proposed finding of fact 544, Vose [WDT G-1480, page 7, paragraph 25] shows how the CVM Risk Assessment dealt with dose response, "*K* is thus the aggregate probability of all possible pathways via which people get exposed, combined with the conditional probability distribution of how many bacteria would be received in the exposure, and the dose-response probability function added up over the entire population." K was defined in the paragraph above as "$K \cong$ mean number of campylobacteriosis cases per pound of infected meat at slaughter plant."

554. The overall causal relation between chicken consumption and risk of *Campylobacter* infections can be negative if consuming chicken is preventative/protective of getting a *Campylobacter* infection. [Cox (B-1901) P.19; See also Endtz (G-1457) P.4 L.23-24]

CVM CRITIQUE: The proposed finding is misleading because it, is again discussing a principle that is true when one is operating at the level of risk to an individual but not true at the aggregate level discussed in the Vose citation in the critique to proposed finding of fact 553.

555. In traditional risk assessment frameworks, risk characterization is supposed to integrate hazard identification, exposure assessment, and dose-response information to determine the probable frequency and severity of adverse health effects that exposure to a hazard causes in a population. [Cox (B-1901) P.20]

CVM CRITIQUE: The proposed finding is misleading because it fails to recognize that the authoritative bodies such as the NRC who developed guidance to perform Risk Assessments in according to steps with the names given in the proposed finding have been refining their guidance. The process of integrating the steps is called risk characterization. See Vose [G-1580, page 3] where he quotes the NRC in their 1996 book saying that they felt they needed a more robust construction of risk characterization than that in their NRC 1983 statements. They said: "Risk characterization must be seen as an integral part of the entire process of risk decision making: what is needed for successful characterization of risk must be considered at the very beginning of the process and must to a great extent drive risk analysis. If a risk characterization is to fulfill its purpose, it must (1) be decision driven, (2) recognize all significant concerns, (3) reflect both analysis and deliberation, with appropriate input from the interested and affected parties, and (4) be appropriate to the decision."

556. In the CVM/Vose Risk Assessment framework, neither hazard identification, nor exposure assessment, nor hazard characterization (i.e., dose-response modeling) has been carried out according to generally accepted risk assessment standards and principles. [Cox (B-1901) P.20]

CVM CRITIQUE: The proposed finding is misleading. See CVM's critique of proposed finding of fact 555.

557. The case-control data of Friedman et al. (2000) show that the correct proportion of human *Campylobacter* illnesses attributable to chicken consumption must be much smaller than 60%. [Cox (B-1901) P.20, citing The 1998-1999 FoodNet *Campylobacter* Case-Control Study data set (e.g. G-1644) and B-1020]

CVM CRITIQUE: The proposed finding is misleading because Friedman et al., [G-1488] find an attributable fraction of 24% when considering only chicken eaten at a restaurant. See CVM's critique of proposed finding of fact 484.

558. A recent prospective case-control study from Quebec identifies poultry as the "principal suspected source of infection" in only about 10% of cases, comparable to drinking tap water at home (9%). [Cox (B-1901) P.20, citing G-1681 (Michaud 2002)]

CVM CRITIQUE: The proposed finding is misleading because Michaud et al., [G-1681] were actually unable to attribute 49% of all their cases. Only 10% of cases were attributed to direct consumption of chicken, but 48% of cases reported not washing their cutting boards after handling raw meat and poultry compared to only 18% of well controls. Additionally, the multivariable analysis found occupational exposure to farm animals a risk factor with higher odds ratio than even drinking tap water at home.

559. Genetic data suggest that only about 20% of human CP isolates (5 of 24) were genetically related to genotypes found in chickens. [Cox (B-1901) P.20, citing G-1684 (Nadeau 2002)]

CVM CRITIQUE: The proposed finding is misleading because characterizing the overlap in terms of percentage of isolates is not relevant. The issue is what proportion of disease cases are associated with those that do overlap.

560. Lamb and chicken share a significant proportion of *Campylobacter jejuni* subtypes with humans, suggesting the possibility of a common environmental source and indicating that shared subtypes need not arise from consumption of one species by another. [Cox (B-1901) P.20, citing G-1670 (Kramer 2000)]

CVM CRITIQUE: The proposed finding is similar to proposed findings 523 and 524, so CVM's critique is the same.

561. Despite multiple data sources to the contrary, the CVM/Vose Risk Assessment Model uses 60% as the fraction of human campylobacteriosis cases attributable to chicken consumption. [Cox (B-1901) P.20]

CVM CRITIQUE: The proposed finding is misleading because there are many references on the record stating that 60% of campylobacteriosis cases are associated with handling poultry and consumption of poultry, e.g., B-147 page 2.

562. The CVM/Vose risk Assessment Model uses attributable risk numbers that do not control for known confounders and risk factors for campylobacteriosis (e.g., male sex, contact with puppies and dogs, income and insurance coverage, dining out in restaurants, etc.). [Cox (B-1901) P.21; See also Feldman (B-1902) P.29 L.9-P.30 L.5]

CVM CRITIQUE: The proposed finding is misleading because one of the attributable risk numbers used by CVM is from the Harris article [G-268]. First, all subjects in the study were from the same health coverage plan, the King County Group Health Cooperative (GHC) so that insurance coverage was controlled for, page 1 left column. Then the controls were frequency matched by age and month of interview, thus controlling for those effects, page 1 right column. Next, they controlled the analysis by restriction (see finding of fact 489 indicating that Cox B-1901 and B-1252 uses this same method of controlling for variables) to cases who did not have the two factors with the highest relative risk, travel to underdeveloped countries and drinking raw milk (page 2 lower left column). The Harris King County – Seattle study report, [B-106, page 47] also reported having done analysis that controlled by stratification based on factors with relative risks of more than 1.5 or less than 0.7. Finally, as summarized on page 8 of B-106, etiologic fractions were derived for each significant risk factor determined by this method of controlling for confounders and other risks. The etiologic fractions (another name for attributable risks) take into account the frequency of exposure to each risk factor. Harris determined that 48.2% of the risk was due to unprocessed chicken, which is the value used by CVM in their risk assessment.

563. The risk of campylobacteriosis that CVM attributes to chicken is in reality primarily due to other, non-chicken sources. [Cox (B-1901) P.21]

CVM CRITIQUE: This proposed finding is an opinion that is contradicted by exhibits by Friedman [G-1488], as indicated in finding of fact 484, and by Effler [G-185] who found chicken consumed from a restaurant, turkey consumed in the past 7 days, and contact with live chicken as poultry-related risk factors remaining in a multivariable analysis that sequentially removed other factors that had been significant univariately. This means that these risk factors could not be accounted for by the removed risk factors. Non-poultry risk factors included ham and the use of antibiotics and medication to reduce stomach acid.

565. Instead of the nearly 60% chicken-attributable fraction used in the CVM/Vose Risk Assessment, a more realistic value of the chicken-attributable fraction for fluoroquinolone-resistant campylobacteriosis, based on the CDC's 1998 - 1999 *Campylobacter* Case-Control study data, is between –11.6% (protective effect) and 0.72%, (not statistically significantly different from zero) depending on how missing data values are treated. [Cox (B-1901) P.22, P.57-64]

CVM CRITIQUE: This finding is misleading because the CVM risk assessment used a distribution for an attributable fraction for chicken with respect to campylobacteriosis that was centered around 57% [Bartholomew, G-1454, paragraph 23]; it was not an attributable fraction for FQ-r campylobacteriosis. Secondly the suggested values or -11.6% and 0.72% are contradicted by the CDC analysis of the Case-Control data by Kassenborg [G-337]. Her attributable fraction for FQ-r campylobacteriosis was 27% for eating chicken or turkey at a commercial establishment.

566. The fraction of nearly 60% chicken-attributable fraction used in the CVM/Vose Risk Assessment is nearly 80-fold too high compared to the 0.72% fraction for fluoroquinolone-resistant campylobacteriosis (or even higher, if the true chicken-attributable risk is zero, consistent with the data). [Cox (B-1901) P.22, P.57-64]

CVM CRITIQUE: This proposed finding is misleading because the CVM risk assessment used a distribution for an attributable fraction for chicken with respect to campylobacteriosis that was centered around 57% (see the critique for proposed finding of fact 565); it was not an attributable fraction for FQ-r campylobacteriosis. Therefore, it is not comparable to an attributable fraction for FQ-r. As indicated in the critique for proposed 565, the estimated proposed value of 0.72% is contradicted by other testimony.

567. By assuming that its model form (i.e., excess risk = K*exposure) is correct despite overwhelming evidence to the contrary (e.g., risk actually decreases with consumption of chicken and increases disproportionately with microbial loads above 500 CFU), CVM under-states uncertainty in its results and produces artificially narrow confidence bands. [Cox (B-1901) P.23]

CVM CRITIQUE: This proposed finding is contradicted by Rosenquist. See CVM's critique for proposed finding of fact 536.

568. CVM's risk assessment does not address interindividual variability in susceptibility, even though dose-response data show that only about 20% of people experimentally exposed to *Campylobacter* became sick even at the highest concentrations. [Cox (B-1901) P.23, citing B-748/G-629 and G-628 (Teunis 1999 and Teunis 2000)]

CVM CRITIQUE: This proposed finding is misleading. Interindividual variability is inconsistent with a risk assessment on the effects of aggregate exposure. See finding of fact 553.

569. By assuming that one constant, K, essentially plays the role of a dose-response, the CVM/Vose Risk Assessment model fails to address the fact that only a minority of those exposed may be susceptible – and that the factors affecting susceptibility may have nothing to do with chicken consumption. Thus, neither uncertainty nor variability has been correctly characterized in the CVM/Vose Risk Assessment model. [Cox (B-1901) P.23]

CVM CRITIQUE: This proposed finding is misleading. See CVM's critique for proposed finding of fact 568.

571. Analysis of CDC's 1998 - 1999 *Campylobacter* Case-Control study data demonstrates that chicken consumption as a whole is not associated with increased risk of becoming ill with campylobacteriosis. [Cox (B-1901) P.24]

CVM CRITIQUE: This proposed finding is the same as proposed finding 526, taking out the words "Correct causal" in front of analysis and substituting "as a whole" for "per se". The contradictory evidence in Friedman's 24% attributable fraction for chicken eaten at a restaurant [G-1488, Table 4] implicates chicken.

572. Analysis of CDC's 1998 - 1999 *Campylobacter* Case-Control study data demonstrates that consumption of both home-cooked chicken and restaurant-prepared chicken are non-significantly negatively associated with becoming ill with a fluoroquinolone-resistant case of campylobacteriosis. [Cox (B-1901) P.24]

CVM CRITIQUE: This proposed finding is very similar to proposed finding of fact 531 (and so subject to that critique) and is contradicted on page 10 of Kassenborg [G-337].

573. Cases of campylobacteriosis associated with recent chicken consumption are less virulent (fewer average illness-days) than fluoroquinolone-resistant Campylobacteriosis associated with other (non-poultry) sources. [Cox (B-1901) P.24]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Cox testifies that FQ-resistance is *not* associated with a longer duration of illness. [B-1901, p. 24 at "(d)" emphasis in original] While the WDT does not state explicitly longer with respect to what comparison, it seems clear from the context that it would be in comparison to FQ-susceptible, regardless of their source.

574. If attention is restricted to patients who report recently eating chicken, then fluoroquinolone resistance is associated with decreased days of illness. [Cox (B-1901) P.24]

CVM CRITIQUE: This proposed finding suffers from the same error as the preceding proposed finding.

575. People who eat chicken now have significantly lower risk of acquiring fluoroquinolone-resistant campylobacteriosis than people who do not. [B-1252 Figure 4, P. 3832, citing data of Smith et al., 1999).

CVM CRITIQUE: This proposed finding of fact is contrary to Cox's analysis and ignores the plethora of evidence on the record associating campylobacteriosis with poultry consumption or cross contamination with raw or undercooked turkey (see G-162; G-182; G-299; G-268; G-1731; B-561; G-1711; G-474 G-1692; G-602; G-185; G-228; G-337; etc.). See CVM's critique of proposed finding of fact 531.

576. CVM's hazard identification step of the CVM/Vose Risk Assessment incorrectly identifies domestic chicken-borne fluoroquinolone-resistant *Campylobacter* as the predominant cause of adverse health effects (e.g., campylobacteriosis followed by treatment failure and excess days of diarrhea) when in fact these effects are demonstrably caused by other factors including foreign travel and restaurant dining. [Cox (B-1901) P.15, citing B-1020 (Cox 2001), B-1252 (Cox 2002) and G-1711 (Rodrigues 2001)]

CVM CRITIQUE: This proposed finding is contradicted by Kassenborg et al., who cite that travel outside the United States continues to be associated with fluoroquinolone-resistant *Campylobacter jejuni* infections; however, the majority of the resistant infections identified in their 12 month population-based case-control study at FoodNet sites during 1998 – 1999 were domestically acquired [Kassenborg (G-337)]. Dr. Kirk Smith states in his WDT that "we demonstrated a statistically significant link between resistant *C. jejuni* isolates from retail chicken products and domestically acquired resistant *C. jejuni* in humans. Given the vast amount of evidence documenting poultry as the primary source of *Campylobacter* infections in general, along with all of the epidemiologic data described above in my testimony, there is absolutely no doubt in my mind whatsoever that retail poultry is a primary source of fluoroquinolone-resistant *Campylobacter* for humans in the United States and elsewhere in the world." (emphasis added). [Smith (G-1473 P.20 L.24-31]. Smith et al., say that their data suggests that poultry is an important source of quinolone-resistant *Camylobacter jejuni* infections (G-589).

577. Applying conditional independence tests for causality to the CDC 1998 - 1999 *Campylobacter* Case-Control data set reveals that after correcting for confounders (i.e., variables that are associated with both chicken consumption and fluoroquinolone-resistant campylobacteriosis cases), overall consumption of chicken is not a risk factor for campylobacteriosis. [Cox (B-1901) P.29, citing G-1644 (Friedman 2000); Burkhart (B-1900) P.9, L.39-41]

CVM CRITIQUE: This proposed finding is similar to finding of fact 526. It is a statement of opinion without support in the record because it presumes that the tests have been applied appropriately and this has not been demonstrated. The conclusions are contradicted by exhibits on the record and listed in CVM's critique of proposed finding of fact 526.

578. Applying conditional independence tests for causality to Effler data set (funded and supported by CDC under cooperative agreement #U50/912395-03) reveals that after correcting for confounders (i.e., variables that are associated with both chicken consumption and fluoroquinolone-resistant campylobacteriosis cases), overall consumption of chicken is not a risk factor for Campylobacteriosis. [Cox (B-1901) P.29, citing G-185 (Effler 2001)]

CVM CRITIQUE: This proposed finding is a statement of opinion without support foundation in the record because it presumes that the tests have been applied appropriately. The conclusion is contradicted by the Effler [G-185, Table 2] who found chicken consumed from a restaurant, turkey consumed in the past 7 days, and contact with live chicken as poultry-related risk factors remaining in a multivariable analysis that sequentially removed other factors that had been significant univariately. This means that these risk factors could not be accounted for by the removed risk factors.

579. Preparation and consumption of chicken at home and buying or handling raw chicken are statistically significantly protective against campylobacteriosis. [Cox (B-1901) P.29, citing G-1644 (Friedman 2000); Burkhart (B-1900) P.9, L.39-41]

CVM CRITIQUE: This proposed finding is contradicted by the WDT of Wegener, where he includes a table showing a survey of risk factors for sporadic *Campylobacter* infections from 16 case-control studies. Despite certain limitations, eating poultry was identified as a risk factor for acquiring *Campylobacter* infections in 12 of the 16 studies. [Wegener (G-1483) P.13 L.13-15; P. 14 Table 4; P.15 L.1-41]. Additionally, Dr. Wegener cites three "natural intervention" studies from which he concluded that poultry, notably chicken, constitute a major source of human bacteriosis in Norway, Iceland, and Belgium. [(G-1483) P.18 L.9; P.20 L.9]. Tauxe further contradicts the proposed finding in his WDT [Tauxe G-1475) P.8 L.23-27, P.15 L.38-41] where he documents that handling raw poultry is a risk factor for *Campylobacter* infection. He also demonstrates that chicken is naturally contaminated with *Campylobacter* [Tauxe G-1475 P.10 L.26-43; P.15 L.32-36]. This includes a citation to a United Kingdom study that showed that the number of *Campylobacter* organisms on the surface of a fresh chicken carcass was estimated at 1,000 – 1,000,000 organisms per chicken. While Friedman does state that eating chicken or turkey cooked in the home was a protective factor, she concluded that the study confirmed risk factors for campylobacteriosis examined in previous studies, including consumption of undercooked poultry.

580. The finding that preparation and consumption of chicken at home and buying or handling raw chicken are statistically significantly protective against campylobacteriosis is consistent with conclusions from several studies including Rodrigues et al., 2001 and

Effler et al., 2001. [Cox (B-1901) P.29-30, citing G-185 (Effler 2001) and G-1711 (Rodrigues 2001)]

CVM CRITIQUE: This proposed finding is contradicted by the WDT of Wegener [Exhibit (G-1483) P.13 lines 13-15; P. 14 Table 4 and P.15 lines 1-41]. Dr. Wegener's WDT provides a table that shows 16 case-control studies that identified risk factors for *Campylobacter* infections. Despite their limitations, 12 of the 16 case-control studies identified eating poultry as a risk factor for acquiring a *Campylobacter* infection. The WDT of Tauxe [Exhibit (G-1475) P.8 lines 23-27 and P.15 lines 38-41] also contradicts the proposed finding by identifying the handling of raw poultry as a risk factor for *Campylobacter* infection.

581. The CDC 1998 - 1999 *Campylobacter* Case-Control data set shows that exposure to chicken juice and raw chicken are not risk factors for getting campylobacteriosis but instead tend to reduce the risk of being a campylobacteriosis case. [Cox (B-1901) P.29, citing G-1644 (Friedman 2000)]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Friedman [Exhibit (G-1644) P.10] does not refer in any way to the CDC 1998 - 1999 *Campylobacter* case-control data set, but to other case-control studies conducted in the United States. These other case control studies referred to in (G-1644) found that eating chicken, eating undercooked chicken, and/or handling raw chicken were risk factors for acquiring campylobacteriosis.

582. Because exposure to chicken juice and raw chicken are not risk factors for getting campylobacteriosis but instead tend to reduce the risk of being a campylobacteriosis case, it is not plausible that chicken per se is usually well cooked and safe, but still causes excess risk of campylobacteriosis via cross-contamination in the kitchen. [Cox (B-1901) P.29]

CVM CRITIQUE: This proposed finding is contradicted by the Harris study [G-268, Table 2] which found that consumption of rare or raw chicken had a strong association with being a case, 95% confidence interval on the relative risk is (2.1 – 27.6) and the association was still strong after restriction to cases who had not traveled to underdeveloped countries or had raw milk. [G-268, page 2] Rosenquist et al, [G-1788], on page 3, right column say "The high prevalence rates in chicken meat at retail and the fact that case-control studies conducted worldwide repeatedly have identified handling raw poultry and eating poultry products as important risk factors for sporadic campylobacteriosis seem to support that chickens play an important role in the transfer of *Campylobacter* to humans..." They then proceed to list 12 references, including Friedman et al, and Effler. This indicates that although some studies find raw chicken and cross-contamination the issue and some find chicken eaten at commercial establishments the issue, the global conclusion is that chicken is a risk factor.

583. The CDC 1998 - 1999 *Campylobacter* Case-Control data set shows that restaurant dining/consumption of commercially prepared food, including chicken, is a risk factor for

campylobacteriosis – but not significantly more so for chicken than for other meats. [Cox (B-1901) P.29, citing G-1644 (Friedman 2000)]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibit. The Friedman study cited does not refer to the CDC 1998-1999 *Campylobacter* Case-Control data set and does not discuss dining/consumption of commercially prepared food as a risk factor for campylobacteriosis. Further, Endtz sites several studies that contradict this proposed finding. (G-1457, page 4, lines 12-17; page 26, paragraph 5; page 570, page 584)

584. The CDC 1998 - 1999 *Campylobacter* Case-Control data set and other studies show that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. [Cox (B-1901) P.29, citing G-1644 (Friedman 2000), G-185 (Effler 2001), G-1711 (Rodrigues 2001) and other international studies G-10 (Adak 1995), G-182 (Eberhart-Phillips 1997) and Kassenborg testimony G-1460 P.8); Newell (B-1908) P.25 L.15-18]

CVM CRITIQUE: This proposed finding is contrary to the cited sources. The cited sources do not specifiy restaurant dining as opposed to chicken consumption per se to be the major human health threat for getting campylobacteriosis.

585. The human health risk of campylobacteriosis (cases per capita-year) has steadily decreased in the US since Baytril was introduced [Endtz (G-1457 P.2, Para. 3; Molbak (G-1468) P.4, L.18); CVM Response to Bayer's Interrogatory 28]

CVM CRITIQUE: This proposed finding of fact juxtaposes two observations and finding of fact is taken out of context. Baytril was approved in 1996 for treatment of specific poultry diseases, whereas Dr. Endtz's testimony refers to decreases in the incidence of campylobacteriosis in the United States between 1997 to 1999. Dr. Endtz was not implying that enrofloxacin use in poultry has played a role in the decreasing trend for campylobacteriosis in the United States. Dr. Endtz further states in his testimony (G-1457) on page 8 that "An increase of fluoroquinolone-resistant *Campylobacter* infecting humans from 1.3% in 1992 to 10.2% in 1998 was observed [65]. Although part of the rise of fluoroquinolone resistance may be explained by foreign travel and quinolone use prior to the collection of stool specimens, the prevalence of domestically acquired quinolone-resistant infections, not related to prior human use, also increased during the study period, largely due to acquisition from poultry."

587. Since Baytril was introduced, chicken consumption (pounds per capita-year) has steadily increased while human health risk of campylobacteriosis per pound of chicken consumption has steadily and significantly decreased. [Cox (B-1901) P.36; Endtz (G-1457) P.2 ¶ 3; Molbak (G-1468 P.4 L.18; CVM's Response to Bayer's Interrogatory 28]

CVM CRITIQUE: This proposed finding is contrary to and not supported by the cited testimony. Neither the Endtz nor the Molbak testimony cited addresses the relationship between chicken consumption and the human health risk of campylobacteriosis. The CVM response is as to the number of cases not their risk. The proposed finding does not

account for improvements in chicken-processing sanitation. [Tauxe WDT G-1475, P.16 L.24-P.17 L.40]

588. The fact that campylobacteriosis incidence rate has steadily decreased while chicken consumption has steadily increased argues against CVM's contention that chicken is the predominant source of human campylobacteriosis and that campylobacteriosis rates (as well as fluoroquinolone-resistant campylobacteriosis rates) in the US population are directly proportional to chicken consumed. [Cox (B-1901) P.36]

CVM CRITIQUE: This proposed finding of fact is contradicted by Molbak [G-1468], page 8, paragraph 26 "While the consumer in the United States had a lower risk of getting a Campylobacter infection in 2001 compared with 1996, the risk of getting an infection with a FQ-r infection had increased. Thus the 27% decrease in the incidence is more than outweighed by the 61% to 98% increa in proportion of isolates that are resistant." It should be noted that Pathogen Reduction Hazard and Critical Control Point (HACCP) measures were enacted in slaughter plants at approximately the same time as when fluoroquinolones were approved (1997) [WDT of Minnich G-1467, page 10, paragraph 27].

590. The substantial differences in the incidence of *Campylobacter* case rates among the nine FoodNet sites are not explained by differences in chicken consumption per capita (CDC case-control data) and thus suggest the importance of other, non-chicken factors in causing the observed rates of campylobacteriosis. [Cox (B-1901) P.36]

CVM CRITIQUE: This proposed finding is speculative and without support on the record.

591. Epidemiological data from a recent prospective case-control study from Quebec identifies poultry as the "principal suspected source of infection" in only about 10% of cases – far from the "predominant cause" suggested by CVM. [Cox (B-1901) P.36 citing G-1681 (Michaud 2002)]

CVM CRITIQUE: The proposed finding is the same misleading finding given in proposed finding of fact 558. Michaud et al [G-1681] were actually unable to attribute 49% of all their cases. Only 10% of cases were attributed to direct consumption of chicken, but 48% of cases reported not washing their cutting boards after handling raw meat and poultry compared to only 18% of well controls. Additionally, the multivariable analysis found occupational exposure to farm animals a risk factor with higher odds ratio than even drinking tap water at home.

592. Outbreak data clearly indicate that chicken consumption is not a predominant source of campylobacteriosis outbreaks in humans, but that drinking water is. [Cox (B-1901) P.36]

CVM CRITIQUE: Agrees that this applies to outbreaks.

594. Despite CVM's assertion that "most of the data used [in the CVM/Vose Risk Assessment model (G-953)] were from large national collections." (CVM's Answer to Bayer

Interrogatory 21), the most important part of the risk assessment calculation, the estimation of the chicken-attributable fraction, was based on Harris (G-268) and Deming (G-162), two relatively small, outdated studies that were not from large national collections. [Cox (B-1901) P.50; Feldman (B-1902) P.34 L.12-21]

CVM CRITIQUE: This proposed finding is a statement of opinion, not a statement of fact. Most of the data used were from large national collections (G-1454, pages 5-6). The most important part of the risk assessment calculation was not the estimation of the chicken-attributable fraction (G-953 P.3). The Harris study [G-268] was not small; it included 218 cases and 526 controls. The Harris and Deming studies were appropriately used in the risk assessment.

595. Relying on Harris (G-268) and Deming (G-162), the CVM/Vose Risk Assessment attributed a high proportion (nearly 60%) of campylobacteriosis risk to chicken consumption. [Cox (B-1901) P.38, referring to G-953 (the CVM/Vose Risk Assessment), G-268 (Harris 1986) and G-162 (Deming 1987)]

CVM CRITIQUE: This proposed finding mischaracterizes the attributed proportion as a point estimate. CVM did find chicken to be the predominant source of campylobacteriosis, with an attributable fraction distribution centered at 57% [Bartholomew, G-1454, page 14, line 20]. This means that CVM allowed for the possibility that the attributable fractions could be other values, some higher and some lower than 57%. Other testimony indicates that this is not too high a value. B-147, page 2, adopted the 1988 CDC estimate of 60% as the percent of campylobacteriosis cases associated with consumption of improperly cooked or improperly handled poultry.

596. The populations in the Harris (G-268) and Deming (G-162) studies were not representative of the current US population in terms of age, income, travel habits, dietary habits, and other relevant risk factors. [Cox (B-1901) P.38, P.57-64]

CVM CRITIQUE: The proposed finding is misleading in that implies that the utility of the studies is impaired because they do not represent the current US population. Yet no current study would be said to represent the current US population. Even though there may have been some changes, the studies included people who can represent some subset of the current population. In general, per capita consumption of chicken was lower in the mid 1980's [See finding of fact 586] so that the people included would represent those in the current population whose consumption is lower than others. Travel to Mexico and underdeveloped countries was a significant risk factor in the Harris study [G-268, page 2] and, to about the same extent, contact with animals with diarrhea was a minor factor [B-106, page 9] so that the there seems to be some consistency with expectation.

597. The attributable fractions calculated in the Harris (G-268) and Deming (G-162) studies cannot correctly be applied to US population case rates. [Cox (B-1901) P.38, P.57-64]

CVM CRITIQUE: This proposed finding is actually a statement of opinion which is a reflection of the mischaracterization of the CVM risk assessment in proposed finding of fact 595. The attributed proportion as a point estimate in the CVM RA is not just that

one point estimate calculated from each of the studies. CVM used a distribution for the attributable fraction which was centered at 57% [Bartholomew, G-1454, page 14, line 20]. This means that CVM allowed for the possibility that the attributable fractions could be other values, some higher and some lower than 57%.

598. The Harris (G-268) and Deming (G-162) studies cannot be used to support a correct calculation of the chicken-attributable fraction for fluoroquinolone-resistant campylobacteriosis, since neither contains any data on fluoroquinolone-resistant campylobacteriosis. [Cox (B-1901) P.39, P.57-64]

CVM CRITIQUE: This proposed finding is nonsensical because the nature of risk assessment is to pull together information from different sources and organize it in a manner to estimate required quantities. See for example the Vose WDT 1480, page 3 quoting from the NRC "Risk characterization is a synthesis and summary of information about a potentially hazardous situation that addresses the needs and interests of decision makers and of interested and affected parties." In the CVM risk assessment the value for fluoroquinolone resistance is obtained by removing cases associated with travel and prior use of fluoroquinolones from the NARMS data. See Bartholomew G-1454, page 9.This was done to use annually available national surveillance data.

599. Neither the Harris (G-268) study nor the Deming (G-162) study isolated the portion of campylobacteriosis risk associated with chicken consumption that is actually caused by chicken-borne *Campylobacter*, as opposed to being caused by other things (e.g., restaurant dining, income, male sex) that are correlated with patterns of chicken consumption. [Cox (B-1901) P.38-39, P.57-64]

CVM CRITIQUE: This finding is the same as Bayer's proposed finding 562, so that critique applies here as well.

600. The CVM/Vose Risk Assessment model misidentifies chicken as the predominant cause of Campylobacteriosis. Chicken accounts for 50%-70% of human campylobacteriosis cases in the CVM/Vose Risk Assessment model, but accounts for an undetectably small fraction of cases in reality, based on relatively large data sets such as the CDC 1998 - 1999 *Campylobacter* Case-Control data set, for which univariate logistic regression yields a negative population attributable risk (PAR). [Cox (B-1901) P.38, P.57-64]

CVM CRITIQUE: The proposed finding is the same as proposed finding of fact 562 as to the 50-70% attributable fraction and the same as proposed finding of fact 526 with respect to the CDC showing a negative attributable risk, and is therefore subject to those critiques.

601. A more accurate estimate of the population-attributable risk (PAR) for chicken consumption as a whole, based on the CDC 1998 - 1999 *Campylobacter* Case-Control data set, is negative (protective effect) while that for restaurant chicken is 3.1% (calculated via the standard PAR formula with a = 665, b=341, c=1439, d=976.) These are univariate PARs. A multivariate PAR that removes the effects of confounders would

be closer to zero. Thus, an attributable fraction of 0 to 3.1% is more realistic than CVM's 57%. [Cox (B-1901) P.56, P.57-64]

CVM CRITIQUE: The proposed finding is contradicted by the evidence indicated in the critique of proposed finding of fact 484.

602. CVM's interpretation of PAR (as set out in Angulo (G-1452) P.10 L.38 and Kassenborg (G-1460) P.8 Para.16) as referring to cases that are caused by or "due to" a factor or cases that would be reduced if a factor was eliminated is not correct. For example, PAR fractions for different factors can easily sum to several hundred percent, and it is incorrect to interpret the PAR for a factor as the fraction of cases that it causes or that would disappear if the factor were removed. [Cox (B-1901) P.57]

CVM CRITIQUE: The proposed finding is contradicted by standard textbooks in the field of epidemiology, e.g., Rothman and Greenland's Modern Epidemiology, second edition, where the definition is as given by the CDC

604. The CVM/Vose Risk Assessment attributes none of the risk for domestically acquired, non-treatment-related campylobacteriosis cases to well-known risk factors identified in other studies, such as drinking raw milk or water, restaurant dining and eating non-poultry meat prepared outside the home, sex of the victim, contact with puppies, or income. [Cox (B-1901) P.38, citing G-1711 (Rodrigues 2001), G-589/G-1723 (Smith 2001), G-185 (Effler 2002), G-1644 (Friedman 2000)]

CVM CRITIQUE: The proposed finding is contradicted by the CVM *Campylobacter* risk assessment (G-953) which attributes a proportion of the cases to chicken consumption, while identifying other risk factors for campylobacteriosis cases. The basis for the analysis is limited to that proportion attributable to chicken consumption. The intent of the CVM *Campylobacter* risk assessment was to relate the prevalence of fluoroquinolone-resistant campylobacter infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone resistant *Campylobacter* in chickens. As described in the WDT of Bartholomew [Bartholomew (G-1454) P. 8 L. 13-15], two case-control studies from the literature were used for input values for determining the proportion of all sporadic *Campylobacter* cases attributable to chicken. Although the risk assessment discusses other risk factors for sporadic campylobacterosis (G-953 P. 3-4) for purposes of this analysis, the allocation of attribution among the risk factors responsible for the non-chicken consumption related cases is moot for this purpose.

605. The fraction of campylobacteriosis cases that CVM attributes to chicken is inflated by the exclusion of well-known risk factors that are known to be important in the general population, such as drinking raw milk or water, restaurant dining and eating non-poultry meat prepared outside the home, sex of the victim, contact with puppies, or income. [Cox (B-1901) P.38, referring to risk factors identified in G-1711 (Rodrigues 2001), G-589/G-1723 (Smith 2001), G-185 (Effler 2002), G-1644 (Friedman 2000)]

CVM CRITIQUE: The proposed finding is contradicted by the CVM *Campylobacter* risk assessment (G-953) which attributes a proportion of the cases to chicken consumption, while identifying other risk factors for campylobacteriosis cases. The basis for the analysis is limited to that proportion attributable to chicken consumption. The intent of the CVM *Campylobacter* risk assessment was to relate the prevalence of fluoroquinolone-resistant campylobacter infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone resistant *Campylobacter* in chickens. As described in the WDT of Bartholomew [Bartholomew (G-1454) P. 8 L. 13-15], two case-control studies from the literature were used for input values for determining the proportion of all sporadic *Campylobacter* cases attributable to chicken. Although the risk assessment discusses other risk factors for sporadic campylobacterosis (G-953 P. 3-4) for purposes of this analysis, the allocation of attribution among the risk factors responsible for the non-chicken consumption related cases is moot for this purpose.

606. There is no logically necessary connection between attributable fractions for campylobacteriosis cases in general and attributable fractions specifically for fluoroquinolone-resistant campylobacteriosis cases. [Cox (B-1901) P.39]

CVM CRITIQUE: T his proposed finding appears to be contradicted by the Cox exhibit B-1252 where, in the section called Re-analysis of Factors for Human FQ Resistance, he asks "However, if chicken itself is not a significant carrier of CP to humans, then how can it be a significant carrier of FQ-resistant CP to humans?"

607. The CVM/Vose Risk Assessment calculates the product $p_{ca}*p_{rh}$ = "probability that a *Campylobacter* case is attributable to chicken" * "probability that a *Campylobacter* case from chicken is fluoroquinolone-resistant", but this is mathematically not the same as the probability that a fluoroquinolone-resistant *Campylobacter* case is due to chicken. [Cox (B-1901) P.39]

CVM CRITIQUE: This proposed finding is misleading because it presents the CVM RA calculation out of context. The RA document G-953 and the WDT of Bartholomew G-1454 clearly state that this calculation was made after having removed the only two known other sources of selective pressure, foreign travel and prior human fluoroquinolone use. As there were no other animal fluoroquinolones approved in 1998 and early 1999, this left only the use of fluoroquinolones in chicken as the selective pressure. Under these assumptions, the probability that a case from chicken is fluoroquinolone-resistant it is the same as the probability that a fluoroquinolone-resistant *Campylobacter* case is due to chicken.

608. Results from the large pilot case-control study of sporadic cases of *Campylobacter* infection conducted by the Foodborne Diseases Active Surveillance Network (FoodNet) in 1996-1997 found numerous factors to be associated with increased risk of *Campylobacter* infection, including eating poultry meat in restaurants, eating non-poultry meat in restaurants, eating raw seafood, international travel, contact with puppies and farm animals, and male gender. [G-1452 Attachment 1 P.46]

CVM CRITIQUE: These findings were from the large non-pilot case-control study of sporadic cases of Campylobacter infection conducted by the Foodborne Diseases Active Surveillance Network (FoodNet) in 1998-1999 (see G-1452 Attachment 1 P.62 Reference 16, which is G-228).

609. Results from the large pilot case-control study of sporadic cases of *Campylobacter* infection conducted by the Foodborne Diseases Active Surveillance Network (FoodNet) in 1996-1997 found a number of different exposures to be independent protective factors, including eating poultry meat at home, eating non-poultry meat at home, and eating at fast-food restaurants. [Angulo (G-1452) Attachment 1 P.46; Burkhart (B-1900) P.9, L.39-41]

CVM CRITIQUE: These findings were from the large non-pilot case-control study of sporadic cases of *Campylobacter* infection conducted by the Foodborne Diseases Active Surveillance Network (FoodNet) in 1998-1999 (see G-1452 Attachment 1 P.62 Reference 16, which is G-228).

612. Cindy R. Friedman et. al performed the comparison of *Campylobacter* cases and well community controls to determine the risk factors for becoming infected with *Campylobacter*, the results of which are reported in G-1644 (Friedman 2000) and Attachment 3 to G-1452. [G-1644; Angulo (G-1452) Attachment 3]

CVM CRITIQUE: This proposed finding is contrary to the cited exhibit (G-1644). Exhibit G-1644 P.133-134 refers to a risk factor study that can be found on the docket at G-229. That risk factor study by Friedman et al., compared persons with ciprofloxacin-resistant *Campylobacter* infections (patients) to persons with ciprofloxacin-sensitive infections (controls) reported during 1997.

614. Jennifer Nelson (nee McClellan), et al., performed the comparison of the medical consequences of ciprofloxacin-resistant and ciprofloxacin-susceptible *Campylobacter* cases, the results of which are reported in G-1679 (McClellan 2000), G-780 (McClellan 2002), G-1367 and Attachment 4 to G-1452. [G-780; G-1367; G-1432 Attachment 2; G-1699]

CVM CRITIQUE: This proposed finding of fact is misleading. The only "medical consequence" Jennifer Nelson's research addressed was the duration of diarrhea between fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections in humans. Therefore, this proposed finding is overly broad. Further, two references cited to support this proposed finding are not related to Ms. Nelson's work: G-1432 is the CV of Fred Tenover, and G-1699 is a paper entitled, "Molecular epidemiology of *Campylobacter jejuni* in broiler flocks using randomly amplified polymorphic DNA-PCR and 23S rRNA-PCR and role of litter in its transmission," by Payne et al., 1999. Neither reference is even remotely relevant to Dr. Nelson's study.

621. McClellan posits in G-1679 that a bias could have been introduced into her study. She states that a disproportionate number of cultures could have been collected from individuals with fluoroquinolone-resistant infections and that this could have biased the final sample population. [G-1679 McClellan (2000) P.60]

CVM CRITIQUE: This proposed finding is taken out of context of the cited testimony. The reason G-1679 P.60 gives for why a "disproportionate number of cultures [c]ould have been collected from individuals with fluoroquinolone-resistant infections "is that "[p]eople with resistant infections might have been more likely to seek medical care because they had a more severe illness."

622. Selection bias can significantly alter the findings of a study. Inferences may be drawn to the study population but not to the general population. [Feldman (B-1902) P.30 L.6-7]

CVM CRITIQUE: This proposed finding reflects a confusion in terminology and is contradicted by Attachment 1 of the witness's testimony offered to support the proposed finding. Feldman (B-1902) Attachment 1, P.119, states that selection bias is "a systematic error in choosing the study groups to be enrolled (e.g., cases and controls in a case-control study, exposed and unexposed groups in a cohort study) or in the enrollment of study participants that results in a mistaken estimate of an exposure-disease association"; therefore, inferences drawn to the study population can be affected by selection bias.

623. Analysis of the 1998-1999 Campylobacter Case-Control study by Nelson revealed that, when not adjusting for antimicrobial or antidiarrheal use, there was no statistical difference in mean duration of diarrhea between patients with a ciprofloxacin-resistant infection (8 days) compared to patients with a ciprofloxacin-susceptible infection (7 days), (p value = 0.1) [Angulo (G-1452), Attachment #4, P.116; P.117]; [Nelson (G-1489) P.10]

CVM CRITIQUE: This proposed finding is misleading in its use of the term "no statistical difference." The statistical difference is reflected in the cited p-value of 0.1. In addition, the mean duration of diarrhea among persons who did not take an antidiarrheal medication or an antimicrobial agent was 12 days (range, 8 to 20 days) for the 6 persons with ciprofloxacin-resistant infections and 6 days (range, 2 to 21 days) for the 61 persons with ciprofloxacin-susceptible infections ($p<0.01$). [Angulo (G-1452) P.15 L.37-40 and Attachment 4]

624. Analysis of the 1998-1999 Campylobacter Case-Control study by Nelson revealed that adjusting for fluoroquinolone and antidiarrheal use, there was no statistical difference in mean duration of diarrhea between patients with a ciprofloxacin-resistant infection who took a fluoroquinolone and no antidiarrheal agent (8 days) compared to patients with a ciprofloxacin-susceptible infection who took a fluoroquinolone and no antidiarrheal agent (6 days), (p value=0.08). [Angulo (G-1452), Attachment 4, P.118]; [Nelson (G-1489) P.11]

CVM CRITIQUE: This proposed finding is misleading in its use of the term "no statistical difference." The statistical difference is reflected in the cited p-value of 0.08.

625. Nina Marano et. al also performed a comparison of the medical consequences of ciprofloxacin-resistant and ciprofloxacin-susceptible *Campylobacter* cases, the results of which are reported in G-394 (Marano 2000). [G-394]

CVM CRITIQUE: Bayer's proposed finding is not supported by the cited exhibit. Marano's comparison of "medical consequences" was limited to looking at the comparison of the duration of diarrhea between fluoroquinolone-resistant and fluoroquinolone-sensitive cases of *Campylobacter*. Therefore, Bayer's proposed finding of fact is overly broad.

626. G-1644 Friedman (2000), G-337 Kassenborg (2000), G-1679 McClellan (2000), G-394 (Marano 2000) and G-780 (Nelson 2002) all analyze and report on data from the 1998-1999 FoodNet *Campylobacter* case-control study. [Angulo (G-1452) P.10 L.7-12]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. In addition, it is clear from Exhibit G-1644 itself that that exhibit does not analyze or report on data from the 1998-1999 FoodNet Campylobacter case-control study.

632. The 1998-1999 FoodNet *Campylobacter* case-control study found independent risk factors for acquiring a *Campylobacter* infection included drinking untreated water from a lake, river, or stream, drinking raw milk, eating undercooked poultry, eating raw seafood, having a pet puppy, having contact with farm animals, and having contact with animal stool. [Angulo (G-1452) Attachment 3 P.88]

CVM CRITIQUE: This proposed finding is misleading because the statement is taken out of context of the cited exhibit. Angulo (G-1452) Attachment 3 P.88 actually states: "In the final multivariate model eating chicken, turkey, or non-poultry meat that was prepared at a restaurant were independently associated with illness. ... Other factors independently associated with illness included drinking untreated water from a lake river or stream ...."

640. In the Kassenborg case-control study (G-337), potential subjects were interviewed with 21 days of their stool sample collection date; potential controls were interviewed within 7 days after the case subject's interview. All subjects were asked about food and water consumption, child daycare, travel, animal exposures, and food-handling practices during the 7-day period before the case subject's onset date. Thus controls were questioned about foods consumed as long as 35 days previously. [Angulo (G-1452), Attachment 3, P.83] [Friedman (G-1488) P.5] [Kassenborg (G-1460) P.4 L.21-23] [Feldman (B-1902) P.28 L.7-17]

CVM CRITIQUE: CVM assumes that Bayer intended "interviewed with 21 days of their stool sample" to be "interviewed within 21 days of their stool sample." This

proposed finding is misleading in its characterization of the length of time between consumption of food and interview of controls. Based on the cited testimony, although controls could have been questioned about foods consumed possibly up to 35 days prior to the interview, this time frame was a maximum. For each control, the establishment of the actual time frame was based on seven days plus the number of days (21-day maximum) within which the case subject was interviewed plus the number of days (seven day maximum) within which the control was interviewed; therefore, the actual time frame could have been far shorter than 35 days.

650. The human health impact of interest is campylobacteriosis caused by *Campylobacter jejuni* and/or *Campylobacter coli* that are resistant to fluoroquinolones, a class of antimicrobials including molecules such as ciprofloxacin, lomefloxacin and norfloxacin for use in human medicine and enrofloxacin and sarafloxacin developed for use in veterinary medicine. [JS 41; (B-549) P. 6]

CVM CRITIQUE: This proposed finding is not supported by the cited record references. CVM notes that the citations to the record provided by Bayer in support of its proposed finding of fact only support that *C. jejuni* amd *C. coli* can be human pathogens. Bayer's attempt to rely on these references for the rest of its opinion as to what is relevant is unfounded. Also see CVM critique of Bayer's proposed finding of fact 653.

There is a strong overlap in susceptibility of *Campylobacter* to these agents, so called "cross resistance", i.e. resistance to one fluoroquinolone implies resistance to all fluoroquinolones. [Newell (B-1908) P.18 L. 3-4]

CVM CRITIQUE: The proposed finding is not established by the cited testimony. Dr. Newell's testimony at that point actually states "Spontaneous single-point mutations in the *gyrA* gene of *Campylobacters*, which occur at a rate of about 1 in $5x10^9$ organisms, confers resistance to fluoroquinolones" and that paragraph ends with: "In those poultry flocks, already colonized with *Campylobacters*, treatment with fluoroquinolones selects for such mutants." [Newell B-1908 P.18 L.6-7]

653. Campylobacteriosis infections of relevance to this hearing are restricted to:

- infections from *Campylobacter jejuni* and/or *Campylobacter coli* which are,
- fluoroquinolone resistant due to use of Baytril in poultry in the United States, to the extent that they:
- result in less effective treatment in people treated with a fluoroquinolone,
- result in more protracted illness because the *Campylobacter* are resistant, and/or
- result in increased hospitalization.

[CVM Answers to Interrogatories 51-60; 67 FR 7700, 7701 (February 20, 2002); Tollefson (G-1478) P.15, L.34-39]

CVM CRITIQUE: This proposed finding is not supported by the cited references and is untrue. For example, since the resistance mechanisms in fluoroquinolones are similar, all fluoroquinolone-resistant *Campylobacter* cases could be relevant to show that fluoroquinolones (including Baytril) act as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone *Campylobacter*.

654. As of 1999, the total number of persons in the United States who contract campylobacteriosis annually, while in the United States or abroad due to foreign travel, has been estimated at about 1.4 million, or about 0.5% of the US population. [Angulo (G-1452) P. 17 L.10]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. The phrase "while in the United States or abroad due to foreign travel" does not appear in the cited testimony.

655. The total number of persons in the United States who contract campylobacteriosis annually, while in the United States or abroad, is estimated to have decreased by about 27% from 1996 to 2001. [Angulo (G-1452) P. 5 L.21-23]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. The phrase "while in the United States or abroad" does not appear in the cited testimony.

656. A number of *Campylobacter* must be ingested to cause a human infection with clinical symptoms. [(G-70) P.3; (G-441) P.3; Nachamkin (G-1470) P. 4 L. 43 - 46, P. 5 L. 1-8]

CVM CRITIQUE: This proposed finding of fact is misleading. "A number of" is too vague. Estimates from experimental human infection suggest an infective dose of as few as 500-800 organisms. With the insertion of the words "only a small" after the first word of this proposed finding, CVM would agree with this proposed finding of fact.

657. Based on experimental data, the minimum number of *Campylobacter* capable of causing Campylobacterioris has been estimated to be about 500 - 800 organisms (minimum infectious dose). [(G-70) P.3; (G-441) P.3; Nachamkin (G-1470) P. 4 L. 43 - 46, P. 5 L. 1-8]

CVM CRITIQUE: The cited exhibits and WDT do not support this proposed finding of fact. The exhibits cited in support of this proposed finding do not indicate that a dose lower than 500 organisms failed to cause campylobacteriosis. In fact, in one study, 800 organisms seems to be the lowest dose given to the study participants, and this dose did produce illness. Further, Bayer's citation to Nachamkin WDT P.5 L.3-4 ("Whether doses <500 organisms are capable of causing human illness is unknown.") does not support Bayer's proposed finding of fact, and, in fact, calls into question the accuracy of this proposed finding.

659. The capability of *Campylobacter* to cause illness (its "pathogenicity") is dependent in part on the susceptibility of the potential host, in addition to the inoculum size, or minimum infectious dose. [(B-205) P.3; (G-70) P. 3; (G-707) P. 9]

CVM CRITIQUE: The exhibits cited by Bayer do not support its proposed finding. CVM notes that the references cited by Bayer to support this proposed finding do not mention inoculum size or minimum infectious dose.

662. Nearly all *Campylobacter* infections remain localized in the small and large intestines, where they cause inflammation i.e., *Campylobacter* enteritis ("enteritis" means inflammation of the intestines, which can be caused by microbes including bacteria and other agents). [Ohl (G-1485) P.6 L.20-21; Kist (B-1906) P.4 L.17-18]

CVM CRITIQUE: Bayer's proposed finding of fact mischaracterizes the WDT. CVM notes that Bayer's finding that "Nearly all..." is not supported by Dr. Kist's WDT. The referenced portion of Dr. Kist's testimony states "Most *Campylobacter* infections..." "Most" does not equate to "Nearly all."

663. In approximately 1% or less of reported campylobacteriosis cases, the bacteria penetrate the intestinal lining and enter the blood stream, a condition known as bacteremia. [Tauxe (G-1475) P. 18 L. 28-30; (G-511) P. 1, 4; (B-742) P. 1]

CVM CRITIQUE: This proposed finding: "...1% or less.." is not supported by the cited evidence, and Bayer's cited exhibit actually supports a level 2.3 times as high. The Tauxe WDT does include the statement on P.18, L.28 that "About 1 % of infections with *Campylobacter* are documented to be systemic, because the organism is cultured from the blood." But G-511 does not provide a numerical statistic at the cited location. G-511 P.1, L.4 of Introduction reads "Bacteremia caused by these microorganisms is uncommon [1-4], and most reports of bacteremia due to *Campylobacter* species describe only a small number of cases [5-8]."

And the cited page of B-742 (P.1) includes this statement without numerical quantitation: "The organism is frequently isolated from fecal specimens from infected patients but rarely from blood from these subjects [I , 2, 8]. Unlike other enteric infections such as salmonellosis, *Campylobacter* infection (excluding infection due to *Campylobacter fetus)* is not often associated with a systemic illness." Significantly, Bayer's exhibit does provide a numerical statistic later in that same article at page 2: "From January 1985 to December 1995, a total of 24 cases of *Campylobacter* bacteremia were found in 1,006 patients with campylobacter enteritis". This would be over 2.3 %.

The difference between the Bayer-proposed finding's "1% or less" and Bayer's own Exhibit (B-742)'s 2.3% is at least 1.3%. Applying the 1.3 additional percent to the estimated 2.4 million cases of Campylobacter cases in the United States [Kassenborg WDT p. 2, line12; G-410] means that the Bayer-proposed finding would have understated

the number of cases of *Campylobacter* bacteremia by 0.013 x 2,400,000, or 31,200 cases per year in the United States.

665. In very rare cases, campylobacteriosis can cause systemic illness once in the blood stream (sepsis) and in extremely rare cases, infections can become present in extra-intestinal organs. (Blaser 1992) [Ohl (G-1485) P.7 L.1-3; (G-580) P.7, 8]

CVM CRITIQUE: Bayer's proposed finding is not supported by Dr. Ohl's WDT or by the cited Exhibit G-580. Dr. Ohl stated that "[R]arely, *Campylobacter jejuni*...can invade the bloodstream and subsequently other organs..." Bayer's characterization that other organs may become infected "in extremely rare cases" is unfounded. Likewise, Exhibit G-580 does not support Bayer' proposed finding.

668. These clinical symptoms are indicative of campylobacteriosis but are not definitive, since they are similar to the symptoms of other forms of bacterial enteritis, such as those caused by *Shigella*, *E. coli* and *Salmonella*. [(G-191) P. 7; (G-1789) P. 3; (B-205) P.5]

CVM CRITIQUE: The proposed finding is not suported by the record reference. CVM notes that the exhibits cited by Bayer to support its proposed findings do not mention *E. coli* or *Shigella*.

670. Only a very small fraction of persons with campylobacteriosis seek treatment and are evaluated by a physician; e.g., based on 1996 - 1997 FoodNet data, it was estimated that only 1 in 18 persons with campylobacteriosis seek treatment. [(G-615) P. 3; Pasternack (B-1909) P. 4 L. 4-6]

CVM CRITIQUE: Bayer's proposed finding of fact is not supported by its record reference. CVM notes that the estimate of 1 in 18 persons with campylobacteriosis was based on a small town outbreak of campylobacteriosis in the mid 1980's and not on the 1996-1997 FoodNet data (see G-615 P.3 and P.6 referring to Sacks, et al,.). The author of G-615 then uses this ratio to estimate the estimated number of *Campylobacter* cases in the United States. According to Bayer's Appendix A of its Proposed Findings, Exhibit G-615 was published in 1992, well before the 1998-1997 FoodNet data existed.

672. Administration of fluids, orally or intravenously, to correct or prevent dehydration is the most common form of treatment. [Kist ((B-1906) P.9 L. 17-20]

CVM CRITIQUE: The proposed finding of fact is not supported by the cited WDT for two reasons: First, Kist's WDT only indicates oral fluids (not intravenous) are commonly used. Second, Kist does not indicate rehydration actually is the most common form of treatment; he indicates most *Campylobacter* patients do not require special treatment other than oral replacement of fluid and electrolytes.

673. Only a small number of individuals with moderate to severe symptoms may require antibiotics as part of their therapy. [Ohl (G-1485) P. 9 L. 46, P. 10 L. 1-7; Pasternack (B-

1909) P. 7 L. 17-22, P. 18 L. 15-18; (G-70) P. 6; Iannini (B-1905) P. 5 L. 9-12; Molbak (G-1468) P.3 L.21]

CVM CRITIQUE: This proposed finding is not supported by Dr. Ohl's WDT. Dr. Ohl specifically states, "...moderate to severe inflammatory diarrhea associated with fever, and systemic symptoms with or without blood in the stool should be treated with antibiotics." (Ohl WDT P.10 L.43-45). Dr. Pasternack's WDT, cited by Bayer in support of its proposed finding, does not actually state that a small number of patients with moderate to severe symptoms may require antibiotic treatment. Rather, he states that "a small minority of individuals..." ithout reference to the subgroup of those with moderate to severe symptoms.

674. For this small percentage of people, the antibiotic of choice for treatment of campylobacteriosis is a macrolide such as erythromycin or azithromycin or the new rifaximin. [Iannini (B-1905) P.4 L. 8-11; Pasternack (B-1909) P. 14 L. 1-16; Endtz (G-1457) P. 6 L. 44-45; Thielman (G-1477) P.2 Para. 4; Morris (G-1469) P.5 L. 3-5; (G-557) P. 3; (B-816) P. 2]

CVM CRITIQUE: The proposed finding is contradicted by the WDT of several witnesses. Drs. Ohl (WDT P.13 L.27-38) and Theilman (WDT P3 ¶ 6) indicate that both fluoroquinolones and macrolides are the drugs of choice for campylobcteriosis and that fluorquinolones are the drug of choice for empiric treatment of gastroenteritis. Dr. Iannini agress that "[T]hc broad spectrum of activity offered by fluoroquinolones make these compounds attractive candidates for use where empirical treatment is indicated." Iannini WDT P.4 L.3-4

677. If the treating physician does not have the results of a culture, and must decide on empiric treatment, the common criteria for the antimicrobial treatment of human *Campylobacter* infection include: severe illness, severe systemic toxicity, high fever, severe symptoms of dysentery; prolonged illness; worsening and/or relapsing symptoms despite appropriate supportive therapy; underlying primary and acquired immunodeficiency states such as HIV, immunoglobulin deficiency states, allograft recipients; chronic illness; and the elderly. [JS 42.]

CVM CRITIQUE: This proposed finding is internally inconsistent because of language Bayer inserted at the beginning of what was JS 42. How can there be common criteria for treating *Campylobacter* if the treating physician does not have the results of the culture and must decide on empiric treatment? The better finding would delete the words "If the treating physician does not have the . . . empiric treatment."

680. Even without correcting for foreign travel and prior fluoroquinolone use, it has been estimated that the potential number of treatment failures in the US due to fluoroquinolone-resistant *Campylobacter* infections would be less than 150, or less than 0.00005% of the US population, which is over two orders of magnitude less (< 1 in a million) than the 1 in 10,000 risk level that FDA accepted as safe in its bottled water

standard for microbial infections. [Kist (B-1906) P. 11 L. 15-22 - P. 12 L. 1-11; Bayer Response to NOOH P. 16 and authorities cited]

CVM CRITIQUE: The references cited in support of this proposed finding do not support it. First, Kist WDT P.11, L.15-22 does not address treatment failures and neither section of Dr. Kist's WDT have anything to do with bottled water standards for microbial infections. Second, Bayer cites to a document not in evidence.

681. The need for empiric treatment of campylobacteriosis by fluoroquinolones has been diminished by the recent introduction of a new test which allows *Campylobacter* infections to be identified within two hours [(B-1143) P. 1-3]; and by the emergence of azithromycin as an effective, broad-spectrum antibiotic that is well tolerated and to which resistance is low, and a soon to be approved antimicrobial rifaximin. [Pasternack (B-1909) P. 13 L.11-21, P.14 L.1-16; Iannini (B-1905) P.4 L.9-16, P. 6 L.1-5; Ohl (G-1485) P. 13 L.31-33]

CVM CRITIQUE: The proposed finding of fact has no support in the record for this proposed finding. First, there is nothing in the record indicating whether this new test is widely available or widely used. Further, Bayer has provided no information on rifaximin, and rifaximin is not currently approved in the United States.

685. Traveler's Diarrhea is the most common travel-related medical problem, afflicting 20-50% of travelers visiting the developing world, including 7 million US residents. [Ohl (G-1485) P. 7 L. 22-24]

CVM CRITIQUE: This proposed finding is not supported by the cited record reference. Dr. Ohl does not state that the 7 million figure is specifically US residents as stated in the proposed finding. Further, the exhibits cited by Dr. Ohl to support this portion of his WDT indicate that the 7 million figure refers to travelers from industrialized countries (not just the United States) to developing countries. (B-121)

691. Based on the CDC 1998-1999 *Campylobacter* case-control study, Traveler's Diarrhea may account for 13% of the campylobacteriosis cases for which persons seek treatment in the United States each year. [Angulo (B-1452) P. 81, Attachment 3]

CVM CRITIQUE: CVM assumes that Bayer intended "Angulo (B-1452)" to be "Angulo (G-1452)." This proposed finding is contrary to the cited testimony. The cited testimony refers to the percentage of cases who reported foreign travel; however, the attributable risk of foreign travel is 12%, as explained on P.89 of the citation (G-1452, Attachment 3).

692. In addition to being acquired outside the United States from sources outside the United States, Traveler's Diarrhea is also distinctive in that it has a longer mean duration of diarrheal symptoms than campylobacteriosis acquired in the United States, regardless of whether the disease is due to *Campylobacter* which are susceptible or resistant to fluoroquinolones. [Burkhart (B-1900) P. 36 Table 8]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of Ohl (G-1485) P.7 L.20-22, which states that traveler's diarrhea is a specific term describing a short duration diarrhea that is acquired by those traveling to less developed countries. Moreover, the proposed finding is not supported by the cited testimony in that the cited Table 8 does not show any tests for statistical significance when comparing the duration of diarrhea: (1) in resistant cases with foreign travel and resistant cases without foreign travel; or (2) in susceptible cases with foreign travel and susceptible cases without foreign travel.

693. This longer duration may be caused by some other risk factor for which foreign travel is a marker, such as exposure to more heavily contaminated foods or water, or to novel strains of *Campylobacter* to which the traveler has no immunity. [(G-1711) P. 5, 6; Feldman (B-1902) P.37 L.6-8]

CVM CRITIQUE CVM assumes that, by "longer duration," Bayer means "longer duration of diarrhea." This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The cited testimony does not offer support for the hypothesis suggested in the proposed finding: Exhibit G-1711 does not deal with duration of illness; B-1902 P.37 L.6-8 does not provide any supporting reference for its statements, which do not deal with duration of diarrhea either.

696. Empiric treatment of enteritis with a fluoroquinolone has been shown to select for fluoroquinolone resistant *Campylobacter* during treatment in 25% of the cases, constituting a further reason not to routinely treat adult patients empirically. [(B-816) P. 2; (B-857) P. 1; (G-250) P. 4; (G-529) P. 2; (G-589) P. 4; (B-127) P. 2-4]

CVM CRITIQUE: This proposed finding is not supported by the reference cited. For example, B-857 does indicate that fluoroquinolone-resistant *Campylobacter* did emerge after norfloxacin use; however, they do not state that fluoroquinolones should not be routinely used to treat adult patients empirically. B-816 does indeed mention that in a study the authors performed that 25% of *Campylobacter* spp developed quinolone resistance. However, there is no information on the study (i.e., size of patient population; prior fluoroquinolone use; day of treatment initiation, etc.) as it is just mentioned in this letter to the New Zealand Medical Journal. The authors also state in the next paragraph that a later and more detailed study of the Swedish study showed the severely ill (fever > 38°C, abdominal pain and > 6 loose stools/day) and especially those treated within 48 hours of onset benefited clinically from norfloxacin. G-589 (Smith et al.,) does not state that resistance emergence during therapy constitutes a further reason not to routinely treat adult patients. B-127 also reports on emergence of fluoroquinolone resistance in *Campylobacter* during norfloxacin treatment, but their conclusion is very different than Bayer's proposed finding of fact. They state that quinolones are very effective for intestinal infections of unknown origin due to their effectiveness against all bacterial enteropthogens and are often thought to be the antibiotics of choice in such situations. They also mention that erythromycin has excellent activity against *Campylobacter*, but it has no effect against most other enteric pathogens.

697. When performing quantitative assessments of domestically acquired campylobacteriosis, it is necessary to remove cases of Traveler's Diarrhea as it consistently appears as a confounder in the population group or subgroup under consideration. [Burkhart (B-1900) P.4 L.16-18, P.13 L.20-46, P.14 L.1-22; Cox (B-1901) P.5 L.14-21, P.31, Attachment 1; Feldman (B-1902) P.16 L.3-14, P.36 L.13-21, P.37 L.1-8, P.38 L. 20-22, P.39 L.1-7, P.42 L.5-14]

CVM CRITIQUE: This proposed finding is vague in that it does not specify what "quantitative assessments" it is referring to and, therefore, it is unsupported.

698. Traveler's Diarrhea is a confounder (it is significantly positively associated with both fluoroquinolone resistance and days of illness) and is significantly different from domestically acquired diarrhea. [Cox (B-1901) P.22]

CVM CRITIQUE: This proposed finding of fact is unsupported by its only citation. A careful reading of the cited page of that reference will reveal not a trace of support for the proposed finding.

699. When performing quantitative assessments of domestically acquired, fluoroquinolone-resistant campylobacteriosis, it is necessary to remove cases of Traveler's Diarrhea and cases previously treated with fluoroquinolone from the population group or subgroup under consideration. [Burkhart (B-1900) P.4]

CVM CRITIQUE: This proposed finding is vague in that it does not specify what "quantitative assessments" it is referring to and, therefore, it is unsupported.

700. When cases of Traveler's Diarrhea and previous fluoroquinolone treatment are removed from the "CDC 1998-1999 *Campylobacter* case-control study" and Smith et al. study populations, there is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. [Burkhart (B-1900) P. 35 L. 4-6; P. 36 L. 4-5]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. The cited testimony, Burkhart (B-1900) P.35 L.4-6; P.36 L.4-5, does not even address the Smith et al. study. Moreover, the proposed finding is contradicted by Burkhart (B-1900) P.37 L.6, which says that Burkhart's findings from his purported reanalysis of the CDC 1998-1999 *Campylobacter* case-control dataset "are similar to those reported by Marano [who analyzed duration of diarrhea in the data from the reference case-control study]. Irrespective of foreign travel or prior FQ use, resistant cases with no use of an [antidiarrheal] agent tended to have a longer duration of diarrhea by 1-2 days."

701. CVM does not have any facts or data demonstrating any increase in the rate or extent of complications (including but not limited to Guillain-Barre Syndrome) from infections caused by fluoroquinolone-resistant Campylobacter as compared to infections caused by

fluoroquinolone-susceptible (non-resistant) Campylobacter. [CVM Interrogatory Answer 60]

CVM CRITIQUE: The proposed finding is now contradicted by testimony on this record. [Molbak WDT (G-1468) P.18-22]

703. There are no data associating either complications or increased mortality with fluoroquinolone resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. [Kist (B-1906) P.16 L.6-7, P.18 L.6-7, 12-13; Newell (B-1908) P.47 L.23-24, P.48 L.1-2]

CVM CRITIQUE: This proposed finding is contradicted by Molbak (G-1468) P.20 L.11-13 and L.38-40; P.22 L.23-25. In his WDT, Dr. Molbak presents previously unpublished data from a Danish study where rates of complications and mortality are compared between patients infected with fluroquinolone-resistant and fluroquinolone–sensitive strains, there is an increased risk of intestinal and extraintestinal complications and also a possibility of increased mortality.

704. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or - elderly patients, almost always with an underlying serious disease. [Kist (B-1906) P.3 L.19-20; (B-44) P. 1; (G-580) P. 4; (G-1644) P. 4]

CVM CRITIQUE: The proposed finding is not consistent with the record. The fatal outcome rate is 1.18% in the first year after *Camplylobacter* infection, roughly 1.5 to 2 times the mortality in controls. [G-1799 P.2]

706. Reactive arthritis is characterized by pain and swelling of joints, typically 1 to 2 weeks after onset of enteritis, caused by agents such as Campylobacter. [Kist (B-1906) P. 7 L.3-4]

CVM CRITIQUE: Bayer's proposed finding is not supported by the cited reference because the quoted portion of Dr. Kist's testimony does not include the words "enteritis, caused by agents such as." CVM only objects to the addition of those words. There is no basis on the record for a finding that reactive arthritis occurs after enteritis causing bacteria, other than *Campylobacter*.

708. *Campylobacter* associated reactive arthritis is rare (0-1.7% of reactive arthritis cases) and is not affected by prior antibiotic treatment. [Kist (B-1906) P. 7 L.11-13; Pasternack (B-1909) P. 19 L.6-8]

CVM CRITIQUE: Bayer's proposed finding is contradicted by Kist's WDT. The same portion of the cited WDT of Kist cites to another study showing 1 - 3% incidence of reactive arthritis following *Campylobacter*.

710. The potential benefits of empiric treatment of campylobacteriosis with a fluoroquinolone are uncertain because the data from the relevant studies are conflicting regarding whether

the duration of diarrhea will be shortened and whether treatment requires "early" treatment, i.e., before the elapse of the time it takes to obtain the results of a stool culture or other test. [Pasternack (B-1909) P. 11 L.19-22, P.12 L.1-22, P.13 L.1-8; (B-44) P. 7; (B-127) P. 4; (G-705) P. 1]

CVM CRITIQUE: Bayer's proposed finding of fact is not supported by the exhibits cited in support thereof. B-44 is a study reporting the efficacy of erythromycin and azithromycin not fluoroquinolones. Exhibit B-127 is a study involving fluoroquinolone use; however, the study population consisted of only five patients, one of who was HIV positive with karposi sarcoma. Further, G-705, cited by Bayer in support of its proposed finding is indeed a study of fluoroquinolone (norfloxacin) use versus placebo use with the results indicating a statistically significant shorter median duration of diarrhea for patients treated with norfloxacin (three days vs. five days). Further, of the many references provided within the cited portion of Dr. Pasternack's WDT, only three appear with associated exhibit numbers in the references to his WDT (see Pasternack WDT P.22-25). Of these exhibits, B-1127 involved the study of the effectiveness or erythromycin versus placebo in children; B-289 involved a study of the effectiveness of ciprofloxacin on gastrointestinal illness, and noted "This study demonstrated that a 5-day course of therapy with oral ciprofloxacin reduces the duration of diarrhea and other symptoms in patients with severe acute community-acquired gastroenteritis." (B-289 P.4); and G-250, which involved a study comparing ciprofloxacin with sulfamethoxazole and trimethoprim versus placebo showed that, "[B]y study days 1, 3, 4 and 5, patients receiving ciprofloxacin had a better clinical response (percent cured or improved) than those receiving placebo ($P < .05$). Although differences between sulfamethoxide and trimethoprim and placebo were seen, only the difference on day 3 was significant ($P < .05$)." [G-250 P.4]

711. Some of the relevant studies show no statistically significant benefit, in the form of reduction of the mean duration of diarrhea, from treatment of susceptible *Campylobacter* with fluoroquinolones. [(B-816) P. 2-3; (G-188) P. 1, 3, 4, 5; (G-172) P. 3]

CVM CRITIQUE: The cited exhibits do not support Bayer's proposed finding of fact. G-172 shows there is a significantly longer mean duration for patients treated with a placebo rather than a fluoroquinolone; G-188 examined patients treated only after the identification of the bacterial agent and states that the study only examined patients whose diarrheal disease had persisted for longer than previously investigated. Since early initiation of treatment leads to more effective treatment (Theilman WDT P.2-3 4; Morris WDT P.4 L.21-22; Ohl WDT P.15 L. 23-25) this study cannot be used to support Bayer's proposed finding of fact. And, B-816, also cited by Bayer, does not support its proposed finding; the chart on P.3 consistently shows studies demonstrating a shorter duration of diarrhea for those infections treated with a fluoroquinolone compared to a placebo.

712. While some studies claim that "early" treatment of campylobacteriosis is required to obtain a reduction in the mean duration of diarrhea, the study that shows the greatest benefit from such treatment (Dryden et al.) concerned patients who had received

treatment, on average, 4 or more days after the onset of their diarrhea. [(B-1127) P.1; (G-172) P. 3; Pasternack (B-1909) P. 12 L. 14-20]

CVM CRITIQUE: This proposed finding of fact is unsupported by the cited reference. Bayer provides no support for the assertion that the Dryden study is "the study that shows the greatest benefit from such treatment."

713. On the other hand, empiric treatment of enteritis with fluoroquinolones entails the risk that, if the disease is caused in whole or in part by *Salmonella* bacteria, carriage of the bacteria will be prolonged and an acute infection may be turned into a chronic one. [Pasternack (B-1909) P.5 L.18-20, P.8 L.17-18]

CVM CRITIQUE: This proposed finding is not supported by the cited WDT. Bayer is confusing symptomatic relapse with chronic infection. Neither portions of Pasternack's WDT address chronic infection.

714. Further, empiric treatment of enteritis with antimicrobials such as fluoroquinolones also presents a risk of a life-threatening complication of hemorragic *E. coli* infection known as the hemolytic-uremic syndrome, whose risk is thought to be increased significantly following antibiotic treatment of hemorrhagic *E. coli* enteritis. This is less common in adults than in children, but is present nonetheless. [Iannini (B-1905) P.3 L. 19-21, P.4 L.1-2; Pasternack (B-1909) P.5 L.8-17, P.8 L.18-21; (B-1559) P.1, 3, 4, 6]

CVM CRITIQUE: Bayer's proposed finding is misleading. As admitted by Dr. Pasternack, *E. coli* 0157 occurs mainly in children and fluoroquinolones are not used in children, (see also Ohl WDT P.9 L.8-13), significantly lessening the likelihood of problems associated with empiric fluoroquinolone therapy.

715. Empiric use of antimicrobials, including fluoroquinolones, for the treatment of enteritis is undergoing reexamination, and more recent treatment guidelines are more cautious about recommending the use of such therapy. [Pasternack (B-1909) P. 4 L.10-21, P.5 L.1-20, P.11 L.1-18, P.18 L. 21-22, P.19 L.1-22, P.20 L.1-2; Iannini (B-1905) P. 3 L.15-18; (B-857) P.2; (G-253) P.5; (G-707) P.9]

CVM CRITIQUE: Bayer's proposed finding is misleading. Empiric treatment with antimicrobials, including fluoroquinolones occurs and, in fact, fluoroquinolones remain the recommended therapy (see Pasternack WDT P.11 L.4-5 and P.18 L.4-5; Kist WDT P.11 L.13-14; Morris WDT P.6 L.2-5 and P.6 L.8-12; Thielman WDT P. 3 6 and P. 4 10; Ohl WDT P.11 L.44-46), when antimicrobial therapy is indicated.

716. As a consequence of the emerging and improved knowledge of the relative risks and benefits of empiric treatment of enteritis with fluoroquinolones, such empiric treatment of enteritis which is not Traveler's Diarrhea is properly, and increasingly, limited to adult patients with severe abdominal pain, frequent episodes of diarrhea, fever, blood or white blood cells in the stool, who seek medical attention relatively early, and those individuals

who weakened as a result of any of a variety of medical illnesses or conditions due, e.g., to age, pregnancy, etc. [(B-127) P.1; (G-172) P.5,6; (G-292) P.1]

CVM CRITIQUE: The cited record references do not support this proposed finding. Two of the three exhibits cited by Bayer as support for this finding do not address empiric treatment criteria (Exhibits B-127 and G-292). Further, Dr. Ohl states, "My opinion coincides with that of most experts, treatment guidelines, and treatment guidebooks, that . . . moderate to severe inflammatory diarrhea associated with fever, and systemic symptoms with or without blood in the stood should be treated with antibiotics . . ." (Ohl WDT P.10 L.41-45)

721. The prognosis of campylobacteriosis in HIV-infected individuals depends on the severity of immunodeficiency rather than on issues of initial antibiotic susceptibility: there are well-documented cases of fluoroquinolone-susceptible *Campylobacter* enteritis and bacteremia who nevertheless failed therapy. [Pasternack (B-1909) P. 6 L.11-12, P. 7 L.8-12]

CVM CRITIQUE: Bayer's proposed finding of fact is an opinion without factual basis in the record. While host immunity plays a part in the response to therapy receipt of an appropriate antimicrobial to which the organisms is susceptible may also play an important part. The relative contribution of each probably varies from patient to patient but, as a rule, clinicians prescribe drugs to which the organism is susceptible. If only host effects were important than it would it would follow that one would not treat highly immunocompromised patients at all since they have a high chance of failure. Clearly this is not the case. See Ohl WDT [Exhibit (G-1485) P.11 L.11-20]. Therefore, at least 26% and as many as 42% of patients in this one study with fluorquinolone-resistant *Campylobacter* isolates did not achieve a cure. If the three ciprofloxacin-treated patients lost to follow-up were assumed to be cured, then maximal cure rate would still be only 75%." (Exhibit B-1920 P.4). Exhibit B-50 is an abstract which gives no information on the criteria used to determine response to ciprofloxacin therapy, not gives patient data on length of illness prior to initiation of fluoroquinolone treatment, bot important variables to consider.

722. In the most thoroughly reported case study, the deaths of three HIV-infected patients were attributed to *Campylobacter jejuni* bacteria infections, however, fluoroquinolone resistance was not a factor in causing the deaths. [(B-742) P. 3-5; Pasternack (B-1909) P. 6 L.17-22, P.7 L.1-13]

CVM CRITIQUE: Bayer has provided no citation supporting its contention that B-742 is "the most thoroughly reported case study." Further, B-742 does not provide enough information to base a conclusion that fluoroquinolone resistance was not a factor in the deaths.

723. Resistance of domestically acquired *Campylobacter* to fluoroquinolones in patients not recently treated with fluoroquinolones does not appear to be a very significant clinical concern in the United States: the most recent, broad-based studies in the United States

"CDC 1998-1999 *Campylobacter* case-control study" and Smith et al. do not show any difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. [Burkhart (B-1900) P. 36 (Table 8); (B-50) P. 2]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. First, the cited testimony, Burkhart (B-1900) P.36 (Table 8), does not even address the Smith et al., study and the cited exhibit, Exhibit B-50, is not even related to the issue of the proposed finding, i.e., resistance, prior antimicrobial use, and foreign travel. Moreover, the proposed finding is contradicted by Burkhart (B-1900) P.37 L.6, which says that Burkhart's findings from his puported reanalysis of the CDC 1998-1999 *Campylobacter* case-control dataset "are similar to those reported by Marano [who analyzed duration of diarrhea in the data from the reference case-control study]. Irrespective of foreign travel or prior FQ use, resistant cases with no use of an [antidiarrheal] agent tended to have a longer duration of diarrhea by 1-2 days."

724. Even outside the United States, where infections may be more serious, recent studies of patients receiving fluoroquinolone for enteritis in settings where fluoroquinolone resistance among *Campylobacter* isolates was almost universal show that treatment failures are limited (approximately 2.6-25%), even among populations with very high in vitro resistance rates (in vitro means outside the host, e.g. laboratory tests). [(B-1920) P.4; (B-50) P.2]

CVM CRITIQUE: There is no support in the exhibits Bayer cites to support its finding that *Campylobacter* infections outside the United States may be more serious than those inside the United States, nor for the percentage of treatment failures presented in this proposed finding. B-1920 P.4 states that "of the 23 *Campylobacter* cases, 22 showed *in vitro* resistance to ciprofloxacin. The patient with the sensitive isolate was treated with ciprofloxacin and was cured. Of the 22 patients with a resistant isolate, 19 were treated with ciprofloxacin, and 11 (58%) achieved a cure, 5 (26%) were not cured at 72 hours, and 3 (16%) were lost to follow-up." Therefore, at least 26% and as many as 42% of patients in this one study with fluoroquinolone-resistant *Campylobacter* isolates did not achieve a cure. If the three ciprofloxacin-treated patients lost to follow-up were assumed to be cured, then maximal cure rate would still be only 75%." (B-1920 P.4)

Exhibit B-50 is an abstract which gives no information on the criteria used to determine response to ciprofloxacin therapy, nor gives patient data on length of illness prior to initiation of fluoroquinolone treatment, both important variables to consider. Further, Bayer's characterization of treatment failures as high as 25% as "limited" is unsupported.

725. Treatment failures among patients with susceptible *Campylobacter* isolates receiving fluoroquinolones are in a similar range to such treatment failures among patients with resistant isolates:

- In the Piddock study, the frequency of treatment failures for fluoroquinolone resistant *Campylobacter* was approximately 2.6% (1/39), and in the Sanders

study the treatment failure rate was approximately 25%, producing a fluoroquinolone-resistant treatment failure range of approximately 2.6% to 25%.

- In the Kuschner study, the frequency of treatment failures for fluoroquinolone-susceptible *Campylobacter* was approximately 4.2% (1/24), and in a clinical trial of empiric ciprofloxacin treatment for acute diarrhea, the treatment failure rate for fluoroquinolone-susceptible *Campylobacter* was approximately 20% (2/10), producing a fluoroquinolone susceptible range of approximately 4.2% to 20%. [(B-20) P.2; (B-1920) P.4; (G-354) P.3; Pasternack (B-1909) P.12 L.20-22, P.13 L.1]

CVM CRITIQUE: This statement of opinion is without factual basis on the record; it is an erroneous conclusion based on invalid comparisons between different exhibits. (See CVM's critique of Bayer's proposed finding of fact 724). Furthermore, this finding mischaracterizes and in some cases is contrary to the exhibit(s) cited. The statement is also misleading.

Exhibit B-20, entitled "In Vitro Susceptibility of *Campylobacters* Isolated from Poultry to Enrofloxacin and Ciprof;oxacin" by Diker, does not support this finding. Further, "The Piddock study" (we assume Bayer is referring to B-50 although B-50 is not cited) is not truly a "study," but rather an abstract which includes a sentence stating "Preliminary data showed that only 1/39 patients with ciprofloxacin-resistant *Campylobacter* enteritis did not respond to ciprofloxacin therapy..." The reference does not describe in any way the cases included and it does not define "response to therapy." Because many *Campylobacter* enteritis cases are self-limiting, without a comparison group, it is impossible to attribute recovery to antibiotic use. Since case inclusion criteria were not described, it is also impossible to know the representativeness of the cases.

Further, it is unclear how a treatment failure of 4.2% (1/24) is derived from the Kuschner paper. There were 44 *Campylobacter* isolates from 42 patients and 22 of the isolates were resistant to ciprofloxacin. In any case, it is a misuse of the data. The study looked at the use of azithromycin for the treatment of *Campylobacter* enteritis in Thailand. With regard to isolate susceptibility, the study found "Among patients who had only *Campylobacter* species isolated and were treated with ciprofloxacin, four (57%) of seven with susceptible isolates recovered by 48 house compared with two (29%) of seven with resistant isolates." Depending on how one defines "treatment failure rate," this could mean that the treatment failure rate was 65% higher in the resistant group (five of seven vs. three of seven), which contracts the proposed finding of fact.

726. It is likely that the apparent efficacy of fluoroquinolone in "resistant" cases can be attributed to the very high concentrations of fluoroquinolone achieved in vivo in the human intestine and found in stool samples. The achievable stool concentration of fluoroquinolone typically exceeds the in vitro benchmarks for "resistance" (which are

based on blood concentrations for other bacteria) for fluoroquinolone in *Campylobacter* by an order of magnitude or more. [(G-172) P. 1]

CVM CRITIQUE: This proposed finding is not supported by the cited reference Exhibit G-172. Exhibit G-172 makes no reference to the above claim. In fact the authors of G-172 report that high level resistance to ciprofloxacin (MIC > 32 μg/ml) was detected in strains (4%) of *Campylobacter* species. Two of the patients received placebo and recovered without further treatment, indicating that the most likely explanation of the apparent efficacy of fluoroquinolones in "resistant" cases is spontaneous resolution of the disease, which is the typical course of events in *Campylobacter* diarrhea. The third patient received ciprofloxacin, and although the diarrhea resolved after four days, the patient continued to have severe abdominal pain, which was considered a treatment failure. This patient was given erythromycin. The organism continued to be isolated from the patient's stool after ciprofloxacin therapy but was absent 6 weeks after treatment with erythromycin.

727. There is both conceptual evidence as well as clinical experience to suggest that the current definition of in vitro *Campylobacter jejuni* resistance to ciprofloxacin is overly stringent and not relevant to the clinical management of *Campylobacter jejuni* enteritis in almost all cases. [Pasternack (B-1909) P. 17 L. 4-6]

CVM CRITIQUE: Bayer's proposed finding of fact is contradicted by the WDT of Dr. McDermott P.4 L.44-P5 L.6 and Walker WDT P.6 L.42—P.7 L.6. Moreover, it is not discernable from Bayer's proposed finding what Bayer thinks is the current definition of in vitro *C. jejuni* resistance to ciprofloxacin. This is especially important since Bayer claims there is no "breakpoint" for *Campylobacter jejuni* resistance to cirprofloxacin (see Bayer's proposed finding 730). CVM, however, disagrees with the proposed finding, assuming the breakpoint is 4 μg/mL because while researchers in the United States commonly use a breakpoint of 4 μg/mL to define *Campylobacter jejuni* resistance to ciprofloxacin (i.e., B-868, G-1800); other countries use lower breakpoints (see CVM critique to Bayer's proposed finding of fact 730) and Bayer's witness Newell admits that "...although MICs of 4 μg/mL may be considered resistant..." In addition, CVM notes that in most studies, *Campylobacter* MICs have been bimodal; that is, either low (fluoroquinolone-sensitive) or very high (MIC >32 μg/mL. (see B-868; McDermott WDT P.4 L.44 and P.5 L.6; Walker WDT P.6 L.42-P.7 L.6)

728. Epidemiological data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. [Cox (B-1901) P. 78]

CVM CRITIQUE: This proposed finding is contradicted by much evidence on the record, including the CVM RA [G-953] on page 3 of the Introduction, first paragraph lists 4 references to this effect: Blaser's chapter in Mandell, Bennett and Dolan, Goodman et al., Piddock (1995), and Wistrom, et al. The Engberg exhibit, G-191, page 1 also indicates that this proposed finding is incorrect.

729. Treatment results, in combination with pharmacokinetic data, support the conclusion that the breakpoints for fluoroquinolone resistance in *Campylobacter* set based on extrapolations from in vitro testing are too low to have clinical significance. [Silley (B-1913 P. 17 L. 15-23, P. 18 L. 1-15; Pasternack (B-1909) P. 14 L. 19-22 – P. 15 L. 1-16]

CVM CRITIQUE: The proposed finding is an opinion of the witness that is not supported by the weight of current scientific evidence. Dr. Robert Walker, an expert in this area gives the following reason from his testimony, G-1481, Page 7, lines 13-35:

"In my opinion, in the absence of NCCLS interpretive criteria, the use of 4 μg/mL as a ciprofloxacin resistant breakpoint for *Campylobacter* is too high. The reason for this is there are numerous articles that have stated that the fluoroquinolones are concentration- dependent drugs. In other words, the clinical efficacy of the fluoroquinolones is dependent on achieving high peak serum concentrations to MIC ratios (8 to 12) or high AUC/MIC ratios (> 125 or more with ratios of 100 or less more likely to select for resistance) (G-679). For example, when a human is dosed at an approved FDA labeled dose of ciprofloxacin, 500 mg every 12 hours, the peak serum concentration of ciprofloxacin is approximately 3.0 pg/mL and the AUC is approximately 12 1-19 X hour/mL. Thus, when dosed at 500 mg, which is the standard dose for an adult human, the serum Cmax/MIC ratio (using an MIC of 4 μg/mL) would be 0.75 and the AUC/MIC ratio would be 3. Based on these values one would expect that a resistant breakpoint for a bacterium should be no higher than 1 μg/mL for a fluoroquinolone. In other words, a resistant breakpoint of 1 μg/mL should translate to a susceptible breakpoint of 0.25 μg/mL (traditionally, MIC breakpoints are based on doubling dilutions). For ciprofloxacin and *Campylobacter*, a susceptible breakpoint of < 0.25 μg/mL would result in serum Cmax/MIC ratios of 12 and AUC/MIC ratios of 100. These ratios have been shown to correlate well with clinical efficacy (G-143)."

Bayer's witness Newell uses in her testimony "resistance" for *Campylobacter* to mean an MIC of 4 μg/mL, measured in vitro. [Newell WDT P.11 L1] In the United Kingdom, the Public Health Laboratory Service has adopted an MIC of 1 μg/mL, measured in vitro. [Newell WDT P.13 L.21-22]

730. There is no clinically established threshold or official breakpoint for resistance to ciprofloxacin among *Campylobacter* isolates in any country. [Kassenborg (G-1460) P.4 L.3-4; (B-44) P. 6; (G-1789) P. 11; (G-191) P. 4;(G-624) P. 1; Silley (B-1913); citing Piddock et. al., 2000, Attachment 1 P.46 ¶ 2]

CVM CRITIQUE: The proposed finding is not supported by the cited references. Though there is no NCCLS ciprofloxacin resistant breakpoint for *Campylobacter*, both the British Society for Antimicrobial Chemotherapy and the Comite de L'Antibiogramme de la Societe Francaise de Microbiologie report interpretive criteria. The resistance breakpoints put forth by the British Society for Antimicrobial Chemotherapy (BSAC) for *Campylobacter* are > 4 μg/mL for ciprofloxacin and > 2 μg/mL for erythromycin (G-

776). Those proposed for *Campylobacter* by the Comite de L'Antibiogramme de la Societe Francaise dc Microbiologie (http://www.sfm.asso.fr/) are >2 μg/mL for ciprofloxacin and > 4 μg/mL erythromycin. Dr. Silley cites to a three year old article by Piddock to support his testimony. If he truly were an expert in this field he would have known that the BSAC put forth its interpretative criteria since that time. See Walker WDT P.6 L.34 P.7 L.6.

731. There are no standardized methods for the measurement of fluoroquinolone resistance in *Campylobacters*. Both the methods used and the breakpoints adopted by different studies vary so the comparison of studies between countries within laboratories in the same country, is difficult. [Newell (B-1908) P.13 L.17-20]

CVM CRITIQUE: This proposed finding of fact is contradicted in Joint Stipulation 29. There is an NCCLS approved standardized testing method and quality control ranges for five antimicrobial agents (ciprofloxacin, doxycycline, erythromycin, gentamicin, and meropenem) (G-1789; G-1796).

732. In general, CDC uses a breakpoint of 4 ug/ml because the National Committee for Clinical Laboratory Standards (NCCLS) uses an MIC of 4 ug/ml for ciprofloxacin resistance to Enterobacteriaceae. [Kassenborg (G-1460) P.4 L.4-6]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. Dr. Kassenborg stated "we chose" not that it is CDC policy to choose a breakpoint of 4 μg/ml because the National Committee for Clinical Laboratory Standards (NCCLS) uses an MIC of 4 μg/ml for ciprofloxacin resistance to Enterobacteriaceae.

733. The in vivo clinical importance of *Campylobacter* deemed to be "resistant" by in vitro testing remains unknown. [Newell (B-1908) P.14 L.1-2; Burkhart (B-1900) P.4 L.22-24, P.10 L.1-2]

CVM CRITIQUE: This finding of fact is misleading when taken out of context as Dr. Newell in earlier testimony on Page 13, lines 21-24 states that "In the United Kingdom, the Public Health Laboratory Service has adopted an MIC of 1 μg/ml as resistant (Thwaites & Frost, 1999) but studies in our laboratory indicate that at this level not all strains may have the *gyrA* mutation. As validated breakpoints have not yet been established, although, MICs of 4μg/ml may be considered resistant." Furthermore, testimony provided by Walker (G-1481) contradicts this claim. In addition, the authors of G-172 report that high level resistance to ciprofloxacin (MIC > 32 μg/ml) was detected in three strains (4%) of *Campylobacter* species. Two of the patients received placebo and recovered without further treatment; the third received ciprofloxacin, and although the diarrhea resolved after four days, the patient continued to have severe abdominal pain, which was considered treatment failure. This patient was given erythromycin. The organism continued to be isolated from the patient's stool after ciprofloxacin therapy but was absent six weeks after treatment with erythromycin.

Testimony from Dr. Molbak (G-1468, Page 19, lines 15-37), states that "There are, nevertheless, data that suggests that infections with fluoroquinolone resistant *Campylobacter* are associated with an increased morbidity compared with sensitive strains. This hypothesis has been supported, at least in part, from four studies (G-394, G-589, G-780, and G-1367). Although the results from these studies are not all statistically significant, the estimates point in the same direction, and hence suggest that there is a longer duration of diarrhea in patients infected with resistant strains."

734. For fluoroquinolones, the best clinical outcomes are associated with peak/MIC ratios >/= 10. [Silley (B-1913) attachment 1 P.50 ¶ 2]

CVM CRITIQUE: This proposed finding does not accurately represent the cited testimony. Dr. Silley's testimony actually states "The authors further analyzed the data and found that a peak/MIC ratio of >12 was associated with both the best clinical and microbiological outcomes."

735. If a high enough peak to MIC ratio can be achieved then not only will the parent organism be killed but also the "resistant" mutant. [Silley (B-1913) attachment # 1 P.51 ¶ 1]

CVM CRITIQUE: The proposed finding could only be ture if there were no toxic limit to antimicrobial dosing. G-668, Page 178, describes adverse effects with very high doses of fluoroquinolones which would prohibit certain peak to MIC ratios from being achieved. Additionally, it is important to remember that there are many other factors that contribute to illness that may effect eradication of the pathogen (e.g. immune status, G-1470).

736. Peak to MIC ratios can easily exceed 10 in the gastrointestinal tract of patients with *Campylobacters* that have an MIC of 32 when patients are treated with 500mg ciprofloxacin BID. [Silley (B-1913) attachment # 1 P.51 1, 2]

CVM CRITIQUE: The proposed finding is not supported by its only citation. For example, Dr. Silley cites Brumfitt et al., (B-1098), a study with twelve healthy male subjects aged 19 to 40 years showed ciprofloxacin concentrations in the faeces immediately post-treatment ranging from 185 to 2220 μg/g following a 500mg oral dose twice a day. Only two of the subjects had a concentration less than 300 μg/g. However, upon closer inspection of this cite, two other subjects had concentrations of 300 μg/g, so in actuality, 4/12 (33%) patients in this study had fecal ciprofloxacin concentrations < 300 μg/g. This fecal concentration is below the peak/MIC ratios of ≥ 10 that Dr. Silley states in his testimony (concentration of ciprofloxacin in feces < 300 μg/ml / MIC of 32 μg/ml = 9.3). Therefore, *Campylobacter* with MICs of 32 μg/ml would in fact not be associated with the best clinical and microbiological outcomes as Dr. Silley defines them himself. Additionally, these values were only obtained on the last day of treatment (day seven) and there are no other values from any other day in the study (subjects were given 500 mg of ciprofloxacin every 12 h for 7 days). Lastly, the subjects in this study were

not colonized with *Campylobacter*, so this reference is being mischaracterized when descibed in the proposed finding as "patients with *Campylobacters*."

The Robinson et al,. reference cited by Silley on page 51 of his WDT is an abstract and is not included in the docket. Further PubMed searches on Dr. Robinson do not reveal any peer reviewed publications on this material, raising the question of its validity. The Goodman reference in the Silley testimony is not included on the docket either. This reference states that stool concentrations showed a mean concentration of 49.2 μg/g, which by no means would satisfy the peak/MIC ratios ≥ 10 versus a *Campylobacter* with an MIC of 32 μg/ml (49.2/32 = 1.5 ratio) for a successful treatment outcome.

None of the studies in the cited portions of Dr. Silley's testimony have anything to do with *Campylobacter* at all, certainly none with MICs of 32 μg/mL.

738. Given the high levels of ciprofloxacin reported in the gastro-intestinal tract it is not surprising that clinical cure can be demonstrated for organisms with an MIC of 32 ug/ml. [Silley (B-1913) attachment # 1 P.52 ¶ 1]

CVM CRITIQUE: This statement is not supported by any evidence in the cited paragraph. None of the studies that Dr. Silley cites for support of this proposition have anything to do with *Campylobacter* at all, certainly none with MICs of 32 μg/mL.

739. A proportion of the isolates tested in the NARMS program have been shown to be impure cultures, this will lead to a degree of misinterpretation of the data. [Silley (B-1913) attachment # 1 P.55 4]

CVM CRITIQUE: This proposed finding is without support on the record. The only support offered for this proposed finding was stricken by Order of 3 March 03, at page 4.

740. It is highly inappropriate to consider that *Campylobacter* spp. With an MIC of 4 ug/ml will be clinically resistant to ciprofloxacin. [Silley (B-1913) attachment # 1 P.55 ¶ 6]

CVM CRITIQUE: This proposed finding is without support on the record. The only support offered for this proposed finding was stricken by Order of 3 March 03, at page 4.

741. Available data supports a breakpoint of 64 ug/ml. Such a breakpoint would need to be substantiated in accordance with NCCLS guidelines. [Silley (B-1913) attachment # 1 P.56 ¶ 2]

742. The NCCLS breakpoint for two different bacteria to the same antimicrobial may be very different. [Walker (G-1481) P.5 ¶ 10]

CVM CRITIQUE: This proposed finding of fact is taken out of context. While Dr. Walker does indeed say in his testimony on P.5, ¶ 10, that "[f]or example, the NCCLS susceptible breakpoint for ampicillin when tested against *Staphylococcus aureus* is ≤ 0.25 μg/mL versus ≤ 8.0 μg/mL when tested against bacteria belonging to the

Enterbacteriaceae (i.e., *E. coli*)." The very next sentence states that "[o]n the other hand, the NCCLS susceptible breakpoint for both of these organisms, when tested against ciprofloxacin, is 1 μg/mL."

743. Testing methods not endorsed by NCCLS and interpretive criteria that are not set by NCCLS may be of questionable value. [Walker (G-1481) P.9 ¶ 13]

CVM CRITIQUE: This proposed finding is misleading because it is taken out of context of the witness' testimony. First, there is no paragraph 13 on page 9 of Dr. Walker's testimony. Second, on P.9, paragraph 23, Dr. Walker states that "when performed correctly, results generated from standardized in vitro antimicrobial susceptibility testing provide a reasonably accurate indication of how a bacterium may respond to an antimicrobial agent in vivo. In the United States, the NCCLS has defined those testing conditions. . .as the standards setting body for in vitro antimicrobial susceptibility of testing in the United States, the NCCLS" (see P.9).

744. Epidemiological data also suggest that treatment of fluoroquinolone-resistant Campylobacter illness patients with ciprofloxacin is usually effective. [Cox (B-1901) P.78, citing G-394 (Marano 2000 data)]

CVM CRITIQUE: This proposed finding is contradicted by the cited testimony which finds significantly increased durations of illness among cases with fluoroquinolone-resistant infections. Increased durations of illness are indicative of treatment failure.

745. CVM's risk assessment does not show that harm to human health has occurred, can occur, or is likely to occur as a result of continued use of Baytril. It does not provide valid evidence that harm to human health is likely or plausible, nor does it quantify harm to human health caused by enrofloxacin use (or by a ban). [Cox (B-1901) P.7 L.4-7]

CVM CRITIQUE: This proposed finding is a statement of opinion and is contradicted by the CVM RA [G-953] and its conclusion that about 8500 patients in 1998 and 9200 in 1999 were harmed by having fluoroquinolone-resistant infections and being prescribed a fluoroquinolone.

746. CVM's hazard identification step of the CVM/Vose Risk Assessment does not identify any adverse human health effects specifically caused by fluoroquinolone-resistant campylobacteriosis in humans. [Cox (B-1901) P.14]

CVM CRITIQUE: This proposed finding is a statement of opinion and is contradicted by the CVM RA [G-953] as illustrated in the critique of proposed finding of fact 728.

747. CVM's hazard identification step of the CVM/Vose Risk Assessment does not identify by objective causal analysis of data any adverse human health effects caused (or probably caused) specifically by fluoroquinolone-resistance in *Campylobacter*. [Cox (B-1901) P.15]

CVM CRITIQUE: This proposed finding is contradicted by the exhibit of Marano [G-394] cited in the critique of proposed finding of fact 744 which finds significantly increased durations of illness among cases with fluoroquinolone-resistant infections by means of analysis of data. Increased durations of illness are indicative of treatment failure. Thus adverse human health effects were identified in the CVM RA [G-953].

748. Analyzing the recent large case-control data set provided by "CDC 1998-1999 *Campylobacter* case-control study" shows that, with high statistical confidence, there is no detectable causal relation between fluoroquinolone-resistant campylobacteriosis in humans and adverse human health consequences (excess days of diarrhea). [Cox (B-1901) P.15]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony in that the cited testimony (B-1901 P.15) does not present an analysis of "the recent large case-control data set provided by 'CDC 1998-1999 *Campylobacter* case-control study'." Moreover, the testimony of Angulo (G-1452), P.15 L.37-40 and Attachment 4, shows a highly statistically significant difference in duration of diarrhea between persons having resistant infections compared with persons having susceptible infections (12 days versus 6 days, $p<0.01$); specifically, the mean duration of diarrhea among persons who did not take an antidiarrheal medication or an antimicrobial agent was 12 days (range, 8 to 20 days) for the 6 persons with ciprofloxacin-resistant infections and 6 days (range, 2 to 21 days) for the 61 persons with ciprofloxacin-susceptible infections ($p<0.01$).

749. Analyzing the recent large case-control data set provided by "CDC 1998-1999 *Campylobacter* case-control study" shows that, with high statistical confidence, there is not a significant statistical association between fluoroquinolone-resistant campylobacteriosis in humans and days of diarrhea, after correcting for confounders. [Cox (B-1901) P.15; Burkhart (B-1900) P.49 L.12-14]

CVM CRITIQUE: This proposed finding is not supported by the WDT of Burkhart [Burkhart (B-1900) P.35 L.4-P.36; P.37 (Tables 8,9)]. Because Dr. Burkhart did not provide the details of his analysis, including statistical measures of significance such as p-values or confidence intervals to allow for adequate statistical interpretation of the values presented, it is impossible for CVM (or anyone) to ascertain whether or not Burkhart demonstrated the absence of any statistically difference between days of diarrhea for resistant and non-resistant cases when controlling for confounders. The citation to the Cox WDT is to an allegation, not any demonstration in the WDT of the "fact" proposal.

750. The excess days of diarrhea attributed by CVM to fluoroquinolone-resistant campylobacteriosis are completely explained away by foreign travel (Cox and Popken, 2002) – a key confounder not correctly controlled for in the statistical analyses that CVM has relied on. [Cox (B-1901) P.15; Burkhart (B-1900) P.49 L.12-14]

CVM CRITIQUE: This proposed finding is not supported by Burkhart (B-1900) P.37 Table 9, which reports the following differences in days of diarrhea between resistant and

non-resistant cases who were in the "no foreign travel" category: for those with no use of an antidiarrheal agent, there were 8.0 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea; for those with no prior antibiotic use and no use of an antidiarrheal agent, there were 8.6 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea.

751. If the statistical analyses that CVM relies on to demonstrate that fluoroquinolone-resistant campylobacteriosis leads to excess days of diarrhea are completely explained away by foreign travel as a confounder, then no hazard to human health from chicken-borne fluoroquinolone-resistant *Campylobacter* has been demonstrated. [Cox (B-1901) P.15; Burkhart (B-1900) P.49 L.12-14]

CVM CRITIQUE: This statement is a hypothetical opinion, not a proposed finding of fact. It is without factual basis in the record. Moreover, this proposed finding is not supported by Burkhart (B-1900). For example, Burkhart (B-1900) P.37 Table 9 reports the following differences in days of diarrhea between resistant and non-resistant cases who were in the "no foreign travel" category: for those with no use of an antidiarrheal agent, there were 8.0 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea; for those with no prior antibiotic use and no use of an antidiarrheal agent, there were 8.6 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea. Additional evidence of the public health harm incurred with resistant Campylobacter is presented in the WDT of Dr. Molbak (G-1498, P.16-22).

752. CVM's risk assessment has not identified or quantified any adverse human health effects specifically caused fluoroquinolone-resistant *Campylobacter*. Although CVM has discussed various adverse health effects of campylobacteriosis in connection with its risk assessment, including excess days of diarrhea, Guillian-Barre Syndrome, and death, the risk assessment model itself identifies no specific adverse human health effect(s) that are caused by chicken-borne fluoroquinolone-resistant *Campylobacter*, as opposed to *Campylobacter* in general. [Cox (B-1901) P.25]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

753. Analysis of "CDC 1998-1999 *Campylobacter* case-control study" data demonstrates that fluoroquinolone-resistant campylobacteriosis is not associated with longer illness duration. [Cox (B-1901) P.24]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony in that the cited testimony (B-1901 P.24) does not present an analysis of "'CDC 1998-1999 *Campylobacter case*-control study'." Moreover, the proposed finding is contradicted by the testimony of Dr. Angulo (G-1452). For example, G-1452, P.15 L.37-40 and Attachment 4, shows a highly statistically significant difference in duration of diarrhea between persons having resistant infections compared with persons having susceptible infections (12 days versus 6 days, $p<0.01$); specifically, the mean duration of diarrhea among persons who did not take an antidiarrheal medication or an antimicrobial agent

was 12 days (range, 8 to 20 days) for the 6 persons with ciprofloxacin-resistant infections and 6 days (range, 2 to 21 days) for the 61 persons with ciprofloxacin-susceptible infections ($p<0.01$).

754. After correcting for confounding due to foreign travel, there is no significant association between fluoroquinolone-resistant campylobacteriosis and duration of diarrhea in the "CDC 1998-1999 *Campylobacter* case-control study" data set. [Cox (B-1901) P.30-31; Newell (B-1908) P.46 L.10-13; Burkhart (B-1900) P.49 L.12-14]

CVM CRITIQUE: This proposed finding does not appear to be supported by Burkhart (B-1900). Burkhart (B-1900) P.37 Table 9 reports the following differences in days of diarrhea between resistant and non-resistant cases who were in the "no foreign travel" category: for those with no use of an antidiarrheal agent, there were 8.0 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea; for those with no prior antibiotic use and no use of an antidiarrheal agent, there were 8.6 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea. Burkhart, however, does not provide details of his analysis, including statistical measures of significance such as p-values or confidence intervals to allow for adequate statistical interpretation of the data presented.

755. After correcting for confounding due to foreign travel, there is no significant association between fluoroquinolone-resistant campylobacteriosis and duration of diarrhea in the Smith et al. data set. [Cox (B-1901) P.30-31; Newell (B-1908) P.46 L.10-13; Burkhart (B-1900) P.49 L.12-14]

CVM CRITIQUE: This proposed finding does not appear to be supported by Burkhart (B-1900). Burkhart (B-1900) P.20 L.13-18 reports that, in patients without foreign travel, the mean duration was 10.3 days in resistant cases who were treated with a fluoroquinolone compared with 9.9 days in non-resistant cases who were treated with a fluoroquinolone. Burkhart, however, does not provide details of his analysis of "the Smith et al., data set," including statistical measures of significance such as p-values or confidence intervals to allow for adequate statistical interpretation of the data presented.

756. CDC researcher Jennifer Nelson (a/k/a Jennifer McClellan) anticipated that after correcting for confounding due to foreign travel, there might be no significant association between fluoroquinolone-resistant campylobacteriosis and duration of diarrhea in the "CDC 1998-1999 *Campylobacter* case-control study" set, stating in her thesis; "An alternative explanation of why people with fluoroquinolone-resistant *Campylobacter* infections have an increased hazard of having longer diarrhea could be unmeasured confounders. For example, if people were more likely to acquire fluoroquinolone-resistant bacteria during international travel..." [Cox (B-1901) P.31, citing (G-1679) (McClellan 2000)]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. The fact that a careful researcher considers alternative explanations of data does not mean that she anticipates particular results. Travel was not one of the co-variates used in this analysis.

The complete quote, which Dr. Cox truncates (from G-1679, P.59, starting under "Limitations") is: "An alternative explanation of why people with fluoroquinolone-resistant *Campylobacter* infections have an increased hazard of having longer diarrhea could be unmeasured confounders. For example, if people were more likely to acquire fluoroquinolone- resistant bacteria during international travel, they may postpone a visit to the doctor until they return from their trip. Thus, the time interval from acquiring the infection to when they seek medical care would be longer, delaying treatment and causing a more severe infection."

759. Only by improperly ignoring confounders can an apparent positive association between fluoroquinolone-resistant campylobacteriosis and duration of diarrhea in the "CDC 1998-1999 *Campylobacter* case-control study" data set be created. [Cox (B-1901) P.31]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

760. The finding of no association between fluoroquinolone-resistant campylobacteriosis and excess days of illness in the "CDC 1998-1999 *Campylobacter* case-control study" data set is consistent with data from a recent analysis of 9089 cases of campylobacteriosis, investigated in the Sentinel Surveillance Study of England and Wales (G-1772), in which there was no significant difference in the mean duration of illness associated with a fluoroquinolone-resistant organism (7.9 days) compared to infection with a sensitive organism (7.7 days) (p=0.4). [Cox (B-1901) citing Newell (B-1908); Newell (B-1908) P.46 L.13-22]

CVM CRITIQUE: This proposed finding is contradicted by the findings in Angulo (G-1452), Attachment 4, which report an association between fluoroquinolone-resistant campylobacteriosis and excess days of illness in the 1998-1999 *Campylobacter* case-control study.

762. After correctly accounting for confounding (or "explaining away" of the association) by foreign travel there is no evidence of any excess days of illness caused by a fluoroquinolone-resistant *Campylobacter* infection compared to a susceptible (non-fluoroquinolone-resistant *Campylobacter* infection. [Cox (B-1901) P.39]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence. Moreover, the proposed finding appears to contradict Burkhart (B-1900). For example, Burkhart (B-1900) P.37 Table 9 reports the following differences in days of diarrhea between resistant and non-resistant cases who were in the "no foreign travel" category: for those with no use of an antidiarrheal agent, there were 8.0 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea; for those with no prior antibiotic use and no use of an antidiarrheal agent, there were 8.6 days (resistant cases) versus 6.6 days (non-resistant cases) of diarrhea. Burkhart, however, does not provide details of his analysis, including statistical measures of significance such as p-values or confidence intervals to allow for adequate statistical interpretation of the data presented.

763. The "CDC 1998-1999 *Campylobacter* case-control study" shows no differentiation between hospitalizations related to fluoroquinolone-resistant *Campylobacter* infections and those related to fluoroquinolone-susceptible ones. [Friedman (G-1488) P. 87]

CVM CRITIQUE: This proposed finding is wholly unsupported by the cited testimony. The Friedman analysis of the CDC 1998-1999 *Campylobacter* case-control study can be found on the docket at G-1488 and Angulo (G-1452) P.80 - P.107 (Attachment 3). The Friedman analysis did not evaluate *Campylobacter* infections based on antimicrobial susceptibility; cases were patients with culture-confirmed *Campylobacter* infections and controls were well individuals selected from the community. [G-1488 P.5 - P.6 and Angulo (G-1452) P.83 - P.84]

765. When adjusted to remove Travelers Diarrhea and prior treatment, the "CDC 1998-1999 *Campylobacter* case-control study" showed that campylobacteriosis patients with fluoroquinolone-resistant *Campylobacter* were hospitalized less frequently than *Campylobacter* patients with fluoroquinolone-susceptible *Campylobacter* (9.3% vs. 10.5%) and for fewer days (median of 1 day vs. median of 3 days). [Burkhart (B-1900) P. 38]

CVM CRITIQUE: This proposed finding is not supported by the cited testimony. Burkhart's findings on P.38 (Burkhart (B-1900) in what he purports to be his reanalysis of the CDC 1998-1999 *Campylobacter* case-control study do not show any tests for statistical significance when comparing resistant and susceptible cases on percent hospitalization or on median days of hospitalization.

766. There were no differences in length of illness or admission to hospital between patients with a ciproflaxacin-resistant infections and patients with susceptible infections as reported in a recent large case control study conducted in the United Kingdom, which was stratified by foreign travel. [Molbak (G-1468) P. 19 L. 37-40]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony, as it was lifted from its context. Dr. Molbak's WDT indicates that there were no differences in mean length of illness between patients with ciprofloxacin-resistant *Campylobacter* infections and patients susceptible to all antimicrobials. Additionally, Dr. Molbak's WDT indicates that the conducted analysis was not stratified by treatment as evidenced in Exhibit G-1468 P. 20 L. 1-2, and Table 12.

767. Different conclusions, regarding significance of duration of diarrhea, were drawn by Marano compared to McClellan following the evaluation of the same "CDC 1998-1999 *Campylobacter* case-control study". [Molbak (G-1468) P. 19 L. 25-26 & L. 35]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the conclusions drawn out of context. Dr. Molbak's WDT including Exhibits G-394, G-780, and G-1367 concludes that patients with ciprofloxacin-resistant *Campylobacter* infections had a longer duration of diarrhea than susceptible patients.

768. The Danish registry data set utilized for (G-1799) and Molbak (G-1468) did not contain adequate information to study the effects of antimicrobial drug resistance or treatment with antimicrobial drugs. [(G-1799) P. 4; Molbak (G-1468) P. 20 L. 11-13]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion not a statement of fact, and is contrary to the cited references.

771. Among the patients studied in (G-1799) and (G-1468), the diagnosis of a gastrointestinal infection such as *Campylobacter* may be a marker of excess mortality rather than a contributing cause. [(G-1799 P. 4]

CVM CRITIQUE: This proposed finding of fact is misleading because it is taken out of context. The next two sentences of the cited support note that: "However, only a small proportion of patients had a coexistent illness, and the excess mortality was similar in patients with and without underlying illness. Furthermore, there was an excess mortality independent of invasive illness." [(G-1799 P. 4]

773. The relevance to this proceeding of the *Campylobacter*-related mortality inferences drawn in (G-1799) and Molbak (G-1468) is unknown and in doubt, since they provide no information regarding the species of *Campylobacter* involved in the Danish register data set or in their analyses of it, and c. fetus, which is not generally thermophilic or relevant to this proceeding, is well-known to cause or to be associated with many of the life-threatening conditions identified in those data. [G-444 P. 323-324]

CVM CRITIQUE: This proposed finding is inappropriate and contradicted by WDT to the effect that most human *Campylobacter* illness is caused by *C. jejuni*, and to a much lesser extent *C. coli*. (Endtz WDT P.2 L.17-20; Jacobs- Reitsma WDT P.2 L.4-5; Nachamkin WDT P.3 L.37-41; Smith P.4 L.32-33; Tauxe WDT P.2 L.40-42; Kist WDT P.2 L.15; Newell WDT P.19 L.7-8; Robach WDT P.5 L.2-3; Russell WDT P.24 L.18-19; Tompkin WDT P.14 L.12-13), calling into question the appropriateness of such a proposed finding. In addition, this proposed finding is misleading as the *Campylobacter* incidence reported for this study population (the population of Denmark) is 94% *C. jejuni*, 6% *C. coli*, and no reported C. fetus. (G-459, P.5.)

774. In a study in Denmark, Neimann, Molbak et al. found no statistically significant difference between the mean duration of illness from fluoroquinolone-resistant *Campylobacter* and the mean duration of illness from fluoroquinolone-suspectible *Campylobacter* ($p = 0.109$). [(G-455) P. 1]

CVM CRITIQUE: This proposed finding of fact is contrary to the cited exhibit. The cited exhibit reported *median* duration of illness, not *mean* duration.

776. Neimann, Molbak et al. also found that fluoroquinolone resistance in *Campylobacter* isolates was highly associated with foreign travel (75.6% for resistant isolates vs. 22.3% for susceptible isolates). [(G-455) P. 1]

CVM CRITIQUE: CVM notes that this proposed finding would not be appropriate because the "foreign travel" in this exhibit could have been to any country, including the United States (study was conducted in Denmark).

777. The hypothesis that *Campylobacter* which are intrinsically resistant to fluoroquinolones are capable of producing illness (virulence) that is more severe than *Campylobacter* which are intrinsically susceptible to fluoroquinolones, is based on a paucity of data which have methodological limitations, and does not apply to domestically acquired fluoroquinolone-resistant *Campylobacter*, since domestically acquired fluoroquinolone-resistant *Campylobacter* do not produce more prolonged or severe illness. [Pasternack (B-1909) P.20 L.12-15; Burkhart (B-1900) P.40 L.3-7]

CVM CRITIQUE: This proposed finding is contradicted by, among others, the findings of Nelson, et al., Exhibit G-1452, Attachment 4.

778. There is no evidence in the epidemiological experience available to date that there is an increase in virulence associated with FQ resistant *Campylobacter*. [Burkhart (B-1900) P.3 L. 17-18]

CVM CRITIQUE: This proposed finding is contradicted by Angulo (1452) P.15 L.37-40, P.16 25-37 and Attachment 4 P.13-14, which states that the longer duration of diarrhea seen in patients with ciprofloxacin-resistant infections and who have not been treated with ciprofloxacin (after collection of stool specimen) may be caused by an increased virulence in resistant, compared with susceptible, isolates.

779. There are no robust data that existed prior to the approval of FQs for use in US poultry that provide an estimate of the pre-approval background (baseline) rate of domestic FQ resistance. [Burkhart (B-1900) P.3 L. 35-37]

CVM CRITIQUE: This proposed finding is contradicted by Tollefson (G-1478) P.15 L.16-32 and the K. Smith study (G-589) P.3.

780. The Minnesota 1992-1998 database, cited by Smith, (G-589) does not adjust for foreign travel or prior FQ use. Therefore these data can not be used to determine whether domestic cases without FQ use have increased in incidence. [Burkhart (B-1900) P.3 L. 39-41]

CVM CRITIQUE: This proposed finding is contradicted by the K. Smith study (G-589) Fig. 2. This figure shows that, among the population who did not use a quinolone before stool-specimen collection, the number of domestic cases (black squares) increased between 1996 and 1998. This corresponds to an increase in incidence.

781. There is no public health basis to conclude that the approval of NADA 140-828 should be withdrawn. [Burkhart (B-1900) P.3 L.5-6]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Moreover, the proposed finding is contrary to the weight of the evidence, which shows an increase in the number of fluoroquinolone-resistant *Campylobacter* infections in humans, an association between the use of enrofloxacin in poultry and fluoroquinolone-resistant *Campylobacter* infections in humans, and adverse human health effects associated with fluoroquinolone-resistant *Campylobacter* infections.

782. Temporal reporting data from other countries cited by the FDA as affirming that FQ use in US poultry is significant cause of resistant *Campylobacter* in the US, cannot be used to reach such a conclusion. [Burkhart (B-1900) P.3 L.27-29]

CVM CRITIQUE: This statement is contradicted by Smith (G-1473) P.15 L.37-40, P.16 L.18-27, P.17 L.1-46, P.18 L.1-46, and P.19 L.1-37. NARMS and temporal reporting data from other countries can be used as evidence that fluoroquinolone use in U.S. poultry is a significant cause of resistant *Campylobacter* in the United States, particularly when that information is combined with the plethora of other data from the United States and numerous other countries that support this conclusion.

783. The FoodNet case control study has severe limitations in its questionnaire design that limit its overall value for both resistant and non-resistant *Campylobacter*. [Burkhart (B-1900) P.4 L. 12-14]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. The proposed finding is also contradicted by the testimonies of Angulo (G-1452) and Kassenborg (G-1460). The questionnaire used in the 1998-1999 FoodNet *Campylobacter* case-control study allowed the identification of risk factors for acquiring a (fluoroquinolone-susceptible or -resistant) *Campylobacter* infection [Angulo (G-1452) P.10 L.22-43] and for acquiring a fluoroquinolone-resistant *Campylobacter* infection [Kassenborg (G-1460) P.3 L.1-3 and P.14 Table 1].

784. Both the Smith study and the CDC *Campylobacter* case-control study have too few domestic FQ resistant cases without prior FQ use to be of value in studying the cause of FQ resistance. [Burkhart (B-1900) P.4 L. 14-15]

CVM CRITIQUE: The proposed finding is contradicted by the K. Smith study (G-589) P.5 – P.6 and the Kassenborg study (G-337) and (G-1460) P.5 L.16-20. In Kassenborg's study, patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infections were statistically significantly more likely (10 times more likely) to report having eaten chicken or turkey at a commercial establishment than were well control subjects (MOR 10; 95% CI 1.3-78). (In Kassenborg's study, patients with fluoroquinolone-resistant *Campylobacter* infections were no more likely to have taken a fluoroquinolone before specimen collection than were patients with fluoroquinolone-

sensitive infections. [Kassenborg (G-1460) P.10 L.22 – P.11 L.2]) In K. Smith's study, there were enough cases to demonstrate a statistically significant increase in domestic cases in Minnesota and a statistically significant association with resistant strains recovered from retail chicken products. In both of these studies, if there were not enough cases, then statistically significant results could not have been achieved.

785. It is scientifically reasonable to consider the possibility that human benefits could be attributable to the treatment of poultry with FQs. [Burkhart (B-1900) P.7 L. 18-19]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

788. Cases of FQ resistant *Campylobacter* caused by either foreign travel or prior FQ use before culture are not germane to an individual country's concern that FQ us in farm animals in that country could be causing domestically acquired FQ resistant cases. [Burkhart (B-1900) P.8 L. 44 – P.9 L. 1]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

789. The FDA also believes that temporal correlations observed in other countries provide supporting evidence that FQ use in US poultry production accounts for a significant degree of the FQ resistance that has been observed in the US. Interpretation of the foreign data hinges on the same problem that exists in the US data in that there are limited historical resistance data for comparison. [Burkhart (B-1900) P.8 L.30-34]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Moreover, the proposed finding is contradicted by Smith (G-1473) P.15 L.45 – P.16 L.16, which shows that temporal relationships between fluoroquinolone use in food animals and a subsequent increase in human fluoroquinolone-resistant *Campylobacter* infections have been observed again and again in many countries. As detailed in Smith (G-1473) P.16 L.29 – P.18 L.35, some of those countries (e.g., United Kingdom and Spain) provide good baseline data.

790. It is not so clear how foreign data generalizes to the use of FQs to treat specific microbial infections in the US. [Burkhart (B-1900) P.8 L.37-38]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed

finding. Moreover, the proposed finding is contradicted by Smith (G-1473) P.15 L.45 – P.16 L.16, which shows that temporal relationships between fluoroquinolone use in food animals and a subsequent increase in human fluoroquinolone-resistant *Campylobacter* infections have been observed again and again in many countries. Smith (G-1473) states:

> In other words, in numerous countries, independent studies have indicated that quinolone resistance in *Campylobacter* from humans follows closely after the use of fluoroquinolones in veterinary medicine in those countries. In several of these countries, fluoroquinolones had been used in human medicine for years, but significant increases in resistant *Campylobacter* infections in humans did not happen following this use. Rather, the increase in resistant infections in humans happened years later, immediately following the introduction of fluoroquinolone use in veterinary medicine.

Smith (G-1473) P.16 L.4-L.12.

791. There are fairly high resistance rates that have been reported in several countries that do not even have FQs approved for use in farm animals. [Burkhart (B-1900) P.8 L.38-40]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. Neither the proposed finding nor the cited testimony specify which countries are being referring to. Moreover, the testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

792. Both human use of FQs and the rate of international travel have increased dramatically in the 1990's. [Burkhart (B-1900) P.9 L.1-2]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. Neither the proposed finding nor the cited testimony specify whether the hypothesis relates to the United States or elsewhere. Moreover, the testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Finally, the proposed finding (as it relates to the United States) is contradicted by DeGroot (A-200) P.24 L.20-22, and the FoodNet Atlas of Exposures cited therein, which shows that foreign travel is uncommon (less than 1.0% and 1.5% of the population surveyed in 1998-1999 and 2000, respectively) and, therefore, any change over time would result in a fairly large percent change even if the difference is not meaningful.

793. One cannot interpret trends from data when missing information on foreign travel and prior FQ use given that both human use of FQs and the rate of international travel have increased dramatically in the 1990's and that a significant proportion of FQ resistant cases are attributable to these two factors. [Burkhart (B-1900) P.9 L. 1-4]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. Neither the proposed finding nor the cited testimony

specify whether the hypothesis relates to the United States or elsewhere. Moreover, the testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding. Finally, the proposed finding (as it relates to the United States) is contradicted by the testimony of DeGroot (A-200) and Kassenborg (G-1460). DeGroot (A-200) P.24 L.20-22, and the FoodNet Atlas of Exposures cited therein, shows that foreign travel is uncommon (less than 1.0% and 1.5% of the population surveyed in 1998-1999 and 2000, respectively) and, therefore, any change over time would result in a fairly large percent change even if the difference is not meaningful. Kassenborg (G-1460) P.6 L.22 – P.7 L.1 found that fluoroquinolone use prior to specimen collection was not statistically associated with acquiring a fluoroquinolone-resistant *Campylobacter* infection.

794. The belief that foreign travelers who develop FQ resistant *Campylobacter* because of FQ use in farm animals in another country is not evidence that can be used to evaluate the cause of resistance in the country of interest. [Burkhart (B-1900) P.9 L. 4-7]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence, as exemplified in the testimonies of Smith (G-1473) and Wegener (G-1483). According to Smith:

> [I]n numerous countries, independent studies have indicated that quinolone resistance in *Campylobacter* from humans follows closely after the use of fluoroquinolones in veterinary medicine in those countries. In several of these countries, fluoroquinolones had been used in human medicine for years, but significant increases in resistant *Campylobacter* infections in humans did not happen following this use. Rather, the increase in resistant infections in humans happened years later, immediately following the introduction of fluoroquinolone use in veterinary medicine.

Smith (G-1473) P.16 L.4-L.12. Wegener states that: "The finding of 12 independent studies from three different continents and nine different countries strongly indicate that chicken is a source of human *Campylobacter*-infection and indeed a common source in most industrialized countries." [Wegener (G-1483) P.15 L.4-7]

795. Based upon the Smith and Kassenborg data, a significant proportion of resistant cases that are observed in US residents are unlikely to be linked to enrofloxacin use in poultry production. [Burkhart (B-1900) P.13 L. 13-15]

CVM CRITIQUE: This proposed finding is contradicted by Smith (G-1473) P.20 L.26-31 and Kassenborg (1460) P.11 L.10-11.

796. Since it is well established that prior FQ use quickly selects for *Campylobacter* that are resistant in vitro, it is epistemologically difficult to assign causality for such resistance to another factor, given the prior FQ use. [Burkhart (B-1900) P.13 L. 22-25]

CVM CRITIQUE: This proposed finding is unclear and therefore unsupported. In any event, Kassenborg (G-1460) P.6 L.22 – P.7 L.1 found that fluoroquinolone use prior to specimen collection was not statistically associated with acquiring a fluoroquinolone-resistant *Campylobacter* infection.

797. *Campylobacter* caused by some exposure associated with foreign travel can not address the question of whether FQ use in US poultry production causes a significant degree of resistant disease in US residents. [Burkhart (B-1900) P.13 L. 35-37]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence, as exemplified in by Smith (G-1473). According to Smith:

> [I]n numerous countries, independent studies have indicated that quinolone resistance in *Campylobacter* from humans follows closely after the use of fluoroquinolones in veterinary medicine in those countries. In several of these countries, fluoroquinolones had been used in human medicine for years, but significant increases in resistant *Campylobacter* infections in humans did not happen following this use. Rather, the increase in resistant infections in humans happened years later, immediately following the introduction of fluoroquinolone use in veterinary medicine.

Smith (G-1473) P.16 L.4-L.12.

798. Controlling for foreign travel in case control studies requires that sufficient numbers of controls with foreign travel be included in the study. [Burkhart (B-1900) P.13 L. 43-44]

CVM CRITIQUE: This proposed finding is not supported by the testimony of Feldman (B-1902) Attachment 1 P.120 (Gregg, P. 130), which says that, in observational studies, "confounding can be addressed through restriction, matching, stratified analysis, or modeling."

799. Foreign travelers must be excluded from primary analysis when sufficient numbers of controls with foreign travel are not included in a case control study. [Burkhart (B-1900) P.13 L. 44-46]

CVM CRITIQUE: This proposed finding is vague in that it does not specify what "primary analysis" is being referring to. In conducting a case-control study, if one wants to examine whether foreign travel is a risk factor for acquiring a fluoroquinolone-resistant *Campylobacter* infection, it may be unreasonable to exclude foreign travelers.

800. International travelers may delay seeking medical treatment until returning to the US, thereby self selecting for longer courses of illness. [Burkhart (B-1900) P.14 L. 5-6]

CVM CRITIQUE: This proposed finding is merely conjecture. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding.

801. NARMS/ FoodNet sites do not capture data on foreign travel or prior FQ use on a routine basis. [Burkhart (B-1900) P.17 L. 6-8]

CVM CRITIQUE: This proposed finding is contradicted by Angulo (G-1452), P.9 L.46 – P.10, L.12, which explains that the largest case-control study of sporadic *Campylobacter* infections in the United States was conducted in FoodNet sites; the data from this case-control study, including information on foreign travel and prior fluoroquinolone use, have been analyzed to determine the risk factors for becoming infected with *Campylobacter* and ciprofloxacin-resistant *Campylobacter.*

802. The Smith study (G-589) failed to identify any risk factor for the 20% of resistant cased that were acquired domestically and did not have prior FQ use before culture. [Burkhart (B-1900) P.18 L. 27-29]

CVM CRITIQUE: This proposed finding is misleading in that it fails to recognize that the K. Smith study (G-589) used quinolone-sensitive *Campylobacter* cases as the comparison (i.e., control) group; therefore, any risk factor that is a risk factor for both quinolone-sensitive and quinolone-resistant infections would not necessarily be revealed.

803. The Smith analysis (G-589) did not consider the possibility that foreign travel could confound an evaluation of illness duration. [Burkhart (B-1900) P.18 L. 34-35]

CVM CRITIQUE: This proposed finding appears to be an unjustified statement of opinion not a statement of fact. The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis suggested by the proposed finding, i.e., that a resistant infection is somehow different if acquired during foreign travel instead of domestically. Quinolone resistance is chromosomally mediated and the same mutations occur all over the world.

804. In the Smith data set (see, e.g., G-589), foreign travel is associated with longer duration of illness irrespective of in vitro FQ resistance. [Burkhart (B-1900) P.19 L. 37-38]

CVM CRITIQUE: This proposed finding is misleading. First, the finding is not based on the K. Smith study (G-589) but rather it is based on Burkhart's purported reanalysis of the K. Smith dataset. Second, the cited testimony does not reveal any tests for statistical significance. Third, the cited testimony does not take into account fluoroquinolone treatment (i.e., use of a fluoroquinolone after collection of stool specimen), as does K. Smith. K. Smith demonstrated that, among patients who were treated with a fluoroquinolone, the duration of diarrhea was 3 days longer than for patients with quinolone-resistant infections than for those with sensitive infections (G-589) (G-1473).

806. In the Smith data set (see, e.g., G-589), patients from 1997 without foreign travel, had a mean duration of illness of 9.2 in the resistant cases and 9.0 in the 144 non-resistant controls. Likewise, in patients with foreign travel, the mean duration was 11.1 in the 52 patients with resistant *Campylobacter* compared to 12.2 in the 32 patients with non-resistant *Campylobacter*. [Burkhart (B-1900) P.19 L. 43 – P.20 L.4]

CVM CRITIQUE: This proposed finding is misleading. First, the finding is not based on the K. Smith study (G-589) but rather it is based on Burkhart's purported reanalysis of the K. Smith dataset. Second, the cited testimony does not reveal any tests for statistical significance. Third, the cited testimony does not take into account fluoroquinolone treatment (i.e., use of a fluoroquinolone after collection of stool specimen), as does K. Smith. K. Smith demonstrated that, among patients who were treated with a fluoroquinolone, the duration of diarrhea was 3 days longer than for patients with quinolone-resistant infections than for those with sensitive infections (G-589) (G-1473).

807. Smith's finding of a longer duration of illness in patients with resistant *Campylobacter* must have been because of his failure to control for foreign travel. [Burkhart (B-1900) P.20 L. 21-23]

CVM CRITIQUE: This proposed finding is based on pure speculation. The mere assertion in Burkhart (B-1900) that his reanalysis of what he purports is the K. Smith dataset does not appear to reveal the same results as in the K. Smith study published in the New England Journal of Medicine does not call into question the published findings of K. Smith.

808. Burkhart, after analyzing Smith's data, found that chicken and turkey exposure was less likely in resistant cases. [Burkhart (B-1900) P.20 L. 38]

CVM CRITIQUE: This proposed finding is vague in that it is unclear what is meant by chicken and turkey "exposure." Moreover, Burkhart does not provide statistical measures such as p-values or confidence intervals to allow for adequate statistical interpretation. Finally, although not revealed in the proposed finding, the comparison group to resistant cases was non-resistant cases, and any risk factor that is a risk factor for both quinolone-sensitive and quinolone-resistant infections would not necessarily be revealed.

809. There is no evidence of any difference in risk factors between resistant and non-resistant cases in the Smith data. If anything, the Smith data suggest that resistant cases are less likely to be associated with consumption of chicken/turkey compared to non-resistant cases." [Burkhart (B-1900) P.22 L. 40-43 referring to G-589 (Smith 1999)]

CVM CRITIQUE: This proposed finding is contradicted by G-589 and Smith (G-1473) P.9 L.12 – P.10 L.19, which demonstrate statistically significant differences in risk factors between resistant and non-resistant cases.

810. McClellan and Marano reanalyzed the Kassenborg dataset and reported their findings in G-1679 and G-394. [Burkhart (B-1900) P.25 L. 4-7]

CVM CRITIQUE: This proposed finding is contradicted by the cited testimony. Neither McClellan nor Marano reanalyzed Kassenborg's study; they each conducted their own analyses based on data collected in the 1998-1999 FoodNet *Campylobacter* case-control study. Kassenborg enrolled 646 patients into her study and obtained 62 age-matched well controls for patients with fluoroquinolone-resistant *Campylobacter.* [Kassenborg (G-1460) P.6 L.7-10] Neither McClellan nor Marano had well controls in their studies; they were analyzing duration of diarrhea among *Campylobacter* cases.

811. The questionnaire used in the 1998 - 1999 CDC *Campylobacter* case-control study, was different for collection data on chicken/turkey consumption than that for other foods and meats. [Burkhart (B-1900) P.25 L. 27-28]

CVM CRITIQUE: This proposed finding is misleading to the extent that it implies that the questionnaire design was inappropriate. When designing a study, reviews of previous studies are conducted to find what factors have been found to be associated with the disease in question. Poultry consumption has been documented to be a risk factor with *Campylobacter* infections so it is logical to include additional questions on poultry in the questionnaire to try and tease out what factors may influence this risk.

812. The 1998 -1999 CDC *Campylobacter* case-control study questionnaire asked about the cumulative consumption for each poultry product, but skipped collecting such data for other foods. [Burkhart (B-1900) P.25 L. 31-33]

CVM CRITIQUE: This proposed finding is misleading to the extent that it implies that the questionnaire design was inappropriate. When designing a study, reviews of previous studies are conducted to find what factors have been found to be associated with the disease in question. Poultry consumption has been documented to be a risk factor with *Campylobacter* infections so it is logical to include additional questions on poultry in the questionnaire to try and tease out what factors may influence this risk. To ask detailed questions about every food item is impractical and unwarranted.

813. After analyzing data from the 1998 - 1999 CDC *Campylobacter* case-control study, Burkhart finds no evidence of increased morbidity with resistant *Campylobacter* when controlling for foreign travel and prior FQ use. [Burkhart (B-1900) P.33 L. 2-4]

CVM CRITIQUE: The proposed finding is contradicted by Burkhart (B-1900) P.37 L.6, which says that Burkhart's findings from his purported reanalysis of the CDC 1998-1999 *Campylobacter* case-control study "are similar to those reported by Marano [who analyzed duration of diarrhea in the data from the reference case-control study]. Irrespective of foreign travel or prior FQ use, resistant cases with no use of an [antidiarrheal] agent tended to have a longer duration of diarrhea by 1-2 days."

814. After analyzing data from the 1998 - 1999 CDC *Campylobacter* case-control study, Burkhart found patients who claimed foreign travel had a longer duration of diarrhea than patients who did not travel (7.8 days vs 6.9 days). [Burkhart (B-1900) P.34 Table 5]

CVM CRITIQUE: This proposed finding is misleading because the cited testimony Table 5 states that the information presented in the table is from the "Kassenborg dataset." As can be seen from the testimony of Dr. Kassenborg (G-1460) P.6 L.6-10, her study enrolled 646 patients with *Campylobacter* infection. Although there are no sample numbers in Burkhart's Table 5, according to Burkhart (B-1900) P. 34 L.5, his analysis began with 716 resistant and non-resistant cases and 716 is not 646. Moreover, Burkhart does not provide statistical measures such as p-values or confidence intervals to allow for adequate statistical interpretation.

815. After analyzing data from the 1998 - 1999 CDC *Campylobacter* case-control study, Burkhart found that patients with resistant infections had less days of illness than those with susceptible infections when they reported no foreign travel, had no prior FQ use, and were treated with a FQ following culture. (6.0 days vs 6.9 days) [Burkhart (B-1900) P.36. Table 8]

CVM CRITIQUE: This proposed finding is misleading to the extent that it is suggesting that Burkhart reanalyzed any of the studies conducted by Kassenborg, Nelson, or Marano, which were based on the 1998-1999 *Campylobacter* case-control study. For his analysis, Burkhart selected his own cases and controls from the dataset. Further, Burkhart does not provide statistical measures such as p-values or confidence intervals to allow for adequate statistical interpretation.

816. After analyzing data from the 1998 - 1999 CDC *Campylobacter* case-control study, Burkhart found that resistant cases who use an antidiarrheal agent tended to have 1-2 days less diarrhea. [Burkhart (B-1900) P.37 L.7]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony and is also contradicted by Burkhart (B-1900) P.37 Table 9. The cited testimony (L.7) does not discuss resistant cases who used an antidiarrheal agent but rather it discusses resistant cases with no use of an antidiarrheal agent, who had a longer duration of diarrhea. Burkhart's Table 9 (in the "Overall subheading) shows that resistant cases who use an antidiarrheal agent other than Immodium or Lomotil appear to have a longer duration of diarrhea than non-resistant cases (8.2 days versus 7.4 days, respectively).

817. Burkhart found, after analyzing data from the 1998 - 1999 CDC *Campylobacter* case-control study, that foreign travel must be controlled for when analyzing illness length. [Burkhart (B-1900) P.40 L. 3-4]

CVM CRITIQUE: The testimony cited in support of the proposed finding does not identify any source of support for the hypothesis implied by the proposed finding, i.e., that a resistant infection is somehow different if acquired during foreign travel instead of domestically. Quinolone resistance is chromosomally mediated and the same mutations occur all over the world. Moreover, the proposed finding is contradicted by Burkhart (B-1900) P.37 L.6, which says that Burkhart's findings from his purported reanalysis of the CDC 1998-1999 *Campylobacter* case-control study "are similar to those reported by

Marano [who analyzed duration of diarrhea in the data from the reference case-control study]. Irrespective of foreign travel or prior FQ use, resistant cases with no use of an [antidiarrheal] agent tended to have a longer duration of diarrhea by 1-2 days."

819. NARMS has no value in estimating the incidence or in determining if there has been a temporal decrease or increase in resistance after enrofloxacin approval. [Burkhart (B-1900) P.50 L. 8-10]

CVM CRITIQUE: This proposed finding is contradicted by Tollefson (G-1478) P.5 L.29-38 and Angulo (G-1452) P.8 L.35 - P.9 L.7. The analysis presented in Dr. Angulo's testimony reveals a statistically significant trend, i.e., increase, in the proportion of fluoroquinolone-resistant *Campylobacter* in 2001 compared with the proportion of fluoroquinolone-resistant *Campylobacter* in 1997 (adjusted OR 2.5, 95% CI: 1.4, 4.4). [Angulo (G-1452) P.8 L.35-38 and Attachment 2 P.77]

843. Respiratory colibacillosis is the most common manifestation of *E. coli* infectious disease in broilers. In this case, the damage is done to the non-specific pulmonary defense mechanisms. [Smith (B-1914) P.18 L.16-18]

CVM CRITIQUE: This proposed finding of fact misstates Dr. John Smith's WDT. Bayer is attempting to make an absolute statement in this proposed finding when its own witness only testified that "[R]espiratory collibacillosis is probably the most common manfestation of *E. coli* infectious disease in broilers." (emphasis added). As seen by his WDT, Dr. John Smith acknowledges the uncertainty of this statement. (J.Smith WDT, P.18 L.16-18).

844. The virus that most often causes *E. coli* infections in broiler chickens is IBV. IBV is a coronavirus that easily undergoes genomic reassortment and homologous recombination in the bird. Over time, new genotypes of the virus arise and large populations of birds may be susceptible. This necessitates development and production of a new vaccine for billions of birds throughout the U.S. Since it takes from 3-5 years to produce a USDA-approved live virus vaccine, the only ways to control losses in the interim are to prevent introduction of the virus and to treat the secondary *E. coli* infections with antibiotics when prevention fails. [Hofacre (A-202) P.10 L.17 through P.11 L.2].

CVM CRITIQUE: CVM agrees to the above statement, with the clarification that viruses **predispose** for, but do not **cause**, *E. coli* or any other bacterial infections.

849. Poultry veterinarians know that the poultry industry is presently (2002 - 2003) in one of the periods where the IBV virus has not shifted its genome enough to elude available vaccines, however, it is inevitable that this will occur. When that happens, the need for Baytril will again be high to treat *E. coli* infections in broiler chickens. [A-202 P.12 L.12 through P.13 L.2]

CVM CRITIQUE: The section of testimony cited as support for this proposed finding has been stricken from the record and therefore this proposed finding is without record reference.

856. In a broiler house with *E. coli* infection, all birds are in a stage of morbidity and all need treatment. Although the signs may be obvious to the practiced observer, it is difficult to stage the disease in an individual, short of a post mortem examination. The disease progresses extremely rapidly in both the individual and in the flock. The presence of the inciting factors almost guarantees the occurrence of *E. coli*, especially if the presence of pathogenic strains is established and they are currently circulating in sick birds in the house. [Smith (B-1914) P.22 L.9-14]

CVM CRITIQUE: Bayer's proposed finding appears to be the opinion of Dr. J. Smith, but he does not provide any basis in the record for this opinion, and Bayer fails to provide an adequate record reference supporting this proposed finding. Also see CVM's critique of Bayer's proposed findng of fact 898.

863. Poultry veterarians must treat the entire house of birds whenever viral-induced *E. coli* is diagnosed. By the time the grower notices sickness, dying, or dead birds in a particular house, there are already a tremendous number of animals who have been exposed and are incubating the virus and exposing more birds. The grower may even have inadvertently carried the virus on his/her shoes or clothing into the next house, etc. This is the reason poultry veteranrians must treat the entire house of birds as sick, because the vet cannot tell which birds are incubating the disease once it is introduced into the house. [Hofacre (A-202) P.13 L.15-22; Carey (G-1456) P.4 L.34-37; TerHune (B-1915) P.4-5]

CVM CRITIQUE: The proposed finding is contrary to Dr. Carey's cited testimony. Dr. Carey's WDT indicates that the entire flock not house is treated.

867. Because of the high drug cost, the decision to write a prescription for enrofloxacin will be based on how high the mortality has gone or if the farm has a history of previous treatment failures with the tetracyclines. Only a house with elevated mortality will be treated. [Hofacre (A-202) P.20 L.14-17]

CVM CRITIQUE: CVM agrees that this is the ideal situation. However, Dr. Hofacre (P.27 L.1-4 and P.30 L.19-20) also assumes that the tetracyclines are very seldom effective, leaving Baytril as the most likely drug used.

868. The decision to use enrofloxacin is not taken lightly. Veternarians will not use an intervention unless they expect to at least break even on the cost of treatment. The return on treating *E. coli* is based primarily on prevention of mortality, condemnation, and interruptions in the processing plant. There are likely also benefits from reduction in morbidity (in terms of growth rate and feed conversion, by getting sick birds back on feed), but these are hard to quantitate and are usually not considered. The bottom line is that enrofloxacin is used only in those cases where extreme mortality or condemnation is

expected. The drug is used only by prescription. [Smith (B-1914) P.25 L.20 through P.26 L.4].

CVM CRITIQUE: This proposed finding of fact is contradicted by Dr. J. Smith's later testimony which states, "[v]eterinarians have a duty to treat sick animals in their care with the most effective treatments so they do not suffer unnecessarily." (J. Smith WDT P.31 L.17-18). Further, since economic evidence is not relevant to the issues of this hearing (Order 3/3/03), this proposed finding is inappropriate.

871. The only opportunity to treat broilers individually (such as by injection) is in the hatchery, on the day of egg transfer or hatch. The broiler industry categorically and voluntarily rejected the use of the only approved injectable fluoroquinolone (sarafloxacin) for mass, prophylactic use in the hatchery. [Smith (B-1914) P.20-23]

CVM CRITIQUE: CVM notes that Bayer has failed to provide a correct record reference. J. Smith's WDT P.20-23 does not address this issue. CVM believes the correct citation to be P.26 L.20-23.

874. Water delivery has long been accepted by the industry. FDA has long accepted drinking water delivery as a safe and effective means to administer therapeutic animal drugs, including antibiotics, to commercially grown broiler chickens and turkeys." [Joint Stipulation 18]

CVM CRITIQUE: The first sentence of this proposed citation is not part of the Joint Stipulation 18 and is therefore without record reference.

877. Baytril is used according to the label instructions. Since the label instructions allow a dosage of 25 ppm – 50 ppm for 3-7 days (B-1011, G-822), the veterinarian has some choice in the prescribed treatment. This choice is influenced by the veterinarian's assessment of the severity of the disease and the relative value of the affected flock. In general, because of the proven high efficacy in broilers of a 25-ppm, 3-day regimen, as well as for economic considerations, the lower dosage and shorter duration of treatment is commonly used. [Glisson (B-1903) P.5 L.7-12; TerHune (B-1915) P.6 L.6-11; A-54]

CVM CRITIQUE: CVM agrees with the remainder of this proposed finding. The first statement of this proposed finding appears to be a statement of opinion not a statement of fact. The last statement of this proposed finding is contradicted by . . .

878. The use of enrofloxacin in the United States poultry industry is well-controlled. It is only used under veterinary prescription and supervision and is generally used as the treatment of last resort. It is not being used for growth promotion, but only for therapeutic uses. It is delivered through the drinking water in a manner that insures proper dosing, minimizes development of resistance, and minimal contamination of the environment. [Glisson (B-1903) P.11 L.20 – P.21 L.2; TerHune (B-1915) P.6 L.11-14; A-54; Wages (B-1917) P.21 L.8-11]

CVM CRITIQUE: Dr. Wage's testimony offered in support of this opinion (Wage P.21 L.10) was stricken from the record in the ALJ's 3/3/03 Order. This proposed finding is contrary to Dr. Wage's WDT P.21 L.11 because his testimony discusses alternatives to Baytril in the market. The proposed finding in the last sentence on minimized resistance is contradicted by Exhibit B926, referenced in 869 above, which clearly states that the present dosing of enrofloxacin does **not** minimize bacterial resistance.

881. Even if one could isolate and treat individual birds, or even sections of a poultry house (which one cannot in the broiler industry), such a course would not be indicated, and in fact would be guaranteed to fail with the dynamics of the disease. The assertion by some that the poultry industry routinely treats the entire house when a few birds show signs is patently false. Once the presence of the disease is established, and professional opinion indicates the likelihood of progression, then treatment of the entire flock is the only medically valid course of action. [Smith (B-1914) P.22 L.19 – P.23 L.2; Carey (G-1456) P.4 L.34-37]

CVM CRITIQUE: Bayer's proposed finding of fact is contradicted by the record. Bayer states that it is "patently false" that the industry treats the entire house when only a few birds show signs. However, its own witness suggests that the entire house is treated when only a small percentage of birds show signs of illness. (see Wages WDT P.15 L.8-9 "Morbidity of >1/2% and/or mortality of greater than or equal to 1 bird per thousand should initiate diagnostic efforts in the case of collibacillosis."); as does an AHI witness (Gonder P.22 L.8-10 "[A] collibacillosis outbreak or mild fowl cholera outbreak, frequently shows a per day ...I would hope to intervene on the day mortality reached 10...A severe fowl cholera outbreak is more rapid and would show a per day mortality pattern more like 4-6-8-7-18-45-150-275. I would hope to be called on or before the day it reached 18. Obviously, waiting "a day or two to see if it went back down" is not acceptable in this situation.") Note, both these WDT address turkeys.

882. A recent study by Glisson et al. demonstrates that Baytril (enrofloxacin) is effective for controlling air sacculitis and other commonly used medications are not. Thus, Baytril is the most effective medication for controlling air sacculitis. [Russell (B-1912) P.26 L.15-17; Glisson (B-1903) P.14-25]

CVM CRITIQUE: The proposed finding is misleading because it is overly broad. The treatments studied by Glisson were: 1) enrofloxacin (25 ppm) administered in the drinking water for three consecutive days, 2) oxytetracycline (400 mg/gal) administered in the drinking water for six consecutive days, 3) sulfadimethoxine (1875 mg/gal) administered in the drinking water for six consecutive days. Since Glisson only studied 2 medications other than enroflaxacin, the proposed finding is far too broad to be supported by the referenced study. Further this proposed finding is based on unpublished data which has not been peer reviewed.

883. Baytril is the only practical efficacious antimicrobial available for poultry veterinarians to use to treat *E. coli*. It can be administered in the drinking water which is the ideal method for treating sick birds. Also, the label dose range and duration of treatment allows the

veterinarian to use his/her professional judgment when writing the prescription that should result in a successful treatment outcome using the least amount of drug. This should maintain the useful life of the drug by limiting the level of resistance development not only in the target *E. coli* but also poultry commensal bacteria. There is really no practical alternative therapy to Baytril for systemic *E. coli* infections in poultry. [Hofacre (A-202) P.30 L.13 - P.31 L.31; Smith (B-1914) P.32 L.8]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which shows the efficacy of neomycin against colibacillosis in turkeys. The fourth sentence is contradicted by Exhibit B926, referenced in 869 above, which clearly states that the present dosing of enrofloxacin does **not** minimize bacterial resistance. The last sentence is contradicted by the WDT of Dr. Hofacre (P. 19 L. 15-P. 20 L. 6), documenting the use of tetracyclines, and Exhibit B-1832, documenting the efficacy of neomycin. Also, the correct cite for Dr. Hofacre's WDT is P. 30 L. 19-P. 31 L. 4.

884. Enrofloxacin is the most efficacious antibiotic available in the United States for treatment of *E. coli* infections in broiler chickens and *E. coli* and Pasteurella multocida infections in turkeys. The pharmacokinetics of the compound are such that high levels of enrofloxacin are reached in the respiratory tissues of treated birds, which is the desired site for effective treatment of both *E. coli* and P. multocida infections. This characteristic, coupled with the typical low Minimum Inhibitory Concentration (MIC) values of enrofloxacin against avian *E. coli* and P. multocida, (G-59, G-256) insures that levels reached at the site of infection are far higher than the MIC required for an effective outcome. This also minimizes the potential for resistance development in the target organism. [Glisson (B-1903) P.5 L.21 - P.6 L.7; B-1914 P.32 L.4]

CVM CRITIQUE: See the response to proposed finding of fact 883 above. The last sentence is contradicted by Exhibit B-926, referenced in proposed finding of fact 869 above, which clearly states that the present dosing of enrofloxacin does **not** minimize bacterial resistance.

885. Enrofloxacin is needed by poultry producers to treat *E. coli* respiratory infections. *E. coli* strains that infect poultry are highly resistant to sulfa drugs and tetracyclines. [TerHune (B-1915) P.8 L.13-14)

CVM CRITIQUE: Dr. TerHune provides no reference within his WDT that supports his statement with respect to sulfa drugs. B-1579 does not support this proposed finding. It is a CV for Mr. Martin, whose entire WDT was stricken from the record (Order 3/3/03). And, B-1376 is a study of the efficacy of danofloxacin, not enrofloxacin, compared to oxytetracyclene (not sulfa drugs).

886. Bayer selected the prescribed dose range based on the pharmacokinetics of the drug, the characteristics of the commercial delivery systems, the resulting serum levels that could be obtained under commercial conditions, and known sensitivity patterns of broiler *E. coli* isolates. [B-1914 P.28 L.6-8]

CVM CRITIQUE: Bayer provides no appropriate citation to the record to support this proposed finding because this portion of WDT cited by Bayer has been stricken from the testimony.

887. Enrofloxacin almost uniformly produces a dramatic, measurable clinical response, and controls morbidity, mortality, and condemnation in the manner expected of an effective antimicrobial. [Smith (B-1914) P.L.15-17]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. The complete reference is P. 28 L. 15-17.

888. Enrofloxacin is the product of choice to treat broiler flocks infected with air sacculitis. [Robach (B-1911) P.15 L. 18]

CVM CRITIQUE: This proposed finding of fact is based on the opinion of the witness who does not provide any factual basis for his opinion. While CVM is not disputing the effectiveness of Baytril in this hearing (the hearing concerns the safety not the effectiveness of Baytril), CVM contends there are other drugs approved for the diseases in question. (See Tollefson WDT P.18 L.34- P.19 L.2)

889. The safety and efficacy for enrofloxacin were established using data obtained from studies where groups of birds (houses or pens) were the experimental unit. [B-926; B-1117; TerHune (B-1915) P.5 L. 7-8]

CVM CRITIQUE: CVM notes that while TerHune's WDT does contain this language, of one the two Exhibits he cites as support does <u>not</u> support this statement. (B-926) does not support the statement. B-1117 is a 247 page exhibit. Bayer should not expect CVM nor the ALJ to have to read through 247 pages to see if it accurately cited any support for its proposed finding of fact.

891. The current label dose for enrofloxacin is 25 to 50 ppm for broiler chickens and turkeys. The safety and efficacy studies demonstrate that when medicating the drinking water with enrofloxacin, individual birds are dosed adequately, even at half the lowest recommended dose. This study also indicates that a superior result could not have been obtained with the use of an individually dosed injectable product. [B-1117; TerHune (B-1915) P.5 L. 16 through P.17 L. 5)

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. An injectable product was not compared to Baytril in the study mentioned, (B-1117), nor does TerHune provide any other support in the record to support the last sentence in the proposed finding of fact. Further, the proposed finding covers both broilers and turkeys but the study cited by Bayer appears to only address the effectiveness of Baytril in turkeys.

892. The pharmacokinetic data were provided on the Baytril label along with Minimum Inhibitory Concentration (MIC) data for label pathogens allow for the selection of peak

serum concentrations (Cmax) to MIC ratios that minimize the selection of resistant organisms. [B-1117; TerHune (B-1915) P.7 L. 12-15]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926, P. 3-4, which states ". . . enrofloxacin are approved for treating *E. coli* infections in chickens and turkeys, and enrofloxacin is also approved for treating P. multocida infections in turkeys. Unfortunatly, their labeled dosage has not addressed the pharmacokinetic and pharmacodynamic properties determining clinical efficacy. Neither recommends pulse dosing, which would maximize bacterial killing and therefore would also maximize clinical efficacy and decreased selection of resistant bacterial. Instead both drugs are administered in water as a continuous medication over the entire treatment period." (B-926, P. 3-4).

894. Exhibit G-52 is the Baytril® product information document from Bayer that describes the variables associated with poultry water consumption, and the appropriate levels of enrofloxacin to use in different circumstances. The labeling of enrofloxacin for poultry explicitly addresses the variables associated with poultry water intake and allows the veterinarian to administer the product in a safe and efficacious manner. [TerHune (B-1915) P.6 L. 19 - P.7 L. 1]

CVM CRITIQUE: CVM agrees with the first sentence, however, the remainder of this proposed finding is contradicted by Exhibit G-52, where on page 28 paragraph 2, Bayer states "The intake of drinking water by poultry is determined by many factors, especially age and environmental temperature. Therefore, medication of poultry via the drinking water, expressed in ppm (= active substance per litre of water) does not always ensure a corresponding intake of active ingredient by the birds, calculated in mg/kg b.w." Continuing on P. 29, "As far as Baytril is concerned this means that while in young birds up to approximately 4 weeks of age a dose of 50 ppm still results in adequate active concentrations, there is a risk of underdosing in older birds with a relatively lower water intake. When medicating older birds via the drinking water it is therefore important to check each time whether the minimum intake of 10 mg/kg b.w. per day is being met."

895. Dr. McDermott's concern, stated in his testimony (G-1465) that birds do not or may not birds receive an adequate dose of a medication when it is administered in the drinking water, conflicts with the efficacy data submitted to CVM in support of the NADA and published data which clearly demonstrate that adequate quantities of enrofloxacin are consumed. [TerHune (B-1915) P.6 L. 15 - 7 L. 3]

CVM CRITIQUE: See CVM's critique of Bayer's proposed 894.

896. Dr. McDermott's testimony about how sub-optimally dosed birds lead to an increase in the probability for selecting for resistant *E. coli* in healthy and diseased birds is not supported by available data that clearly demonstrate that poultry receive an adequate dose. [TerHune (B-1915) P.7 L. 1-7]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926, which clearly states that the present dosing of enrofloxacin does **not** minimize bacterial resistance, indicating that the dosing is sometimes less than ideal.

897. The use of enrofloxacin to treat respiratory *E. coli* infections such as air sacculitis in broilers results in healthier birds during grow-out and entering the processing plants. [Robach (B-1911) P.15 L.23 through P.16 L.2]

CVM CRITIQUE : This proposed finding is misleading. First, alternative drugs are approved to treat respiratory *E. coli* infections in broilers (See Tollefson WDT P.18 L.34-P.19 L.2). Bayer's proposed finding does not indicate whether it means ill broilers treated with enrofloxacin are healthier than broilers NOT treated with any medication or whether it means ill broilers treated with enrofloxacin are healthier than birds treated with alternative medications. Further, Bayer does not indicate what "healthier" means. And, as it appears from the cited WDT that Bayer's witness Robach is relying on Russell's study to support this statement, CVM notes: 1.) Russell's study actually produced mixed results; 2.) Russell's study has not been published or peer reviewed; 3.) Russell's study compared birds treated with enrofloxacin to birds treated with only two other drugs. (Russell WDT P.19-26 and Attachment #1). This cannot be taken as representative of all available treatment.

898. When water-soluble medications such as enrofloxacin are used they do not expose a greater numbers of animals than just the few with clinical signs of disease, contrary to CVM's publicly concern stated at 65 Fed. Reg. 64957. [Terhune (B-1915) P.3 L.21-23, P.4 L.1-4; B-1117]

CVM CRITIQUE: This proposed finding is contradicted by the WDTs of J. Smith (P.22 L. 23- P.24 L.2); TerHune (P.4 L.1-4); Wages (P.9 L.20-22 and P.10 L.9-11); and Hofacre (P.13 L.20-22).

899. Water-soluble medication of enrofloxacin for poultry is not non-discriminating for the target (clinically sick animals) as compared to injectable products, and does not raise the possibility of development of resistant organisms in greater numbers than if the drugs were to be administered in an individual injectable dosage form contrary to CVM's publicly concern stated at 65 Fed. Reg. 64957. [Terhune (B-1915) P.5 L.3-10, 12; B-1117]

CVM CRITIQUE: This proposed finding of fact is misleading. TerHune's WDT indicates that the effect of treating the entire house via drinking water or by injecting every bird would be the same with respect to the overall exposure to fluoroquinolones. However, the proposed finding of fact does not indicate that every bird in the house would be injected. Thus, the proposed finding is not supported by the cited record references. Further, TerHune's WDT P.5 L.12 has been stricken from the record (Order 3/3/03).

901. CVM is incorrect if it has concluded if one bird is sick then the entire flock (every house on the ranch) will be treated, because the medication is water-soluble and administered through the water. [Terhune (B-1915) P.4 L.10-12]

CVM CRITIQUE: CVM has not stated that if one bird is sick every house on the ranch will be treated and Bayer has provided no support in the record to that effect.

903. As a house (diseased unit) of birds develops clinical signs associated with disease, the animals with observable clinical signs are at a different progression point of the disease, but the whole house (diseased unit) is exposed and at risk. When a house of birds is medicated, it is the same as systemically treating a sick calf (diseased unit), potentially exposing other portions of the house where bacteria live to drugs in order to save the unit. [Terhune (B-1915) P.4 L.15 through P.5 L.2; B-926; B-1117]

CVM CRITIQUE: This proposed finding of fact is without support. TerHune fails to provide any adequate reference to the record for his comparison of 25,000 broilers to one calf. TerHune cites to B-926 and B-1117, P.33 for support. However, B-926 does not address this issue and B-1117, P.33 is the cover page of a text book and does not address any issue.

904. The overall exposure of poultry and their environment to the fluoroquinolone is the same whether the poultry house is treated through the drinking water, or if theoretically one were able to individually inject every bird, and an increased rate of resistance of *Campylobacter* to fluoroquinolones is not associated with the method of drug delivery. [Terhune (B-1915) P.5 L.3-6]

CVM CRITIQUE: This proposed finding is contradicted by McDermott's WDT P.7 L.8-11 and G-52. See, also, CVM's critique of Bayer's proposed finding of fact 894.

905. CVM's statement that "wide spread contamination by water leakage and animal waste that occurs when large numbers of animals are treated, which result in untreated animals being exposed to the drug" was another concern with water-soluble medications [(65 Fed. Reg. 64957)] is not correct since the whole house is the diseased unit and the treatment target; every bird in the house is a treatment target because every bird is at some stage of disease, from exposure to clinical disease. [Terhune (B-1915) P.7 L.16 through P.8 L.2]

CVM CRITIQUE: See CVM's critique of Bayer's proposed findings of fact 881, 898, and 906.

906. Routine water leakage associated with birds watering at troughs, bells or cups has been eliminated in commercial broiler houses because of the standard use of nipple waterers. Nipple waterers are designed specifically to eliminate water leakage or water spillage when birds drink. In addition, the cost of the medication prohibits the poultry integrator from indiscriminant regard to water leakage. [Terhune (B-1915) P.8 L.3-7]

CVM CRITIQUE: This proposed finding of fact is contradicted by Carey's WDT P.4 L.22-25 ("Since birds are not perfect drinkers, water is splashed onto the litter rather than consumed with all watering systems. Also since the drinker system involves extensive plumbing throughout the facility, leaks and equipment malfunctions can cause increased litter moisture.")

907. There are no viable alternatives to enrofloxacin in the United States poultry industry for treating *E. coli* infections in broiler chickens and turkeys. [Glisson (B-1903) P.12 L. 3-4]

CVM CRITIQUE: This proposed finding is contradicted by the written direct testimony of Dr. Hofacre and Exhibit B-1832. Exhibit B-1832 showed the efficacy of neomycin against colibacillosis in turkeys. Dr. Hofacre (P. 19 L. 15-P. 20 L. 6) has testified that tetracyclines are also used for systemic *E. coli* infections

908. Dr. TerHume's studies in the early 1990s demonstrated the superiority of fluoroquinolones over tetracyclines to treat *E. coli* airsacculitis due to tetracycline resistance. [B-1579; B-1376; TerHune (B-1915) P.8 L. 14-16).

CVM CRITIQUE: This proposed finding is not supported by the exhibits cited in support thereof. Exhibit B-1376 is a brief abstract on one trial of danofloxacin; it is not peer-reviewed and no statistical analysis is provided. B-1579 is a list of the business experience of G. Thomas Martin of Agrimetrics, a witness whose entire testimony was stricken by the Administrative Law Judge's Order of March 3, 2003, and offers no support for the proposed finding of fact.

911. While AMDUCA does allow veterinarians to use some drugs in an extralabel manner, the pharmacokinetics and practicality of administration of these drugs must be taken into account. For commercially grown broiler chickens and turkeys in the United States, it is neither feasible nor practical to administer enrofloxacin on an individual bird basis. (Joint Stipulation 36). The drug ceftiofur (a cephalosporin class of antibiotic) is not effective when administered orally in either the drinking water or feed; therefore it must be administered by injection to each bird individually. Water and feed are the only practical manner to treat poultry. This means ceftiofur cannot be used by poultry veterinarians to treat a flock of 20,000 birds with an *E. coli* infection. For gentamicin (aminoglycoside class), it can only be given by injection. Also, the legal withdrawal time (safety of no drug residue in the meat) for gentacicin is 35 days and since most broilers are slaughtered at 42-49 days of age, this makes it even more impractical to treat with gentamicin. The same is true for spectinomycin (aminocyclitol similar to the aminoglycosides) and sulfomyxin that must be injected, these cannot be practically administered to a commercial flock of birds. This leaves only chlortetracycline, oxytetracycline, and the fluoroquinolones available in Dr. Tollefson's table to treat *E. coli*. [Hofacre (A-202) P.28 L.19 – P.29 L.19]

CVM CRITIQUE: CVM agrees. It should be noted, however, that Dr. Tollefson's table shows those drugs specifically approved for *E. coli* in poultry and for *E. coli* and P.

multocida in turkeys. The list was not intended to be an exhaustive list of those drugs which could be used under AMDUCA. The correct cite is P.29 L.3-19.

912. In general, the alternatives to enrofloxacin for therapeutic use in poultry are the tetracyclines and the sulfa drugs. If the NADA for enrofloxacin is withdrawn, the only available drugs specifically approved to treat *E. coli* infections in chickens older than three days of age and *E. coli* and Pasteurella multocida infections in turkeys older than three days of age are: sulfa drugs (such as sulfamethazine, sulfaquinoxaline, sulfadimethoxine) and tetracyclines (such as tetracycline, oxytetracycline, chlortetracycline). [Glisson (B-1903) P.7 L.5-10; Hofacre (A-202) P.24 L.5-9; Wages (B-1917) P.19 L.6-9]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which showed the efficacy of neomycin against colibacillosis in turkeys.

916. There are only two practical alternatives for treatment of a systemic *E. coli* infection – in poultry, tetracyclines or enrofloxacin. Since nearly 90% of the *E. coli* isolates are resistant to the tetracyclines (Bass, 1999), loss of Baytril would leave poultry veterinarians with no real alternatives. [Hofacre (A-202) P.27 L. 1-4; B-1903; Smith (B-1914) P.32 L. 9].

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which showed the efficacy of neomycin against colibacillosis in turkeys.

917. For commercially grown broiler chickens and turkeys in the U.S., it is neither feasible nor practical to administer antibiotics on an individual bird basis. (Joint Stipulation 36). This limits the extra-label alternatives. For example use of the aminoglycosides and cephalosporins are eliminated as an option due to their very poor oral activity. Although there is a label for streptomycin for water administration for *E. coli* therapy, clinical experience indicates it is not very efficacious. [Hofacre (A-202) P.24 L. 9-14]

CVM CRITIQUE: This finding is contrary to the cited joint stipulation. The joint stipulation states that it is infeasible and impractical to administer enrofloxacin not antibiotics on an individual basis.

918. Since sick birds continue to drink, in a disease situation, as a practical matter, the treating veterinarian will want to choose an antibiotic labeled for use in the drinking water. The veterinarian's choices of antibiotics available for water therapy of chickens are: bacitracin, chlortetracycline, oxytetracycline, tetracycline, erythromycin, enrofloxacin, lincomycin, neomycin, streptomycin, and sulfadimethoxine. However, each of these choices has limitations as follows:

- Bacitracin is a polypeptide antibiotic which is poorly absorbed from the intestine and are primarily effective against gram positive bacteria (*E. coli* is a gram negative bacteria).

- Tetracycline class (chlortetracycline, oxytetracycline, tetracycline) – these are broad spectrum antibiotics that were very effective against gram positive and negative bacteria when first introduced into the market decades ago. They are very safe but no longer very effective for treatment of *E. coli* infections. They are bacteriostatic, meaning they stop growth of the bacteria and the birds' immune system must kill the bacteria, thus any reduction in immune function will result in poor efficacy. However, as seen in figure 4, nearly 90% of the clinical *E. coli* isolates have become resistant to this class of antibiotics since these have been the only reasonably effective drugs for *E. coli* infections for 30 years.

- Erythromycin –this is a macrolide antibiotic that is most effective against gram positive bacteria. It has been tried for use against *E. coli* airsacculitis but has not been effective.

- Enrofloxacin –a fluoroquinolone antimicrobial that has a broad spectrum of activity, readily absorbed from the intestine and very safe and effective.

- Lincomycin is a lincosamide antibiotic that is similar in function to the macrolides. It is poorly absorbed when administered orally, therefore it is used primarily to treat gram positive bacterial enteritis, such as, Clostridium perfringens. This drug is not effective against *E. coli*, which is a gram negative bacteria.

- Aminoglycosides –neomycin and streptomycin are both labeled for drinking water treatment. It is estimated that less than 25% of this class of antibiotics is absorbed when administered orally. Therefore, it would be prohibitively expensive and impractical to administer enough of these drugs to get an adequate drug concentration to kill the bacteria in the respiratory tract.

- Penicillin –penicillin is a beta-lactam antibiotic that inhibits primarily gram positive bacteria. It has little or no effect on *E. coli.*

- Sulfadimethoxine –the sulfonamide antibiotics or "sulfas" have very good activity against gram negative bacteria, like *E. coli.* Also, they are readily absorbed from the intestines into the blood stream. However, the sulfa class has a very narrow margin of safety. This means that birds can become quickly overdosed and die if they drink more water than is anticipated (weather gets too warm). Also, the sulfonamides become protein bound and have long half lives so the withdrawal prior to slaughter becomes a concern. The U.S.D.A.-FSIS has historically had the greatest violations of drug residues due to sulfonamide therapy, so few poultry companies use the sulfas to avoid any residue violation. Also, in some areas of the country, depending on the pH of the water supply, sulfa drugs precipitate out in the water lines. This leaves an available concentration of the sulfa drug to which the birds may be exposed even in the withdrawal period and can impact tissue residues.

[Hofacre (A-202) P.24 L.15 – P.26 L.22)

CVM CRITIQUE: Dr. Hofacre does ot provide a factual basis for his opinion and therefore this proposed finding of fact has not support in the record.

919. Regardless of whether or not, in Denmark: (1) there is always another antibiotic in Denmark, other than enrofloxacin, available to treat bacteria in poultry; (2) enrofloxacin is very easy to use in the absence of a proper diagnosis or accurate identification of the infectious agent; (3) a total ban on all usage of fluoroquinolones would not cause major problems in the food animal production, if any; and, (4) fluoroquinolones are convenient drugs to use in veterinary medicine, but they are rarely important and never essential, none of these statements are true with respect to the U.S. poultry industry. [Hofacre (A-202) P.27 L.6 – P.28 L.11]

CVM CRITIQUE: This proposed finding is contradicted by the written direct testimony of Dr. Tollefson. Dr. Tollefson's table, which Dr. Hofacre discusses in 911 above, shows a number of drugs approved for *E. coli* in poultry and for *E. coli* and P. multocida in turkeys. There are also other drugs which could be used under AMDUCA (21 CFR 530.41).

920. In the U.S., drugs such as ampicillin, colistin, tiamulin are not available to use in poultry. [Hofacre (A-202) P.28 L.8-9]

CVM CRITIQUE: This statement appears to be a statement of opinion not a statement of fact. Colistin is available for use in poultry in the U.S. (21 CFR 522.468). Tiamulin (21 CFR 520.2455) and ampicillin (21 CFR 520.90e) are available in the U.S. for swine and are not prohibited for use in poultry under AMDUCA (21 CFR 530.41).

922. In Dr. Glisson's and Mathis's study:

- 1600 one-day-old broiler chicks were randomly distributed into 80 floor pens. The 80 floor pens were randomly assigned to one of four treatments. One group was to remain untreated and three were to be treated. The treatments were: 1) enrofloxacin (25 ppm) administered in the drinking water for three consecutive days, 2) oxytetracycline (400 mg/gal) administered in the drinking water for six consecutive days, 3) sulfadimethoxine (1875 mg/gal) administered in the drinking water for six consecutive days. All treatments were consistent with industry practices and, where applicable, label indications.

- The birds were reared for 20 days in normal conditions. On day 21, all birds in all pens were sprayed with live Newcastle disease vaccine virus and live infectious bronchitis vaccine virus. Subsequent to the vaccine application, environmental ammonia levels were allowed to elevate above normal levels. These events created an environment conducive to the natural occurrence of respiratory *E. coli* infection in the broilers.

- An outbreak of colibacillosis was confirmed when at least 0.5% of the birds died from colibacillosis in a 72 hour period. At that point, treatment was begun.

- The experiment ended at 42 days of age. The parameters measured were weight gain, feed conversion, mortality, and air sac lesion scores.

- The study data confirmed the greater efficacy of enrofloxacin when compared to the other treatments. All parameters measured favored enrofloxacin treatment, but the two important factors, mortality and air sac lesions, provided the most striking evidence of the efficacy of enrofloxacin. Enrofloxacin treatment prevented all further *E. coli* associated mortality and reduced air sac lesion scores very significantly. Oxytetracycline and sulfadimethoxine provided marginal mortality reductions when compared to the nonmedicated treatment and had essentially no effect on air sac lesion scores.

[Glisson (B-1903) P.9 L. 9 - P.10 L. 9; P.14-25]

CVM CRITIQUE: CVM agrees with the first four paragraphs. The last paragraph appears to be a statement of opinion and not a statement of fact, since there is no indication that the results in the last paragraph were ever published or peer reviewed.

923. Drs. Glisson and Mathis's study reproduced very closely the effect seen when:

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

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

[Glisson (B-1903) P.10 L.10-16]

CVM CRITIQUE: As stated in proposed finding of fact 922 above, this statement appears to be a statement of opinion and not a statement of fact.

924. Drs. Glisson and Mathis's study confirms the results of a previous study that using a similar design and protocol, enrofloxacin treatment provided a significant difference in feed conversion and air sac lesion scores when compared to oxytetracycline treatment. [Glisson (B-1903) P.10 L.20 – P.11 L.2]

CVM CRITIQUE: As stated in 922 above, this statement appears to be a statement of opinion and not a statement of fact. The "previous study" mentioned in Dr. Glisson's testimony is also not peer-reviewed or published.

932. The scientific community and USDA agree that preventing carcass contamination with fecal mater is an essential element in reducing the prevalence of *Campylobacter* and Salmonella on raw poultry. [Tompkin (A-204) P.58 L.3-5]

CVM CRITIQUE: This statement of opinion is without factual basis in the record. Dr. Tompkin includes this opinion in his conclusions section of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT P.30 L.19 - P.34 L.13) was stricken from the record in the ALJ's March 3, 2003 order. Further, CVM finds it curious that Bayer and AHI do not consider USDA to be part of the scientific community CVM must oppose such a finding against its sister agency.

935. Studies by Arakawa et al. (B-1821), Baba et al. (B-1822), and Fukata et al. (1987) (B-1823) demonstrate that poultry with a disease condition, such as coccidiosis, were colonized more effectively by Salmonella compared to poultry that were coccidia free. Thus, there is a relationship between the health of poultry and the ability of intestinal pathogens, such as Salmonella and *Campylobacter* to colonize the chickens. [Russell (B-1912) P.12 L.21 through P.13 L.3]

CVM CRITIQUE: This proposed finding of fact is not supported by the cited exhibits. A review of B-1821, B-1822, and B-1823, shows that the studies did not look at collibacillosis, but at a parasitic condition, coccidiosis, and that the studies did not look at *Campylobacter*, but rather Salmonella.

936. Researchers have demonstrated a link between *E. coli* infection and low body weight in flocks of turkeys. In a study by Marrett et al. (2000), a group of turkey poults exposed to naturally occurring populations of *E. coli* in litter were treated using an antibiotic and another group remained untreated. These researchers found that the antibiotic treated poults had higher body weight after only 15 days than the untreated groups (Marrett et al., 2000). Sell et al. (1997) reported that weight gain and feed efficiency were markedly impaired by *E. coli* infection of turkeys after only 7 days of exposure. These studies suggest that *E. coli* infections impact body weight, and factors that lead to non-uniform or underweight birds should be controlled to prevent fecal contamination during processing. [Russell (B-1912) P.38 L.7-15]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. When read appropriately, the studies do not support Bayer's proposed findingof fact. The Marrett study (B-1832) showed that neomycin is effective in decreasing *E. coli* mortality in turkeys. Marrett et.al. analyzed only the mortality in the poults; while they recorded body weights, they did not analyze the differences statistically. Also, in one of the five replicates the weight gains of the untreated birds were actually greater than the treated birds. Therefore, at best the research results are mixed and the effects on wieght gain are uncertain without a more rigorous statistical analysis. In the Sell study (B-1827) the air sac infections were experimentally induced with an inoculum (30 million *E. coli* bacteria injected directly into each of the left and right air sacs). Therefore, the impact of naturally occuring air sac infections on body weight is uncertain. It is also interesting to note that neither study

looked at fluoroquinolone use. B-1832 invloved the use of neomycin while B- 1827 invloved the use of supplemental Dietary Vitamin E. Finally, in Dr. Russell's study, decreased body weight in air sacculitis positive birds was shown to be statistically significant in only two out of five replications (P.43 L.1-6).

937. The National Advisory Committee on Microbiological Criteria for Foods (NACMCF-1997) reported that because processing of raw broilers does not involve a lethal heat process, such as pasteurization, delivering live chickens to the processing plant with as few pathogens as possible is necessary to control contamination of carcasses with Salmonella and *Campylobacter*. Morishita et al. (1997) stated that reducing *C. jejuni* colonization in live chickens may potentially reduce the incidence of *C. jejuni* infections in humans. Thus, controlling factors that contribute to colonization during growout should significantly impact pathogenic bacterial contamination in the processing plant. [Russell (B-1912) P.37 L.9-16]

CVM CRITIQUE: The last sentence in the proposed finding is an opinion that is not supported by the record. The record shows that "Evisceration can be a major source of additional fecal contamination", and "immersion chilling can be an important site of cross-contamination for spoilage bacteria, indicator organisms, and pathogens". (See B-557). The reduction of pathogens in growout may decrease individual poultry load, however slaughtered birds maybe cross-contaminated at numerous points including evisceration and immersion chilling. See Minnich WDT P.8 L.8- P.10 L.6; B-557.

938. Morishita et al. (1997) observed that intestinal colonization of *Campylobacter jejuni* within a flock plays a major role in carcass contamination during slaughter. [Russell (B-1912) P.39 L.1-3]

CVM CRITIQUE: Bayer's proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. Morishita et al. (1997) conducted a study to evaluate the use of an avian-specific probotic for reducing the shedding and colonization of *Campylobacter jejuni* in the chicken intestinal tract. The study measured intestinal colonization by *Campylobacter* at slaughter but there was no measure done of poultry carcass contamination during slaughter.

940. Chickens that are sick with air sacculitis and are not effectively treated will continue to drink but usually stop eating, especially when they become feverish. They will sit down on the floor and eat any spilled feed from the automatic feeder they can reach. Therefore, they will consume large quantities of bacteria, viruses, and coccidia from the bedding material (litter). [Hofacre (A-202) P.14 L.1-4; Smith (B-1914) P.24 L.5-8; Robach (B-1911) P.13 L.28-29; Glisson (B-1903) P.4. L.6-7]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Hofacre's WDT indicates that sick birds continue drinking not that sick birds with air sacculitis and that are ineffectively treated continue drinking.

941. Turkeys that are sick with pasteurella or *E. coli* and are not effectively treated stop eating. [Gonder (A-201) P.21 L.12-13 and P.22 L. 18-19 and P.26 L.23; Wages (B-1917) P.11 L.21-22]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Gonder's and Dr. Wages' WDT indicate that when poultry get sick they stop eating, not that ineffectively treated poultry stop eating.

942. Studies by Bilgili and Hess (B-1829), Savage (B-1836) and Bilgili (B-1830) have demonstrated the link between decreased feed consumption and poor intestinal tensile strength in chickens and turkeys. [Russell (B-1912) P.16 L.15-17 and P.17 L.8-10 and P.17 L.11-12; Smith (B-1914) P.24 L.5-8 and P.23 L.14-15; Hofacre (A-202) P.16 L.13, 14; Gonder (A-201) P.21 L.15-21 and P.22 L.18-19; Wages (B-1917) P.11 L.22 through P.12 L.4]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. Exhibits B-1829, B-1836 and B-1830 are all forced feed withdrawal studies (i.e., complete feed withdrawal, not just decreased consumption). Bayer has not provided information demonstrating that sick birds who "go off feed" act in a similar manner as birds during forced complete food withdrawal. Further, none of these studies looked at turkeys. Therefore, any proposed finding as to turkeys is not supported with a reference to the record. Also, see CVM critique of Bayer's proposed finding of fact 943.

943. Clinically ill poultry frequently have diarrhea and interrupted eating patterns. Both of these conditions increase intestinal fragility and make it more difficult for the processor to remove the intestines intact. Interrupted eating leads to uneven loading in the intestinal tract, making mechanical or manual evisceration at high speeds more difficult. [Russell (B-1912) P.16 L.21 through P.17 L.2; Wages (B-1917) P.12 L.1-4]

CVM CRITIQUE: Bayer's proposed finding is contrary to the exhibits cited in support thereof. Dr. Russell provides testimony that sick birds eat less, not that they eat nothing. ("Chicken respond to illness similarly to people in that an infection results in fever. The fever causes the animal to decrease food consumption." Russell WDT P.16 L.14-15). Exhibits B-1829 and B-1830 (cited by Russell's WDT) are all feed withdrawal/ starvation studies. These studies did not describe the intestinal tensile strength of sick poultry, rather they were looking at healthy poultry being starved, and the authors do not make the assertion that a starvation situation also applies to sick birds. B-1836, the other exhibit cited to by Russell, is a general paper and not peer- reviewed, which gives information to producers on the proper timing to withhold feed prior to slaughter. It also does not correspond to the interrupted eating of a sick bird.

945. Willis et al. (B-1831) found that the isolation of *Campylobacter jejuni* occurred earlier in broilers that were not given feed immediately and were delayed before placing in the grow-out house, and that extended periods of time without feed on litter increased the

likelihood that the crop of broilers will contain a higher number of *Campylobacter jejuni*. [Russell (B-1912) P.17 L.12-16; Smith (B-1914) P.23 L.22 through P.24 L.2]

CVM CRITIQUE: Bayer's reliance on B-1831 is misplaced. Exhibit B-1831 evaluated the effects of delayed placement on reused litter and the isolation of *Campylobacter jejuni*. The flock which previously used this litter was *Campylobacter* positive and the author stated, "[A]t this time it remains unknown whether the stress from placement on used litter increased the chicks vulnerability to *C. jejuni* infection . . . The early increased isolation rate would have little effect at slaughter based on the fact that all birds were (100%) positive at 28 d of age." (B-1831, P.3).

947. Pilot studies have been conducted by two vertically integrated broiler operations to determine the effect of air sacculitis on *E. coli* and Salmonella populations. In the first study, conducted in 1997, carcasses removed from the line by U.S.D.A.-F.S.I.S. inspectors for visible air sacculitis, and carcasses that were not visibly infected, were evaluated for *E. coli* counts over a 1 wk period (unpublished data). For ASN carcasses, 58% had pre-chill *E. coli* numbers in the acceptable range (0 to <100 CFU/mL) according to the HACCP regulation (U.S.D.A.-F.S.I.S., 1996), 37% were found to be in the questionable range (100 to 1,000 CFU/mL), and only 5% were in the acceptable, questionable, and unacceptable ranges, respectively. Therefore, a total of 96% of AS carcasses had questionable or unacceptable *E. coli* counts. These studies demonstrate a link between the presence of air sacculitis in the flock and increases in indicator and pathogenic bacterial populations. [Russell (B-1912) P.39 L.4-19]

CVM CRITIQUE: The proposed finding is misleading because it overstates the validity, reliability and relevance of the observed outcomes. Dr. Russell's study is not published in a peer- reviewed journal. Russell reported (P.45 L.12-14) that the *E. coli* carcass counts were statistically significantly higher in the AS positive flocks only in 2 of the 5 replications. And, no analysis is given for the total positive versus the total negative birds.

948. Preventing fecal contamination of the carcasses from spillage of digestive tract contents or smearing of fecal material on edible meat surfaces is the single most important aspect of sanitary slaughter. In fact, the F.S.I.S. modified its Finished Product Standards to introduce a "Zero Fecal Tolerance" policy for carcasses entering the chiller (U.S.D.A.-F.S.I.S., 1996). Cut intestines can lead to contamination of equipment, workers, and inspectors, and can be a major source of cross-contamination (NACMCF, 1997). [Russell (B-1912) P.31 L.23 – P.32 L.6]

CVM CRITIQUE: This finding is not supported by the cited written direct testimony of Russell. There is no line 23 on page 31, and page 32 line 6 does not address this topic.

951. The fluid ingesta in the ill bird's gut are more likely to contaminate the carcass if this fragile gut is ruptured during evisceration. [Smith (B-1914) P.23 L.19-21]

CVM CRITIQUE: CVM notes that this proposed finding appears to be an incomplete comparision. More likely to "contaminate the carcass . . . evisceration" than what?

956. Failure to control *E. coli* and Salmonella increases the likelihood of a higher prevalence and concentration of *Campylobacter* on raw poultry. [Tompkin (A-204) P.58 L.13-14]

CVM CRITIQUE: Dr. Tompkin includes this opinion in his conclusions section of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT p. 30, line 19 - p. 34, line 13) was stricken from the record by the ALJ's March 3, 2003 order. Therefore this statement appears to be without support in the record.

960. In the study described in the Written Direct Testimony of Catherine Logue (G-1464) the chill water in Plant B was hyperchlorinated to a concentration of 20 ppm. [Logue (G-1464) P.7 L.5-7, L.16-17]

CVM CRITIQUE: The proposed finding is misleading in that it fails to include Dr. Logue's entire statement on this topic. Dr. Logue's WDT does state that Plant B stated it hypochlorinated its chill tank but the immediate following sentence of Dr. Logue's testimony states that "in both cases, the chlorine concentrations of the water in the chill immersion tanks was not established at the time of the study." Therefore, there was no measure of the actual chlorine concentration at Plant B (Logue WDT P.7 L.5-7).

961. In the study described in the Written Direct Testimony of Catherine Logue (G-1464) the chill water in Plant A was unchlorinated well water. [Logue (G-1464) P.7 L.2-3]

CVM CRITIQUE This proposed finding is misleading because it fails to disclose Dr. Logue's entire statement. Dr Logue's WDT does state that Plant A indicated that it used unchlorinated well water, but Dr. Logue goes on to say that "In both cases, the chlorine concentrations of the water in the chill immersion tanks was not established at the time of the study." Therefore, there is no measure of the actual chlorine concentration at Plant A (Logue WDT P.7 L.2-7).

962. In the study described in the Written Direct Testimony of Catherine Logue (G-1464) more *Campylobacter* isolates from Plant B showed a higher degree of resistance and displayed resistance to more antibiotics compared to isolates from Plant A. [Logue (G-1464) P.8 L.12-20; P.20,21]

CVM CRITIQUE: This proposed finding is contradicted by Logue's WDT P.8 L. 12-20 and P.20 L.21. Dr. Logue did not state that more *Campylobacter* isolates from Plant B showed a higher degree of resistance. Rather, more isolates showed resistance (i.e., the number of isolates, not the MICs of the isolates.

976. Chicken and turkey processing facilities are dependent for efficient operation on processing chicken and turkeys of uniform weight and size. [Carey (G-1456) P.3 L.27; Hofacre (A-202) P.2 L.16-21]

CVM CRITIQUE: The cited references do not support the proposed finding. Carey WDT P.3 L.26-27 states, "Turkey grow-out facilities typically do not have heating systems" and Hofacre P.2 L.16-21 states, "Each poultry company has control over all fiscal and bird husbandry aspects of production, from the day- old parent breeders to the marketing and distribution of the final products to the retailer. The 'poultry industry' is actually three different industries, commercial layers are chickens of the leghorn breed that lay table eggs for human consumption. There are approximately 275 million table egg layers in production in the USA. When these birds begin laying eggs for human consumption at 18-19 weeks of age, they can only . . . " As shown, these portions of the cited WDT do not support Bayer's proposed finding, which is therefore without correct reference to the record.

977. Poultry processing is highly automated. Variable size of poultry is problematic because processing equipment is set for the average size of a uniform flock. [Hofacre (A-202) P.9 L.16-21]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony because it does not state that poultry processing is highly automated.

999. Reducing the prevalence rate of *Campylobacter* and Salmonella on raw poultry requires a farm-to-table approach that incorporates the principles of HACCP and the use of GMPs. [Tompkin (A-204) P.58 L.1-2]

CVM's CRITIQUE: This statement of opinion is without factual basis in the record. Dr. Tompkin includes this opinion in his conclusions section of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT p. 16, line 8 - p. 27, line 22 & p. 28, line 3 - p. 29, line 18) was stricken from the record in the ALJ's March 3, 2003 order.

1004. The potential cross-contamination risk posed by the transportation and processing of poultry increases the likelihood that carcasses leaving the processing plants are contaminated with *Campylobacter*. [Minnich (G-1467) P.11 L.14-17]

CVM CRITIQUE : CVM points out that the actual WDT cited by Bayer also includes the words "including fluorquinolone resistant *Campylobacter*" at the end of the statement above, and CVM urges the ALJ to accept this proposed findng with the addition of the words omitted by Bayer in its proposed finding.

1005. Surveys of chicken, turkeys, ducks and geese, indicate they are all reservoirs of *Campylobacter*. There are large variations in the proportions of flocks that are infected. The large variation depends on the type of production system, the geographical location and on the time of year. [Wegener (G-1483) P.3 L.9-11]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Wegener's WDT states that surveys of poultry, notably chicken, turkeys, ducks, and

geese indicate large proportions of flocks that are infected with *Campylobacter*, not that they are all reservoirs of *Campylobacter*.

1012. A risk/benefit analysis on the withdrawal of the NADA for enrofloxacin should include an analysis of the total effect on human health risks from the withdrawal of the NADA for enrofloxacin, including whether the human health benefits of using the drug outweigh the human health risks from use of the drug. [Cox (B-1901) P.12; ALJ Davidson's March 3, 2003 Order (OR31), P.1]

CVM CRITIQUE: This proposed finding is a paraphrase of the order. T he order specifically states "Risk/benefit evidence is relevant only to the extent it deals with human health effects, i.e. whether the human health benefits of using the drug outweigh the human health risks from use of the drug."

1013. Evaluating the total effect on human health risks from the withdrawal of the NADA for enrofloxacin includes not only the effect on fluoroquinolone-resistant campylobacteriosis, but also the effect on fluoroquinolone-susceptible campylobacteriosis (i.e., illness from susceptible strains) and on illnesses due to other chicken-borne pathogens, such as Salmonella. [Cox (B-1901) P.12]

CVM CRITIQUE: This proposed finding is a misleading statement of opinion because it presents an incomplete picture of total effect. It supposes that the total health effect is expanded by showing increased days of illness due to susceptible strains of Salmonella but fails to indicate that there will also be increased days of illness due to Salmonella that have reduced susceptibility to fluoroquinolone and this problem will emerge more slowly over time than the fluoroquinolone resistance in *Campylobacter*.

1014. CVM did not consider any human health risks and benefits of enrofloxacin use in chickens or turkeys in making the decision to propose to withdraw the NADA for enrofloxacin. [CVM Response to Bayer's Interrogatory 83; Burkhart (B-1900) P.2 L.44-45]

CVM CRITIQUE: This proposed finding is contradicted by the CVM RA [G-953] and its conclusion that about 8500-9200 patients that were harmed in 1998-1999 by having fluoroquinolone-resistant infections and fluoroquinolone treatment.

1015. The CVM/Vose Risk Assessment has not fully assessed the human health effects of withdrawing the NADA for enrofloxacin because it focuses on only one organism (*Campylobacter*) and one main issue (fluoroquinolone-resistance) without evaluating the withdrawal's probable total effects on human health risks. [Cox (B-1901) P.12]

CVM CRITIQUE: This proposed finding is a statement of opinion and is contradicted by the NOOH document, Section IV, Development of Antimicrobial Resistance as a Result of Drug Use in Animals discusses concerns about the loss of fluoroquinolone susceptibility in Salmonella.

1016. The CVM/Vose Risk Assessment model does not identify or quantify any specific adverse human health effects, nor does it show how the frequency or severity of such health effects (e.g., illness-days) would change depending on continued use of enrofloxacin or the withdrawal of the NADA for enrofloxacin. [Cox (B-1901) P.55, P.83-87]

CVM CRITIQUE: This proposed finding is contradicted by the CVM RA [G-953] and its conclusion that about 8500-9200 patients were harmed in 1998-1999 by having fluoroquinolone-resistant infections with fluoroquinolone treatment and it does predict how that number of people would change as fluoroquinolone resistance increases in poultry while consumption, contamination levels, and fluoroquinolone prescription rates stayed stable at their current levels.

1017. The CVM/Vose Risk Assessment does not model how enrofloxacin reduces human exposures to *Campylobacter* and other pathogens by changing the distribution of microbial loads reaching people via chickens. Thus, the model does not and cannot provide accurate or useful estimates of human health risks from use of enrofloxacin in chickens. [Cox (B-1901) P.55, P.83-87]

CVM CRITIQUE: This proposed finding is a statement of opinion contradicted by the CVM RA [G-953] and its conclusion that about 8500 patients are harmed by having fluoroquinolone-resistant infections. The portion of the statement having to do with microbial load distribution is contradicted by proposed finding of facts 546 and 547.

1018. Banning Baytril will greatly increase human health risks from campylobacteriosis and salmonellosis. A ban is expected to cause more than 25 additional days of campylobacteriosis and over 90 days of salmonellosis for each hypothetical day of fluoroquinolone-resistant *Campylobacter* (Fluoroquinolone-resistant CP) illness prevented. [Cox (B-1901) P.7 L.15-18, P.25, P.83-87]

CVM CRITIQUE: This proposed finding is a statement of opinion based on an unvalidated calculation.

1019. Withdrawing the NADA for enrofloxacin will prevent far fewer days of illness than CVM has estimated. Withdrawing the NADA for enrofloxacin may have no human health benefits. [Cox (B-1901) P.7 L.13-14, P.77-79, 82]

CVM CRITIQUE: This proposed finding is a statement of opinion based on an unvalidated calculation.

1020. The CVM/Vose Risk Assessment does not meet the minimal standards of technical competence and correctness necessary for acceptance in peer-reviewed journals because of its failures to correctly characterize risk, scope the enrofloxacin risk management problem, incorporate available relevant data on causality, exposure and dose-response, or alert decision-makers to the potential adverse human health consequences of an enrofloxacin ban. [Cox (B-1901) P.25]

CVM CRITIQUE: This proposed finding is a statement of opinion rather than a fact.

1022. Airsacculitis flocks have higher initial levels of pathogens such as *Campylobacter*, *E. coli*, and Salmonella. [Cox (B-1901) P.84]

CVM CRITIQUE: This proposed finding is a statement of opinion. It appears to be based on a study conducted at one geographic location that does not permit evaluation of such confounding effects as differences in flock management and climate that would be expected to introduce more statistical "noise" into the distribution of loads on the animals than would airsacculitis itself.

1023. A consequence of withdrawing the NADA for enrofloxacin (and probably other therapeutics and growth promoters such as those banned in Europe in 1999) is to increase the variance in the sizes and weights of broilers arriving at processing plants. [Cox (B-1901) P.83, citing B-1912, Attachment _ (Russell, 2002)]

CVM CRITIQUE: See the critique of proposed finding of fact 1022.

1024. During processing, airsacculitis significantly increases the levels and incidence of *Campylobacter*, *E. coli*, and Salmonella. [Cox (B-1901) P.84]

CVM CRITIQUE: See the critique of proposed finding of fact 1022.

1025. Airsacculitis-positive flocks have greater variability in carcass sizes and weakened digestive tracts, which in turn increase processing errors such as tears and cuts in digestive organs. [Cox (B-1901) P.84]

CVM CRITIQUE: See the critique of proposed finding of fact 1022.

1026. Increased variance in the sizes and weights of broilers arriving at processing plants leads to more cuts and fecal contamination during processing, as more birds fall outside the tolerance of the evisceration equipment and process. [Cox (B-1901) P.83]

CVM CRITIQUE: This proposed finding is misleading in that it suggests that processing plants do not make adaptations for sizes and weights of broilers.

1027. Increased processing errors such as tears and cuts in digestive organs increase fecal contamination levels. [Cox (B-1901) P.84]

CVM CRITIQUE: See the critique of proposed finding of fact 1022.

1028. As a result of more cuts and fecal contamination during processing, both the mean and the variance of the microbial load distribution on processed chicken increase, thereby increasing the all-important right tail of the distribution – the fraction of processed

chickens that carry sufficient microbial load to cause illness in humans with relatively high probability. [Cox (B-1901) P.83, citing B-1912, Attachment _ (Russell, 2002)]

CVM CRITIQUE: This proposed finding of fact is contradicted by the WDT of Travis [G-1479] paragraphs 58-61 and the dose response articles discussed therein. There appears to be no more likelihood of becoming ill at higher doses of *Campylobacter.*

1029. A detailed simulation model incorporating available data predicts that a ban on enrofloxacin will cause between about 1 month (25 days) and several years (1000 days) of additional campylobacteriosis illness-days due to increased fluoroquinolone-sensitive *Campylobacter* loads reaching consumers, for each hypothetical illness-day prevented by reduced fluoroquinolone-resistant campylobacteriosis. [Cox (B-1901) P.86, citing B-1020 (Cox 2001)]

CVM CRITIQUE: This proposed finding is a statement of opinion based on an unvalidated calculation.

1030. A quantitative risk model predicts that use of Baytril causes reduced human risk of campylobacteriosis (fluoroquinolone-resistant or not) due to decreased microbial loads on processed chicken. [Cox (B-1901) P.86, citing B-1020 (Cox 2001)]

CVM CRITIQUE: This proposed finding is a statement of opinion based on an unvalidated calculation.

1031. Applying the CVM-Vose approach to risk estimation to the Russell (2002) data (B-1912), (i.e., assuming that excess illness-days are directly proportional to prevalence of contaminated carcasses), indicates that about 97 excess illness-days from salmonellosis would be created per hypothetical fluoroquinolone-resistant campylobacteriosis illness day prevented, as well as an excess 75 fatalities per year from increased Salmonella and Clostridium poisoning. [Cox (B-1901) P.86]

CVM CRITIQUE: This proposed finding is a statement of opinion based on an unvalidated calculation and fails to counterbalance for the effect of resistance in Salmonella discussed in the NOOH as indicated in response to proposed finding of fact 1015.

1040. Dr. Russell examined the impact on processed broilers if Baytril is not available because the health of the incoming bird is important to the pathogen load of the finished product. [Russell (B-1912) P.16 L.11-12]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. See B-1912, Attachment 1, page 36, "[A] study was conducted to determine if the presence of air sacculitis in broiler chickens contributes to loss of saleable yield, lack of uniformity, fecal contamination, processing errors and increases in population of pathogenic and indicator bacteria." This study did not include an examination of the effects of Baytril on pathogen load.

1041. Eliminating the use of Baytril within the poultry industry will dramatically increase the number of human *Campylobacter* infections. [Russell (B-1912) P.26 L.15-22]

CVM CRITIQUE: This proposed finding of fact is contradicted by other WDT and exhibits and CVM disagrees with such a broad and sweeping proposed finding. This proposed finding ignores the availability of other approved drugs (see Tollefson WDT P.18 L.34-P.19 L.2) and their effectiveness (i.e., B-1832) and assumes the industry is unable or unwilling to alter its current practices. Neither of these implicit assumptions are supported by the record and Bayer has not provided any record reference in that regard.

1043. Dr. Russell's research confirms what HACCP managers have long known, that birds that are not treated for diseases like air sacculitis infections will have: (1) greater intra-flock variability in weight at the time of slaughter leading to increased processing errors and increased fecal contamination; (2) higher pathogen contamination due to increased fecal contamination; and (3) increased numbers of infectious processes within carcasses at time of slaughter. This means that birds with untreated air sacculitis are more likely to carry pathogens, cross-contaminate other carcasses during processing, and are more likely to contain pathogens leaving the processing plant than are birds whose disease is treated. [Prucha (A-203) P.11 L.13-21]

CVM CRITIQUE : This finding of fact is unsupported by the record reference. Dr. Russell's research does not confirm anything. It is one study with mixed results and cannot support such a broad proposed finding. Russell's research has not been published or peer reviewed. (B-1912, and Attachment #1). Further, Mr. Prucha provides no support for what, if anything, HAACP managers have "known." Therefore, this proposed finding should be rejected as unsupported by adequate record reference.

1045. Recent data shows that carcasses with high levels of pathogens are more likely to cause disease than product with low levels of these pathogens. [Robach (B-1911) P.15 L.21-23]

CVM CRITIQUE: This proposed finding appears to be Mr. Robach's opinion, unsupported by any reference to factual information on the record. This statement is based on personal communication with Dr. Stern. Personal communications are not peer reviewed nor was data provided to support this statement. CVM urges the ALJ to reject this proposed finding as unsupported. Further, this proposed finding is contrary to other evidence in the record. Several witnesses have provided WDT as to the number of organisms that can illness. (Nachamkin WDT P.4 L.45-P.5 L.1; Tauxe WDT P.5 L.3-6; G-67) and Dr. Tauxe has testified (referring to *Campylobacter*) that, "these are microscopic organisms, far smaller than can be seen with the human eye, and millions would fit on the head of a pin" (Tauxe WDT P.5 L.7-8) and " . . . a drop of chicken juice would often include an infectious dose of 500 organisms." (WDT Tauxe P.10 L. 40-41). Therefore, it appears that low levels of these pathogens can cause disease.

1046. The removal of enrofloxacin from the broiler producer's arsenal of weapons would be a major step backwards in our multiple- threshold strategy to reduce the incidence of enteric pathogens in fresh poultry. [Robach (B-1911) P.16 L.4-6]

CVM CRITIQUE: This proposed finding of fact appears to be Mr. Robach's opinion, unsupported by any reference to factual information on the record and, in fact, contradicted by the record. This statement assumes that there are no other antibiotics that may be effective in treating *E. coli* infections, when, in reality there are other approved drugs for this disease. (See Tollefson WDT P.18 L.34-P.19 L.2).

1047. It is of utmost importance that the poultry industry continue to have access to disease-control agents such as Baytril, in order to implement the multiple control-point strategy so necessary to the continuous improvement of the microbiological quality of our products and the public health. [Robach (B-1911) P.16 L.23 through P.17 L.3]

CVM CRITIQUE: See CVM critique of Bayer's proposed findings of fact 1043 and 1046.

1050. In the absence of an effective disease treatment for *E. coli* respiratory infections it is possible that these diseased and weakened birds will be more susceptible to colonization by enteric pathogens of human health significance. Without an effective treatment for respiratory disease (*E. coli*) in broilers, our industry loses a valuable weapon in our arsenal against foodborne illness. Losing this weapon puts enormous additional pressures on other parts of the process. [Robach (B-1911) P.17 L.11-16]

CVM CRITIQUE : See CVM critique of Bayer's proposed findings of fact 1043 and 1046.

1058. The "risk analysis" prepared by CVM in connection with the proposal to withdraw approval of use of fluoroquinolones (FQ) in chickens has a number of major flaws, errors and omissions. On this basis, it cannot be considered as a reliable basis to estimate the impact of fluoroquinolone use in chickens on occurrence of fluoroquinolone-resistant *Campylobacter* in humans. In particular these flaws, errors and omissions are likely to have resulted in a substantial overestimate of the risk to humans. [Haas (B-1904) P.7 L.21 through P.8 L.4 relying on B-1904]

CVM CRITIQUE: This proposed finding is contradicted by evidence on the record that FQ use in veterinary animals leads to the development of resistance to FQ in humans Anderson, et al [B-167] as indicated in critique of finding of fact 453 and Engberg [G-191] as indicated in finding of fact 728 and by evidence in the RA [G-953] that this resistance results in a human health impact of about 9000 cases per year with FQ-r infections who are treated with fluoroquinolones.

1059. The CVM/Vose Model cannot be considered a "Risk Assessment." [Haas (B-1904) P.8 L.5 through P.10 L.18, excluding P.9 L.3-6, and P.9 L.10 through P.10 L.2]

CVM CRITIQUE: This proposed finding is a statement of opinion and not a fact.

1060. The concept of a risk assessment derives from the 1983 NAS paradigm including steps of hazard characterization, dose-response analysis, exposure analysis, and risk characterization. The recent OIE paradigm bears great similarity to the NAS paradigm. Additionally, a recent consensus document developed under the auspices of the International Life Sciences Institute (ILSI) -- including participation by scientists from USDA, FDA and USEPA -- contains analytical phases that are similar to both the NAS and OIE frameworks. The FDA Center for Food Safety and Applied Nutrition has published a framework for conducting major risk assessments, in which it adopts the elements of the NAS paradigm (both in terminology and in substance). A similar breakdown, specifically for the area of food risk assessment has been adopted by Codex Alimentarius. [Haas (B-1904) P.8 L.6-15]

CVM CRITIQUE: This proposed finding is misleading in that while technically correct, it leaves out the context of flexibility and suitability for purpose in which these authoritative bodies state these generally recognized parts of risk assessment. See Vose [G-1480] page 3 as referred to in critique of finding of fact 532.

1061. While there has been an evolution in the practice of risk analysis, particularly with respect to the integration of communication and stakeholder input at all steps of the process, it is clear that the key technical aspects of risk assessment remain consistent from the 1983 NAS paradigm until today (although terminology may differ with the particular application). In particular, assertions that the 1994 NRC report ("Blue Book") or the 1996 NRC report ("Orange Book") have supplanted the 1983 paradigm are factually erroneous. [Haas (B-1904) P.8 L.15 through P.9 L.2]

CVM CRITIQUE: See response to finding of fact 1060.

1062. It is also noteworthy that an assessment of the impact of fluoroquinolone-resistant *Campylobacter jejuni* derived from beef cattle has been conducted by the Georgetown University Center for Food AND Nutrition Policy using the NRC/Codex paradigm. (B-147). In fact, a co-author (Crawford) of this study is now Deputy Commissioner of FDA. [Haas (B-1904) P.9 L.6-9]

CVM CRITIQUE: Agree. It is also noteworthy that [B-147], as indicated in several of the critiques to previous finding of facts, also attribute 60% of campylobacteriosis cases to poultry (finding of facts 525 and 561)and produce a table indicating a time course of increasing FQ-r in humans as a function of time since approval of veterinary FQs (finding of facts 435 and 453).

1063. It is difficult to associate the steps required for a quantitative risk assessment with the actual tasks performed in the CVM/Vose model (G-953). For example, exposure is only portrayed with respect to pounds of chicken consumed, and pounds consumed containing fluoroquinolone (FQ) resistant *Campylobacter*. In other words, the risk of consuming a

portion of chicken with 1 *Campylobacter* is assumed to be equal to the risk of consuming a portion with 1000 organisms. There is no specific quantification of the number (either of fluoroquinolone sensitive or fluoroquinolone-resistant) of organisms per portion being consumed in the exposed population. There is no specific construction or utilization of a dose-response relationship, despite the availability of a relationship (B-517, B-748), and despite the fact that other risk assessors (B-147) have used that model. [Haas (B-1904) P.10 L.3-12]

CVM CRITIQUE: This proposed finding overlaps with those of proposed finding of facts 533-536 and 543-547, where it is indicated that the concepts described herein are a reflection of failure to acknowledge dose response in the aggregate.

1064. The alternative approaches used by CVM (G-953) are therefore at variance with the steps that have become to be generally regarded as key to the validity and usefulness of quantitative microbial risk assessment. [Haas (B-1904) P.10 L.13-15]

CVM CRITIQUE: This proposed finding of fact is contradicted by the WDT of Vose [G-1480] at page 3. See critiques of proposed finding of fact 532 and finding of fact 1060.

1065. The CVM/Vose Model (G-953) fails to meet the NAS criteria for risk assessments. [Haas (B-1904) P.10 L.16-18]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion rather than fact and is contradicted by the WDT of Vose [G-1480] at page 3. See critiques of proposed finding of fact 532 and finding of fact 1060.

1066. The CVM/Vose Model underestimates the probability that a person with campylobacteriosis will seek care (pmn). [Haas (B-1901) P.10 L. 16 – P. 12 L.5]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion rather than fact and is contradicted by the CVM RA itself [G-953]. The RA document describes that this quantity was estimated based on a population survey conducted by CDC.

1067. The CVM/Vose Model overestimates the attributable risk from chicken. [Haas (B-1904) P.12 L.10 – P.15 L.7, excluding P.12 L.15 through 18 and P.13 Figure 1]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion rather than fact and is contradicted by B-147 which states the value to be 60%. See critique of proposed finding of fact 1062 (referring back to finding of fact 525 and 561).

1068. The CVM/Vose Model shows an inconsistency between "K" values for total and fluoroquinolone-resistant *Campylobacter*. [Haas (B-1904) P.15 L.11 – P.16 L.2]

CVM CRITIQUE: This proposed finding is misleading because it is taken out of context in that the CVM/Vose model gives several potential reasons why there may have

been measurement error that could account for the slight shift of Kres from Kall [g-953, Section 5, page 5].

1069. The K" values in the CVM/Vose risk assessment cannot properly be interpreted as dose-response factors since the K's are ratios between the aggregate case burden and the aggregate consumption. [Haas (B-1904) P.15 footnote 5]

CVM CRITIQUE: This proposed finding is contradicted by the testimony of Vose [G-1480] as indicated in the critique of proposed finding of fact 551.

1070. The CVM/Vose Model dismisses the distributional importance of pathogen load. [Haas (B1904) P.16 L.3-18]

CVM CRITIQUE: This proposed finding is misleading in its interpretation. See critique of proposed finding of fact 536. CVM emphasized the proportional relationship between prevalence on chickens and numbers of human cases. This relationship is corroborated by Rosenquist [G-1788] as discussed in response to proposed finding of fact 536.

1071. Due to the lack of adherence to standard practices in microbial risk assessment, lack of consideration of significant variables, and use of outdated information, the CVM/Vose analysis is not useful in understanding or quantifying the risks posed by the use of fluoroquinolone in treating chickens. Due to the lack of grounding in conventional risk assessment practices, it does not appear possible to quantify the degree of error that may have been made. [Haas (B-1904) P.16 L.19 through P.17 L.2]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion rather than fact and is contradicted by the CVM RA. The results for all outcomes in the RA are expressed in terms of distributions which indicate the range of plausible values for each outcome, thus allowing for error.

1072. The CVM/Vose Model (G-953) does not meet the SDWA Criteria As Required by OMB Regulations in the following among other aspects. Based on his analysis, Dr. Hass concluded that there are significant deficiencies in the CVM/Vose analysis with respect to the OMB guidelines such that it is not an adequate risk assessment under OMB requirements. In particular, the CVM/Vose analysis fails to meet data quality requirements (peer review, objectivity) mandated in the OMB guidelines. [Haas (B-1904) P.17 L.3-10]

CVM CRITIQUE: This proposed finding is opinion as it is interpretative evaluation of regulations, guidelines and requirements.

1073. Although the epidemiological studies used by Vose to estimate the poultry related fraction of campylobacteriosis were peer reviewed in refereed journals, the fact that they are old studies and contain methodological flaws with respect to present practice would lead to questioning with respect to data quality. It would have been possible for these to have been subject to the additional peer review contemplated by OMB, but this has

apparently not occurred. The NARMS data used, to my knowledge, has not been subject to external peer review. The OMB guidelines on objectivity specify that peer review provides a rebuttably presumptive test of data and analytic results. The guidelines themselves appear to be silent with respect to analytic methods. Vose's approach represents a new analytical method, which to my knowledge has not been subject to peer review or other tests of objectivity. [Haas (B-1904) P.17 L.11-20]

CVM CRITIQUE: This proposed finding appears to be opinion based on interpretation of guidelines rather than fact. The statement about the quality of the epidemiologic studies used is contradicted in evidence cited in [G-603] as stated in the critique of proposed finding of fact 562.

1074. It is likely that any risk assessment that used an experimental method (e.g., for determination of concentration of a toxic material) which had not been subject to the objectivity test of OMB (e.g., peer review), would be held up to question. It is therefore reasonable to consider that a method for handling of data (calculation) that had not been subject to the objectivity test would be equally suspect. I am not aware of any peer-reviewed manuscript that delineates the K factor approach. Whether the CVM/Vose analysis went through an alternative independent and open peer review process is not clear, but I have seen nothing to suggest it has. [Haas (B-1904) P.19 L.12 through P.20 L.6]

CVM CRITIQUE: This proposed finding was admitted to be an opinion in the cited text from which it was drawn. [Haas (B-1904) P.19 L. 12]. That opinion is contradicted by the open peer review process on the CVM risk assessment, which is described on this record by Vose (G-1480, P. 6, lines 25-43), including:

> "a public comment period and even a conference dedicated to the assessment, including a food safety and risk assessment expert panel from around the world who provided independent comments on the strengths and weakness of the draft assessment. In my experience, this was at the highest level of effort taken to explain a food safety risk assessment and elicit comments.
> ***
> CVM also made exceptional efforts to incorporate stakeholders' views and data."

1075. The OMB and HHS/FDA guidelines indicate that documents should include "Additional studies not used to produce the risk estimate that support or fail to support the findings of the assessment, and the rationale of why they were not used." This delineation and critique of alternative studies does not appear to be part of the CVM/Vose model. [Haas (B-1904) P.20 L.7-10]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1076. The OIE Risk Assessment Framework does not meet the regulatory requirements of the OMB regulations for risk assessment. There is no intrinsic inconsistency between the OIE risk framework and the OMB guidelines. However, the OMB, in incorporating the Safe Drinking Water Act requirements for health risk assessment, which refer to central tendency estimates and upper and lower bound estimates for risk, would appear to strongly argue for the use of quantitative rather than qualitative risk assessment.

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1077. The CVM/Vose Model (G-953) does not meet the OIE Risk Assessment Framework. The steps of the OIE framework for risk assessment consist of release assessment, exposure assessment, consequence assessment and risk estimation. The OIE definition of Consequence Assessment (in typical US applications, this would be termed Dose Response Assessment) is inVose et al. at page 815, expanded upon at page 816. It is clear that the CVM/Vose model is an attempt to develop a quantitative risk assessment. The CVM/Vose analysis, however, does not meet the OIE framework for quantitative risk assessments, because it does not adequately consider or model the dose at the moment of exposure. The metric for dose used in the CVM/Vose analysis is whether or not a particular amount of chicken does or does not contain fluoroquinolone-resistant *Campylobacter*. It does not consider the amount of fluoroquinolone-resistant *Campylobacter* that might be present. The principle of "The dose makes the poison" is applicable to quantitative risk assessment, and by neglecting the amount of bacteria ingested, the CVM/Vose analysis appears to overlook one of the key principles contemplated in the OIE framework. [Haas (B-1904) P.20 L.20 through P.21 L.23]

CVM CRITIQUE: See critiques of proposed finding of facts 533-535.

1078. The CVM/Vose Model (G-953) does not meet the recently proposed CVM Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern. The CVM Guidance expounds a qualitative risk assessment framework as being appropriate for assessing safety of new animal drugs. Under the CVM Guidance, the evaluation of each of the stages of release assessment, exposure assessment, and consequence assessment are to be conducted using a final descriptor of "high," "medium" or "low." The CVM/Vose analysis does not go through readily separable phases of release assessment, exposure assessment and consequence assessment, nor does it describe in a formal sense any of these aspects using the lexical descriptors designated under the CVM Guidance. Hence, the CVM/Vose model does not meet the CVM Guidance. [Haas (B-1904) P.21 L.24 through P.22 L.9]

CVM CRITIQUE: This proposed finding is misleading in that it fails to recognize that the CVM Guidance applies to pre-approval studies when information will be very scarce.

1079. The CVM/Vose Model (G-953) is not a reliable basis to estimate the impact of fluoroquinolone use in chickens on occurrence of fluoroquinolone-resistant

Campylobacter infections in humans. In the absence of meeting the NAS criteria, or any other recognized criteria (e.g., OIE), the burden is on the risk assessor to establish scientific credibility to demonstrate that the assessment is correct. This is typically done through peer review or validation with existing data. [Haas (B-1904) P.22 L.10-18]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1080. The methodologies used in the CVM/Vose analysis (G-953) have not been subject to peer review. There are some inputs (e.g., NARMS data) that have not apparently been subject to external peer review, and there are other inputs (epidemiological studies) where, despite being published in peer review journals, would require additional peer review to validate their utility. The December 1999 Workshop does not constitute peer review under generally accepted definitions. [Haas (B-1904) P.22 L.18-23]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1081. The CVM/Vose analysis methodology (G-953) is defective in a number of key aspects., including among other defects: (1) There are a number of assumptions that are made which have not be in explicitly grounded in data. For example, at the public meeting in January 2001, Dr. Kimberly Thompson of Harvard questioned whether there is support for a linear assumption between disease burden and frequency of consumption of positive portions. Dr. Condon, as noted above, questioned the appropriateness of analyzing risk without explicitly considering the number of organisms ingested. Therefore, it is reasonable to believe that the methodology as employed would not be capable of meeting the normal tests of adequacy inherent in the peer review process for scientific journals. [Haas (B-1904) P.23 L.1-9]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1082. Based on Dr. Haas analysis, the CVM /Vose analysis (G-953) should not be considered as a reliable basis on which to make a decision. [Haas (B-1904) P.23 L.10-11]

CVM CRITIQUE: This proposal is opinion, not fact.

1083. It is clear both from the Cox study, as well as those of other workers, that a more traditional risk assessment could have been performed on *Campylobacter* in poultry. [Haas (B-1904) P.23 L.11-12]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1084. It is in Dr. Haas' opinion clear from the Cox study, as well as those of other workers, that a more traditional risk assessment should be performed prior to making a decision by CVM to withdraw approval of enrofloxacin in poultry. [Haas (B-1904) P.23 L.11-13]

CVM CRITIQUE: This proposal is opinion, not fact.

1085. The CVM/Vose Analysis (G-953) does not consider potential microbial benefits from the use of fluoroquinolone in chicken production. [Haas (B-1904) P.23 L.14-15]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1086. The literature indicates that the prevalence of air sacculitis in chickens with respiratory diseases increases in flocks that are not administered efficacious antibiotics. Recent work also indicates that chickens that have air sacculitis have greater levels of enteric pathogens such as *Campylobacter* and Salmonella on their carcasses.(B-1912, Attachment 1). Inasmuch as greater carcass bacterial loadings will lead to greater loadings of microorganisms on the food product as prepared or consumed, even considering HACCP, providing that handling and cooking processes do not differ, the diminished use of efficacious antibiotics, all other factors remaining constant, would increase the exposure of people to pathogens and therefore increase the risk of human disease. [Haas (B-1904) P.23 L.16 – P.24 L.2]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1087. The CVM/Vose Analysis (G-953) explicitly considers only chicken and not turkey. [Haas (B-1904) P.24 L.7]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1088. Even if the CVM/Vose analysis was to be regarded as providing a rational basis for making a regulatory judgement with respect to the issue of use of fluoroquinolone in chickens, it could not be regarded as providing a rational basis with respect to turkeys. There is no consideration of distinctiveness in microbial prevalence, exposure (food consumption), case rate or strain differences between turkeys and chickens. These latter factors make the two problems (although perhaps naively similar) different enough to merit distinct and separate analysis. Hence the scientific basis for reaching a regulatory decision in the case of fluoroquinolone use in turkeys is even less than may exist for chickens. [Haas (B-1904) P.24 L.8-15]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1089. The CVM/Vose model (G-953) cannot be considered a risk assessment under the NAS 1983 paradigm. [Haas (B-1904) P.25 L.9-10]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1090. The OIE paradigm has substantive similarities to the NAS 1983 paradigm, and therefore the CVM/Vose model (G-953) does not appear to contain the necessary elements contemplated under the OIE framework. [Haas (B-1904) P.25 L.11-13]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1091. The CVM/Vose analysis (G-953) makes a number of assumptions that are not substantiated by peer reviewed information. [Haas (B-1904) P.25 L.14-15]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1092. Some data used in the CVM/Vose analysis (G-953) is from dated literature no longer likely to reflect actual exposure patterns in the general population. [Haas (B-1904) P.25 L.16-17]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1093. The CVM/Vose analysis (G-953) fails to consider distributional (of organism) and dose-response issues that are essential for an adequate quantitative microbial risk assessment. [Haas (B-1904) P.25 L.18-19]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1094. The overall analytical framework used in the CVM/Vose analysis (G-953) has not been subject to a peer review as required in the OMB guidelines on data quality. [Haas (B-1904) P.25 L.20-21]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1095. The CVM/Vose analysis (G-953) does not provide a basis to perform a qualitative risk assessment according to the CVM Guidelines. [Haas (B-1904) P.26 L.1-2]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1096. The CVM/Vose analysis (G-953) provides an inappropriate basis on which to make a risk-based regulatory decision. [Haas (B-1904) P.26 L.3-4]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1097. The flaws in the CVM/Vose analysis (G-953) rise to the level such that they do not permit the use of the CVM/Vose analysis to infer a risk from the use of FQ in chickens. [Haas (B-1904) P.26 L.5-6]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1098. The CVM/Vose analysis (G-953) neglects potential benefits with respect to human exposure to pathogens resulting from the use of fluoroquinolone in chicken rearing. [Haas (B-1904) P.26 L.7-8]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1099. The CVM/Vose analysis (G-953) neglects the additional risk (in the form of increased carcinogenic water disinfection byproducts) that would result from the withdrawal of use of fluoroquinolone in chicken rearing. [Haas (B-1904) P.26 L. 9-11]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1100. The CVM/Vose analysis (G-953) explicitly considers only risks posed with respect to fluoroquinolone-resistant *Campylobacter* in chicken, and does not provide explicit consideration with respect to turkey. [Haas (B-1904) P.26 L.12-14]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1101. The CVM/Vose Risk Analysis does not objectively address the question of whether data suggest that enrofloxacin use in chickens causes increased risk of harm to humans, such as treatment failures or morbidity, although it is driven by many untested assumptions and opinions on this point. [Cox (B-1901) P.5 L.8-11]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1102. Objective tests for potential causality, though readily available, have not been used by CVM in their Risk Analysis. [Cox (B-1901) P.5 L.11-12]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1103. When objective tests for potential causality are used, they refute the CVM/Vose Risk Assessment's main assumptions and predictions. [Cox (B-1901) P.5 L.11-13]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1104. CVM's risk assessment does not meet widely accepted standards for risk assessment. It lacks generally accepted intellectual foundations for drawing valid conclusions about risk, and, indeed, the conclusions that it draws are not valid. [Cox (B-1901) P.7 L.1-3]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1105. CVM's risk assessment does not use the best available data and methods. [Cox (B-1901) P.7 L.8]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1106. CVM's risk assessment model does not and cannot provide accurate or useful estimates of human health risks from use of Baytril in chickens. [Cox (B-1901) P.7 L.9-10]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1107. CVM's risk model cannot be used to support rational or useful risk-management decision-making. [Cox (B-1901) P.7 L.11-12]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1108. Since the 1970s, human health risk assessment has become a relatively well-established discipline, featuring both well-structured methodological approaches for assessing health risks from known or suspected hazards and also a substantial body of technical content and methods supporting the methodological structure. [Cox (B-1901) P.9-10]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1109. The traditional logical structure of risk assessment includes the following steps: 1) Scoping the analysis to support decisions by estimating the causal relation between decisions, exposures, and their probable total human health consequences (see e.g. Vose testimony, G-1480, P.3, paragraph 7, citing SRA and NRC). To guide rational regulatory

decision-making, traditional quantitative risk analysis seeks to quantify the causal relation between regulatory actions that might be taken and their total probable human health consequences. This step is often not listed explicitly, but it is a crucial part of risk analysis frameworks (e.g., EPA's multipathway risk assessment framework) designed to support effective and rational health risk management decision-making; 2) Hazard identification, which means to use data to provide and assess evidence of a causal relation between exposures (e.g., to *Campylobacter*-contaminated chicken) and adverse human health response (e.g., illness-days per capita per year); 3) Exposure assessment, which means presenting data-based estimates of the population frequency distribution of individual exposures (e.g., frequencies and magnitudes of ingested microbial loads of *Campylobacter*) in a human population (e.g., the population of chicken-eaters in the US). Exposure modeling also addresses how human exposures would change if different risk management actions (e.g., a ban on enrofloxacin) were undertaken. 4) Dose-response modeling or exposure-response modeling, which quantifies the causal relation between levels of exposure and probabilities of specified adverse human health consequences for individuals with various characteristics or risk factors; 5) Risk characterization, which integrates information from the exposure assessment and exposure-response models and presents their implications for the frequency and magnitude of exposure-related adverse health effects in the exposed population; 6) Uncertainty characterization, which describes uncertainty, variability, and sensitivities in the estimated exposure-response relation for the exposed population. It should characterize both model uncertainties and data uncertainties. Variability analysis should describe the extent of inter-individual heterogeneity in risks, e.g., due to differences in other risk factors and covariates among individuals. [Cox (B-1901) P.10]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1110. FDA's Center for Food Safety and Applied Nutrition has offered a definition of risk assessment that is: "The scientific evaluation of known or potential adverse health effects resulting from human exposure to hazards. The process consists of the following steps: hazard identification, exposure assessment, hazard characterization (dose-response), and risk characterization". The Center for Food Safety and Applied Nutrition has offered a definition risk as "The likelihood of the occurrence and the magnitude of the consequences of exposure to a hazard on human health. [Cox (B-1901) P.11]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1111. The CVM/Vose Risk Assessment for enrofloxacin use in poultry does not follow the content or methods of the traditional risk assessment approach. [Cox (B-1901) P.11]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1112. As defined by the Codex Alimentarius Commission, one of the necessary steps of Hazard Characterization as a part of risk assessment is a dose-response assessment should be performed if the data are obtainable. [Joint Institute for Food Safety and Applied Nutrition (A-30)]

CVM CRITIQUE: This proposed finding is not supported by its record reference. CVM disagrees that "one of the necessary steps . . . is a dose response assessment." Exhibit A-30 says that as defined by Codex a risk assessment consists of severeal steps of which one is Hazard Characterization. The description of Hazard Characterization notes that for biological or physical agents, a dose- response assessment should be performed if the data are obtainable. This is far different from the language suggested by Bayer in its proposed finding of fact that one of the necessary steps is a dose- response assessment.

1115. As posted on the foodriskclearinghouse.umd.edu, website for the Joint Institute for Food Safety and Applied Nutrition, the risk assessment step of Exposure Assessment includes an assessment of the extent of actual or anticipated human exposure. [Joint Institute for Food Safety and Applied Nutrition (A-31) P. 2]

CVM CRITIQUE: CVM notes that Bayer has provided an incorrect record reference. CVM believes the correct reference is to A-31, P.3.

1121. Human feeding studies to assess dose-response relationships for various pathogens are referenced on the foodriskclearinghouse.umd.edu, website for the Joint Institute for Food Safety and Applied Nutrition. [Joint Institute for Food Safety and Applied Nutrition (A-33)]

CVM CRITIQUE: The proposed finding of fact is misleading. Exhibit A-33 does not list out or even reference to any human feeding studies. It states "[t]his list of papers includes human feeding studies to assess dose- response relationships for various pathogens" but fails to provide or attach that list.

1122. In a joint document, the FDA's Center for Food Safety and Applied Nutrition and the USDA's Food Safety and Inspection Service indicate that the generally accepted framework for microbial risk assessments divides the risk assessment into four distinct components: (1) hazard identification, (2) exposure assessment, (3) hazard characterization, and (4) risk characterization. [Interpretive Summary: Draft Assessment of the Relative Risk to Public Health from Foodborne Listeria monocytogenes Among Selected Categories of Ready-to-Eat Foods (A-34) P. 5]

CVM CRITIQUE: CVM notes that the risk assessment does not indicate it is the only acceptable model for microbial (or antimicrobial) risk assessment.

1123. In a joint document, the FDA's Center for Food Safety and Applied Nutrition and the USDA's Food Safety and Inspection Service indicate that under the generally accepted framework for microbial risk assessments the steps of exposure assessment, hazard characterization, and risk characterization involve the use available data and, where

necessary, science-based assumptions, to develop mathematical models that estimate how often consumers eat food contaminated with the organism, the number of the bacteria likely to be in that food, and the risk of serious illness or death to the age-based groups when they are exposed to the hazard. [Interpretive Summary: Draft Assessment of the Relative Risk to Public Health from Foodborne Listeria monocytogenes Among Selected Categories of Ready-to-Eat Foods (A-34) P. 5 - 6]

CVM CRITIQUE: See CVM critique of Bayer's proposed finding of fact 1122.

1125. The CVM/Vose Risk Assessment's parameter pca (probability a *Campylobacter* case is attributable to chicken) is too high. [Cox (B-1901) P.77]

CVM CRITIQUE: This proposed finding of fact is an opinion, constructed out of pronouncements later in the cited paragraph. It is contradicted by the explicitly-explained basis for that parameter, provided in this record in G-953, pages 52-55.

1126. The CVM/Vose Risk Assessment's parameter prh (probability a *Campylobacter* case from chicken is fluoroquinolone-resistant) is too high. [Cox (B-1901) P.78, citing B-1260]

CVM CRITIQUE: This proposed finding of fact is an opinion, constructed out of pronouncements on the cited page. It is contradicted by the explicitly-explained basis for that parameter, provided in this record in G-953, pages 55-57.

1127. The CVM/Vose Risk Assessment's chicken-attributable fraction specifically for fluoroquinolone-resistant campylobacteriosis cases is too high; a value based on the data from the CDC 1998 - 1999 *Campylobacter* Case-Control data set is between –11.6% and 0.72% (depending on how missing data are treated) and is not statistically different from zero. [Cox (B-1901) P.78]

CVM CRITIQUE: This familiar proposed finding of fact is essentially a repeat of Bayer's proposed findings of fact 529, 565, and 566, so the critique is also the same.

1128. The CVM/Vose Risk Assessment estimates the total number of cases in which ciprofloxacin is administered to a patient with at least one CFU of fluoroquinolone-resistant *Campylobacter*, but not every case of fluoroquinolone-resistant *Campylobacter* illness treated with ciprofloxacin will experience treatment failure or diminished effectiveness. [Cox (B-1901) P.78, citing B-50 (Piddock 1999)]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1129. Not all domestically acquired, non-medication-related fluoroquinolone-resistant campylobacteriosis cases come from chickens. [Cox (B-1901) P.79]

CVM CRITIQUE: This proposed finding of fact is an opinion, unsupported on the record. A careful reading of the cited page of that reference will reveal not a trace of support for the proposed finding.

1130. By assuming that fluoroquinolone use is the only source of fluoroquinolone-resistant *Campylobacter* chickens, the CVM risk assessment model over-estimates the true fraction of fluoroquinolone-resistant *Campylobacter* in chickens that come from fluoroquinolone use. [Cox (B-1901) P.79]

CVM CRITIQUE: This proposed finding of fact is an opinion, unsupported on the record. A careful reading of the cited page of that reference will reveal not a trace of support for the proposed finding.

1131. A *Campylobacter* risk assessment should take into account on farm strategies and their impact on the level of *Campylobacter* on or in poultry entering the processing plant. [Tompkin (A-204) P.40 L.8-9]

CVM CRITIQUE: This proposed finding is an opinion of the witness not supported by reference to the record.

1132. Existing data from FoodNet fail to show a significant epidemiologic link between the consumption of turkey meat and campylobacteriosis and salmonellosis. [Tompkin (A-204) P.58 L.15-16]

CVM CRITIQUE: This statement of opinion is without factual basis in the record. Dr. Tompkin includes this opinion in his conclusions section of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT p. 15, line 17 - p. 16, line 3) was stricken from the record in the ALJ's March 3, 2003 order.

1134. Female turkeys may be marketed at 10-22 weeks of age and weigh 10-26 pounds; males may be marketed from 16-24 weeks and weigh 25-45 pounds. [Gonder (A-201) P.3 L.10-11]

CVM CRITIQUE: This proposed finding is contradicted by Dr. Carey's WDT which states that hens are marketed at 14-23 pounds and toms are marketed at 22-35 pounds. [Carey (G-1456) P.2 L.11-12.] The correct cite for this proposed finding is P. 4 L. 10-11.

1139. Generally, brooder houses will contain 10,000-20,000 poults, although some very large houses used in a few locations may contain 70,000 poults. Finishing or grow-out houses usually contain one-third to one-half as many birds as brooder houses due to the need to provide additional space for the birds to grow. [Gonder (A-201) P.6 L.9-14; Wages (B-1917) P.4 L.7-9]

CVM CRITIQUE: This proposed finding is contrary to Dr. Wages' cited testimony. Dr. Wages' WDT states that typically 8000-12,000 turkeys are raised in a brooder house and that typically 4000-6000 turkeys are raised in grow-out houses. In addition, Dr. Carey's WDT states that 5000-17,000 turkeys are raised in a house.

1142. All water systems in poultry houses must be managed to avoid spillage and keep the litter as dry as possible to reduce foot and leg problems, and gastrointestinal disease. This is particularly true in turkeys compared to chickens due to their heavier market weights, older ages, and relative intolerance of environmental ammonia (commonly produced by wet litter). [Gonder (A-201) P.7 L.12-15]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact 906.

1149. Turkeys and chickens are different species. Chickens are not just big turkeys. Factors that influence the diagnosis, prevalence and treatment of disease in one are not the same as in the other. [Gonder (A-201) P.11 L.10-12]

CVM CRITIQUE: The second sentence of this proposed finding is contrary to the weight of evidence.

1151. Turkey is a highly unlikely source of infection for human campylobacteriosis [Gonder (A-201) P.13 L.6-7 relying on A-201 generally]

CVM CRITIQUE: This statement is contradicted by Dr. Gonder's WDT which states that *C. coli* is commonly isolated from turkeys and turkey meat [Gonder (P. 12 L. 16-P. 13 L. 3)]. *C. coli* as well as *C. jejuni* can result in human campylobacteriosis (G-444 P. 84-104).

1152. There are relevant grow-out and processing differences between turkeys and chickens that contribute to reduced bacterial loads on turkeys. Turkeys have more frequent house clean-out and their live-haul equipment is more routinely sanitized between processed flocks. [Gonder (A-201) P.11 L.14-17]

CVM CRITIQUE: The first sentence appears to be a statement of opinion and not a statement of fact.

1154. Turkey processing uses higher scalding temperatures than broilers, which can kill more *Campylobacter*. Wempe (Appl Env Micro 45:355-359. 1983) reports *C. jejuni* prevalence in scalding tank overflow water at California chicken plants to be 13.3, 20, and 20% for scalding temperature of 60, 53, and 490C (140, 127, and 1210 F). Yusufu (J Food Prot 46:868-872. 1983) reports California turkey plants had a prevalence of 5.7 and 5.6% at 60 and 57C (140 and 1340F) - rather a large difference. [Gonder (A-201) P.11 L.20 through P.12 L.2]

CVM CRITIQUE: This proposed finding is a statement of opinion without factual basis in the record. Neither study is in the record.

1155. Turkeys undergo manual evisceration and cropping so the risk of enteric pathogen contamination is greatly reduced as compared to automated processing in the broiler industry. Turkeys undergo extended chilling to reduce carcass temperature due to larger

body mass. This uses more chlorinated water (at 3-5 ppm active chlorine) and chilling capacity than chickens so that bacterial loads should be further reduced since both chlorination (Luechtefeld, J Clin Micro 13:266-268, 1981; Genigeorgis, Proceeding of the Western Poultry Disease Conference, 1986; (B-1857) Blaser, Appl Env Micro 51:307-311, 1986)(B-1855)) and washing (Izat, Poultry Sci 67: 1568-1572. 1988) (B-1853) reduce *Campylobacter* levels during processing. [Gonder (A-201) P.12 L.4-11]

CVM CRITIQUE: This proposed findng is contrary to exhibit B- 1857, which is cited in the testimony. B-1857 discusses the isolation of *Campylobacter* fetus sub sp. jejuni faeces of poultry not chlorination reducing *Campylobacter*. B-1857 is by Rosef and Kapperud not Genigeorgis, and is totally irrelevant to this topic.

1156. Turkeys are sold at a more physiologically and immunologically mature age than chickens; therefore it seems reasonable that their intestinal microflora may be more similar to that of adult chickens. Indeed, the microflora from adults has been shown to have protective effects against *Campylobacter* infections in young chicks (Soerjade-Liem, Avian Dis 28:139-146, 1984). (B-1868) [Gonder (A-201) P.12 L.11-15]

CVM CRITIQUE: This proposed finding is contrary to the exhibit cited in support thereof. Exhibit B-1868 studied competitive exclusion cultures in young chicks to prevent colonization by *Campylobacter*. There is no indication that this study would relate to adult turkeys.

1157. Recent studies corroborate an additional major difference between chickens and turkeys. These studies show that the predominant *Campylobacter* recovered from turkeys is *C. coli* not *C. jejuni*. These studies include, Zhao et. al. (G-727), who recently reported on *Campylobacter* prevalences from retail meats in the greater Washington, D.C. area. They report a 14% prevalence on turkey products versus 71% prevalence on chicken products. The major organism recovered was *Campylobacter coli* which was found in 86 of 112 isolates (77%) while *C. jejuni* was only identified 16 of 112 isolates (14%). The remaining isolates were other *Campylobacter* spp. Other studies include 165 ground turkey samples were cultured for *Campylobacter* – 14 (8.5%) were positive for *Campylobacter jejuni/coli*, while 73 of 162 (45%) of ground chicken samples were positive (Food Safety & Inspection Service, USDA, Nationwide Raw Ground Chicken Microbiological Survey and Nationwide Raw Ground Turkey Microbiological Survey, 1994). [Gonder (A-210) P.12 L.16 through P.13 L.3]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact 1471. The cite for Dr. Gonder's WDT should have been A-201 not A-210.

1158. Hollinger (G-945, pg.4 & table #2; pg. 9) has reported that turkey carcasses have a 20 fold lower organism contamination rate with *Campylobacter* spp. than chicken. Other studies show that *C. jejuni* could not be isolated from turkeys or turkey products (Genigeorgis, Rosef, Acta Vet Scand 23: 128-134, 1982 (B-1857); Baker, Poultry Sci 66: 1766-1770, 1987 (B-1858)). [Gonder (A-201) P.13 L.3-9]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony, for the following reasons: 1. The Hollinger paper did report that the total numbers of *Campylobacter* spp. on turkey carcasses was approximately 20-fold less than on chicken carcasses. But the difference in the numbers of *Campylobacter* on ground turkey and ground chicken was less than 2-fold, and the **prevalence** of *Campylobacter* on the carcasses was similar. 2. B-1857 discusses the isolation of *Campylobacter* fetus sub sp. jejuni faeces of poultry not chlorination reducing *Campylobacter*. B-1857 is by Rosef and Kapperud not Genigeorgis, and is totally irrelevant to this topic. 3. B-1858 was only concerned with *C. jejuni*, not with *C. coli* which is commonly isolated from live turkeys and turkey meat (review by Hollinger G-945).

1161. The turkey is more immunologically and physiologically mature at processing, the intestinal microflora should be much more stable. This maturity should result in an intestinal microflora more closely resembling that of a competitive exclusive culture, which should reduce the number of enteric pathogens, including *Campylobacter*, that are present (Snoeyenbos, Avian Dis 22:273-278. 1978) [Gonder (A-201) P.14 L.15-19]

CVM CRITIQUE: The first statement appears to be a statement of opinion and not a statement of fact. The second statement is contrary to the cited testimony. The Snoeyenbos paper (B-1861) dealt with competitive exclusion cultures, which were used to prevent colonization of Salmonella in chicks, which is not relevant to this hearing.

1162. As compared to broiler chickens, far more turkey meat is produced for further processed sales. Such further processing usually includes cooking which kills bacteria, including *Campylobacter*, that may otherwise be present on the raw carcass (Genigeorgis (B-1857)). [Gonder (A-201) P.14 L.19-22]

CVM CRITIQUE: This proposed finding is contradicted by the WDT of Drs. Wegener and Meng. Dr. Wegener's WDT states that cooking kills some bacteria in chicken. [Wegener (G-1483) P.9 L.23-35]. Dr. Meng's WDT states that many *Campylobacter* isolates have been recovered from retail poultry carcasses. [Meng (G-1466) P.5 L.1-4]. In addition, B-1857 is by Rosef and Kapperud not Genigeorgis, and is totally irrelevant to this topic.

1163. Modern consumers buy very little raw turkey, even at Thanksgiving. [Gonder (A-201) P.14 L.22-23]

CVM CRITIQUE: This proposed finding is an opinion that is not supported by the record. There are no studies on the record showing that consumers buy very little raw turkey.

1164. As the consumption patterns changed, it became obvious to producers that plant-cooked turkey is what the individual and food-service consumer desired. [Gonder (A-201) P.14 L.23 through P.15 L.2]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact 1163.

1166. Goldsboro Milling produces about 10 million market turkeys. In 1986, virtually all its product was sold as fresh or frozen turkey. Goldsboro cooks over 70% of product before it leaves the plant. Goldsboro is not unique in the industry. [Gonder (A-201) P.15 L.5-9]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Gonder's WDT does not indicate how many turkeys are produced.

1168. There are many differences between turkeys and chickens including differences in *Campylobacter* prevalence between the two species that have been known for years, and apparently still exist. [Gonder (A-201) P.16 L.15-17]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit G-945. The Hollinger paper (G945), referred to by Dr. Gonder in number 1158 above, plainly stated that the prevalence of *Campylobacter* was similar in turkeys and broilers, not different.

1186. It is not correct that enrofloxacin is not a valuable drug because it is used so sparingly and national average turkey mortality is low and controlled. National average mortality rate is not relevant to this discussion. While the national average mortality rate may decline, there will still be those flocks that may suffer many times that national rate of mortality. Those are the flocks in which enrofloxacin makes a difference – to reduce that damagingly high rate and relieve animal suffering in the individual flock. This is one of the ways in which poultry veterinarians make progress in the national rates of mortality and condemnation. [Gonder (A-201) P.20 L.9-17]

CVM CRITIQUE: This proposed finding appears to be a statement of opinion and not a statement of fact.

1193. If there are 10,000 birds in a house, a colibacillosis outbreak, or mild fowl cholera outbreak, frequently shows a per day mortality daily pattern of 4-6-8-7-10-16-25-45. A veterinarian would hope to intervene on the day mortality reached 10, especially if the flock was showing other signs such as depression, sneezing or coughing and would certainly intervene on the day mortality reached 16. [Gonder (A-201) P.21 L.23 through P.22 L.6]

CVM CRITIQUE: CVM assumes that Bayer's reference to birds means turkeys in this proposed finding.

1196. A common trait of both broilers and turkeys is that when they get sick, they "go off feed," i.e., stop eating. (B-1117, at P.25). As a result, their intestines become fragile. (Russell, 2002) (B-1912). This can be due to increased water consumption, actual intestinal disease resulting in edema of the wall of the intestine (coccidiosis, *E. coli*), or changes in the bacterial population of the intestines due to altered eating patterns (necrotic enteritis), leading to diarrhea, gas, and actual damage to the intestinal lining. (Russell, 2002). [Gonder (A-201) P.22 L.18-23; Wages (B-1917) P.11 L.21-22]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support thereof. Dr. Russell's study appears to show that ill birds are more likely than healthy birds to have their intestines torn during evisceration, not that ill birds have fragile intestines. There is no indication that Russell's study has been peer-reviewed or published, which casts doubts on the reliability of the report. Also, see See CVM's critique of Bayer's proposed finding of fact 942.

1197. Clinically ill turkeys frequently have diarrhea and interrupted eating patterns. (B-322). Both of these conditions increase intestinal fragility and the difficulty of removing intestines intact at the processing plant. Interrupted eating leads to uneven loading in the intestinal tract, making both mechanical and manual evisceration more difficult. This increases the chance that the birds' flesh will be contaminated with intestinal contents and intestinal bacteria at the processing plant. It is an undesirable situation, and an unsafe one if the processor or consumer does not safely handle and cook the meat prior to consumption. [Gonder (A-201) P.23 L.1-7; Wages (B-1917) P.12 L.1-4]

CVM CRITIQUE: This proposed finding is contrary to the weight of the evidence. Also, see CVM's critique of Bayer's proposed finding of fact 943.

1198. When turkeys "go off feed," they are also more susceptible to enteric problems, including parasites such as coccidiosis and the overgrowth of pathogenic bacteria. Some of the problems arise because feed consumption in sick birds may be inadequate to provide enough coccidiostat (anti-coccidial medication) to prevent coccidiosis, or growth-promoting antibiotic to stabilize the intestinal bacterial population and prevent clostridial overgrowth (necrotic enteritis). This is a food safety issue in humans. [Gonder (A-201) P.23 L.8-12; Wages (B-1917) P.12 L.5-8]

CVM CRITIQUE: This proposed finding is contradicted by Dr. Gonder's WDT. Dr. Gonder's WDT stated that turkey coccidia do not infect chickens and chicken coccidia do not infect turkeys (P.16 L. 1-11). Thus, coccidia are very species-specific parasites. Poultry coccidia (Eimeria) and necrotic enteritis are not causes of human disease. The last sentence is a statement of opinion without factual basis in the record because it is not in Dr. Gonder's testimony.

1199. Turkeys that "go off feed" are more likely to be populated with *Campylobacter*, Salmonella, and Clostridia as the nutrient mix and pH of the intestinal contents changes to conditions more suitable to the growth of these bacteria (low volatile fatty acids in the ceca, higher intestinal pH, decreased starch and sugar levels, etc.). [Gonder (A-201) P.23 L.13-16]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. No references were provided in the WDT to support this statement.

1200. In turkeys with intestinal disease and some septic diseases, the intestinal wall actually becomes thinner. This decreases tensile strength and increases intestinal breaking at processing. The intestines may also become swollen with fluid and gas as diarrhea

develops. These swollen intestines are difficult to remove from the bird without breaking them at processing, resulting in fecal contamination. [Gonder (A-201) P.23 L.17-21; Wages (B-1917) P.12 L.9-13]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. No references were provided in the witnesses testimony to support this statement.

1201. In deciding whether to treat a sick turkey flock a veternarian's oath requires that the public health be served, including as part of human health the production of adequate wholesome food for the human population with a minimum of environmental damage. [Gonder (A-201) P.24 L.14-17]

CVM CRITIQUE: This proposed finding of fact is not supported by Dr. Gonder's WDT P.24 L.4-12. In fact, Dr. Gonder states that the portion of his WDT cited by Bayer in this proposed finding is merely his interpretation, not what the veternarian oath actually states.

1205. Enrofloxacin is prescribed for turkeys only in cases of colibacillosis or fowl cholera with severe disease potential, where the mortality may become high quickly. (Joint Stipulation 15). [Gonder (A-201) P.26 L.4-5]

CVM CRITIQUE: This proposed finding is contrary to the cited joint stipulation. The joint stipulation states that enrofloxacin is approved for use only by prescription and under veterinary supervision. The stipulation does not state when enrofloxacin for turkeys is prescribed. This proposed finding is also unsupported by the record. Neither Dr. Gonder nor Bayer provide any prescription or diagnosis data to support this proposed finding.

1206. Most veterinarians must see birds from the flock, obtain cultures, determine the amount of medication required, note it on the case report, and call the company warehouse to authorize disbursement of enrofloxacin, and most follow the Judicious Use Guidelines for Use of Antimicrobials in Poultry. [Gonder (A-201) P.26 L.12-19]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony. Dr. Gonder's WDT indicates what veterinarians in his company do not what most veterinarians do.

1208. Delivery of enrofloxacin through drinking water systems is appropriate and effective. FDA has long accepted drinking water delivery as a safe and effective means to administer therapeutic animal drugs, including antibiotics, to commercially grown broiler chickens and turkeys. (Joint Stipulation 18). [Gonder (A-201) P.27 L.1-5]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit G-52 and Dr. McDermont's WDT [(G-1465)P.7 L.8-11] which indicate that not controlling the amount

of water consumed by birds in administering antibiotics can increase the probability of selecting for resistant *Campylobacter*.

1210. Enrofloxacin is the most expensive medication per unit in the history of poultry medicine – waste is not tolerated. [Gonder (A-201) P.27 L.12-13]

CVM CRITIQUE: This proposed finding is not supported in the record. Bayer has not submitted a price list demonstrating that enrofloxacin is the most expensive medication.

1211. Turkey veterinarians and companies use enrofloxacin prudently since, among other reasons, and unlike most humans, turkey flocks don't have insurance companies paying for the medication. Therefore, it makes no sense to spend money wildly on antibiotics. [Gonder (A-201) P.29 L.11-18]

CVM CRITIQUE: This proposed finding concerns economic evidence which is not relevant to the issues of this hearing according to the ALJ's March 3, 2003, Order.

1212. Enrofloxacin is extremely effective when used prudently and can result in no clinical failures for the treatment of colibacillosis and pasteurellosis (fowl cholera) in turkeys in over one hundred cases. [Gonder (A-201) P.29 L.20-23;Wages (B-1917) P.18 L.19]

CVM CRITIQUE: This proposed finding mischaracterizes Dr. Gonder's testimony. Dr. Gonder states that he has experienced virtually no clinical failures with enrofloxacin not that there are no clinical failures with enrofloxacin.

1214. In general, there are no good alternatives to enrofloxacin for turkey flocks with fowl cholera or colibacillosis. [Gonder (A-201) P.30 L.20]

CVM CRITIQUE: This proposed finding is contradicted by the written direct testimony of Dr. Tollefson. Dr. Tollefson's table, which Dr. Hofacre discusses in 911 above, shows a number of drugs approved for *E. coli* and P. multocida in turkeys. There are also other drugs which could be used under AMDUCA (21 CFR 530.41). This proposed finding also is contradicted by Dr. Hofacre's WDT and Exhibit B-1832. B-1832 indicates that neomycin is an alternative to Baytril. Dr. Hofacre's WDT provides an extensive list of alternatives to Baytril. (A-202 P. 25-26).

1217. Fluoroquinolones are the sole antibiotic effective against enteric-origin systemic colibacillosis at 2-3 weeks of age in Dr. Gonder's company, and produces, against historic standards of treatment for severe cases of fowl cholera and respiratory colibacillosis, truly spectacular, rapid reductions in mortality. [Gonder (A-201) P.31 L.1-4]

CVM CRITIQUE: Dr. Gonder's company may not be representative of the entire turkey industry.

1219. The withdrawal of the approval of enrofloxacin would adversely impact turkey health, primarily in the area of colibacillosis. [Gonder (A-201) P.32 L.8-10]

CVM CRITIQUE: This proposed finding is contradicted by the written direct testimony of Dr. Tollefson. Dr. Tollefson's table, which Dr. Hofacre discusses in 911 above, shows a number of drugs approved for *E. coli* and P. multocida in turkeys. There are also other drugs which could be used under AMDUCA (21 CFR 530.41). There are other alternatives to Baytril, as shown in exhibit B-1832 and the extensive list given by Dr. Hofacre (A-202 P. 25-26).

1220. If increased amounts of colibacillosis-caused airsacculitis, osteomyelitis, and fecal contamination can affect the quality of USDA-inspected turkey product, then FDA withdrawal of enrofloxacin from the market would harm that quality. [Gonder (A-201) P.32 L.10-13]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact.

1221. Fecal contamination is usually increased in flocks marketed with active disease. If that translates into a potential degradation in human health due to increased amounts of enteric pathogens of whatever type entering the food chain, then FDA withdrawal of enrofloxacin wouldn't be good for human health either. [Gonder (A-201) P.32 L.13-16]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. Since Dr. Gonder will sometimes chose to market a sick flock instead of treating it (P. 26 L. 5-9), his "concern" for human health seems to be unsubstantiated.

1222. Due to their bacteriostatic nature, the tetracyclines tend to work rather slowly. This is not a good situation for diseases with rapidly increasing mordidity/mortality rates, like fowl cholera or a severe colibacillosis outbreak. The control achieved with tetracycline products in treatment situtations is generally incomplete; repeat treatment is often necessary due to failure to completely control the situation. At least in vitro, many *E. coli* isolates are resistant to tetracyclines (B-700); this is frequently associated with lack of efficacy in the field. [Gonder (A-201) P.34 L.6-10]

CVM CRITIQUE: This proposed finding is contradicted by the written direct testimony of Dr. Hofacre. Dr. Hofacre (A-202 P. 15 L. 17-18) testified that tetracyclines were the primary antibiotic for treating *E. coli* infections prior to the approval of Baytril. Dr. Hofacre also testified that tetracyclines were often the first choice for *E. coli* infections (P. 20 L. 1-6).

1226. Sulfa medications are generally limited to use in water medication in turkeys since their residue potential greatly complicates controlling their use in a high-volume feed mill. Sulfas use may also be limited by palatability and solubility problems with particular water supplies, and toxicity problems if birds are dehydrated or adequate water

consumption cannot be maintained due to lameness or changes in drinking equipment due to scheduled movements. [Gonder (A-201) P.34 L.19 through P.35 L.1]

CVM CRITIQUE: This proposed finding appears to have its basis in financial issues. There are other drugs are available to treat turkeys as noted in CVM's critique of Bayer's proposed finding 1219. Bayer should follow the withdrawal times required by law. Financial concerns are irrelevant to this hearing based on the ALJ's March 3, 2003, Order.

1227. The lengthy withdrawal period (10-14 day withdrawal period in-house, depending on the particular formulation available) for use of sulfa medications in turkeys also precludes their use in older birds close to slaughter age. The residue limit for sulfa compounds in poultry is ? 0.1 ppm, depending on the compound (21 CFR 556.6xx depending on compound) in edible tissue. Sulfas tend to persist in feed and water systems, tending to aggravate the residue potential. [Gonder (A-201) P.35 L.1-5]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding 1226. Also, the residue limit should be ≤ 0.1 ppm. based on the cited testimony.

1228. Exceeding the residue limit triggers an investigation by CVM. Frequently, flocks sold subsequently from the affected farm must be tested prior to slaughter until a pattern of compliance is established. If several flocks from different farms within the same company are involved, all flocks from the affected company may be tested for a period of time. The test generally requires the submission of 30 birds per flock to the USDA FSIS veterinarian at the slaughter facility within 1-2 weeks of the regular processing date. Capturing, transporting, and processing these birds is difficult and expensive, especially since the birds are usually condemned as offal since they would otherwise be required to be stored under separate seal until testing results are received. Many plants cannot store small numbers of birds for a short period of time in a cost-effective manner. Violations may also be published in the FDA Veterinarian, which is bad publicity. [Gonder (A-201) P.35 L.8-18]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding 1226.

1230. Infections are cyclical and regional. Just because flocks may be in general good health at present and enrofloxacin is not being used extensively, it is only a matter of time before a fowl cholera outbreak hits, or a virus hits that will cause secondary *E. coli* infections. Then enrofloxacin will be needed in that region because an outbreak can devastate a region's production. [Gonder (A-201) P.36 L.1-5]

CVM CRITIQUE: The last sentence of this proposed finding was stricken from the record in the ALJ's 3/3/03 Order.

1231. Baytril is the only efficacious drug for treating *E. coli* or Pasteurella multocida infections in turkeys. [Gonder (A-201) P.36 L. 5-6]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. Dr. Gonder is implying that tetracyclines and sulfas are never efficacious which is not supported by the record. Moreover, Exhibit B-1832, documented the efficacy of neomycin for colibacillosis in turkeys.

1232. Due to high resistance to tetracyclines and sulfa drugs, and the residue concerns with the sulfa drugs, there are no practical alternatives to Baytril on the market. [Gonder (A-201) P.36 L.6-7]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding 1226. Also, this proposed finding is contradicted by Exhibit B-1832 which documented the efficacy of neomycin for colibacillosis in turkeys.

1234. The watering systems in turkey houses are such that Baytril is administered in a manner to minimize spillage and environmental contamination. [Gonder (A-201) P.36 L.10-11]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding 906.

1235. There was no information presented in the Notice of Opportunity for Hearing demonstrating that turkeys should be included. Turkeys have been arbitrarily lumped in with broiler chickens under the heading of "poultry". This is not correct in this instance. [Gonder (A-203) P.36 L.13-15]

CVM CRITIQUE: This proposed finding is not supported by the record. The information presented in the NOOH is not relevant. The NOH was published after the NOOH. CVM and Bayer are involved in an administrative hearing. Many evidentiary records concerning turkeys are on the record.

1236. No information has been presented in the Notice of Opportunity for Hearing showing that the *Campylobacter* risk is similar between turkeys and chickens, and ample information exists showing that it is not. [Gonder (A-201) P.36 L.15-17]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding 1235.

1270. Veterinarians have a duty to treat sick animals. [Wages (B-1917) P.12 L.15]

CVM CRITIQUE: Dr. Gonder has testified, however, that he will send some flocks to slaughter rather than treat them (A-201, p.26 L. 5-9).

1273. Turkeys and broilers get a sufficient dose of enrofloxacin. [Wages (B-1917) P.18 L.19]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926 which stated that if enrofloxacin was used in a pulsed dosing manner rather than the continuous dosing of the current label, it would maximize clinical efficiency and result in less antimicrobial resistance.

1274. The enrofloxacin dose in turkey's is designed to minimize resistance in the target pathogen. [Wages (B-1917) P.18 L.19-20]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926 which clearly stated that the present dosing of enrofloxacin does **not** minimize bacterial resistance.

1278. If the NADA for enrofloxacin is withdrawn, the only available drugs specifically approved to treat *E. coli* infections in chickens older than three days of age and *E. coli* and Pasteurella multocida infections in turkeys older than three days of age are: sulfa drugs and tetracyclines (Tetracycline, Oxytetracycline, Chlortetracycline). [Wages (B-1917) P.19 L.6-9; Gonder (A-201) P.34 L.1-5]

CVM CRITIQUE: This proposed finding is contradicated by Exhibit B-1832, which documented the efficacy of neomycin for colibacillosis in turkeys.

1281. In reality, there are no alternatives to enrofloxacin use in turkeys. [Wages (B-1917) P.19 L.13-16]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which documented the efficacy of neomycin for colibacillosis in turkeys.

1283. Turkeys and chickens are biologically different and there are differences in how the two are reared and raised. Turkeys are not just big chickens. Many of the biological and rearing differences are significant to the issues in this hearing. [Wages (B-1917) P.19 L.20-22]

CVM CRITIQUE: The last sentence of this proposed finding appears to be a statement of opinion and not a statement of fact.

1284. Although *Campylobacter* colonizes both turkeys and chickens, the predominant *Campylobacter* that colonizes turkeys is *C. coli* not *C. jejuni*. In chickens, the predominant species is *C. jejuni*. This means that any risk assessment that takes into account the impact of human illness caused by *Campylobacter jejuni* from chickens is not relevant or applicable to turkeys. [Wages (B-1917) P.20 L.1-5]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. In background section of his WDT, Dr. Wages stated that he is "an expert in poultry medicine, clinical antimicrobial use in poultry, and preventative disease management in poultry." (P. 2 L. 14-15) He did not even allege expertise in risk assessment.

1285. Studies have shown that the overall prevalence of *Campylobacter* is different in chickens and turkeys. [Wages (B-1917) P.20 L.6-7]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit G-945. The Hollinger paper (G-945 P. 4, referred to by Dr. Gonder in proposed finding 1158) clearly reported that the prevalence of *Campylobacter* spp on turkey carcasses and on chicken carcasses was similar.

1286. Any risk assessment that takes into account the prevalence of *Campylobacter* in chickens is not relevant or applicable to turkeys. [Wages (B-1917) P.20 L.7-9]

CVM CRITIQUE: This statement appears to be a statement of opinion and not a statement of fact. In background section of his WDT, Dr. Wages stated that he is "an expert in poultry medicine, clinical antimicrobial use in poultry, and preventative disease management in poultry." (P. 2 L. 14-15) He did n ot even allege expertise in risk assessment.

1289. Baytril is the only consistently efficacious drug for treating *E. coli* or Pasteurella multocida infections in turkeys. [Wages (B-1917) P.21 L.6-7]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which documented the efficacy of neomycin for colibacillosis in turkeys

1290. Baytril is administered in a manner to maximize efficacy. [Wages (B-1917) P.21 L.8]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926 which clearly stated that, if enrofloxacin was used in a pulsed dosing manner rather than the continuous dosing of the current label, it would maximize clinical efficiency and result in less antimicrobial resistance.

1291. Baytril is administered in a manner to minimize resistance. [Wages (B-19179) P.21 L.9]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-926 which clearly stated that, if enrofloxacin was used in a pulsed dosing manner rather than the continuous dosing of the current label, it would maximize clinical efficiency and result in less antimicrobial resistance.

1292. There are no practical alternatives to Baytril on the market. [Wages (B-1917) P.21 L.11]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which documented the efficacy of neomycin for colibacillosis in turkeys.

1304. The most common USDA inspection technique for postmortem dispositions of turkeys is the New Turkey Inspection System (NTIS). It is the oldest of the high line speed methods for inspection and therefore the most common. This system utilizes a method of inspection where the viscera remains attached to the carcass until after passing the USDA inspection area. The average number of slaughter lines in a turkey plant is 2. There are 2 USDA inspectors per slaughter line. Maximum line speeds for NTIS systems ranges from 5 1 turkeys per minute for young turkeys weighing less than 16 pounds, 41 turkeys

per minute for young turkeys weighing over 16 pounds, to approximately 30 turkeys per minute for larger (40 pounds or more) breeder turkeys. This equates to 25 %, 20 %, and 15 turkeys per inspector per minute respectively. [Minnich (G-1467) P.7 L.11-20]

CVM CRITIQUE: CVM notes that the "%" sign in the last sentence of Bayer's proposed finding should be replaced with " ½".

1305. Epidemiologic data in the US made available through FoodNet, the most sensitive means employed by the public health community to document the extent of diarrheal disease in the US, do not support turkey meat as a significant source of human campylobacteriosis or salmonellosis. [Tompkin (A-204) P.15 L.11-15]

CVM CRITIQUE: This statement of opinion is without factual basis in the record. Dr. Tompkin includes this opinion in lines 11-15 of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT p. 15, line 17 - p. 16, line 3) was stricken from the record in the ALJ's March 3, 2003 order.

1306. Existing data from FoodNet fail to show a significant epidemiologic link between the consumption of turkey meat and campylobacteriosis and salmonellosis. [Tompkin (A-204) P.58 L.15-16]

CVM CRITIQUE: This statement of opinion is without factual basis in the record. Dr. Tompkin includes this opinion in his conclusions section of his WDT; however, the testimony offered in support of this opinion (Tompkin WDT p. 15, line 17 - p. 16, line 3) was stricken from the record in the ALJ's March 3, 2003 order.

1307. Few studies have been undertaken in turkeys, or other poultry, and the general assumption has been that the ecology and physiology of *Campylobacters* in all birds is the same. However, there is evidence for differences in the live birds in the pathological consequences of infection (Lam et al., 1992) (Glunder, 1989) (Wallace et al., 1998), on-set and rate of dissemination of colonization (Wallace, et al., 1998), chronicity of infection and shedding (Glunder, 1989) and diversity of infective strains (Wallace, et al., 1998) (Rogol & Sechter, 1987). [Newell (B-1908 P.4 L.1-7]

CVM CRITIQUE: The proposed finding is only partially supported. There is evidence for differences in pathological consequences of *Campylobacter* infection chicken and turkeys. However, much of the cited material does indicate that like chickens, turkeys are commonly colonized with *Campylobacter* early in age and they shed significant numbers of organisms. For example, G-686 (Wallace et al., 1998) reported that colonization with *Campylobacter* by turkey chicks began within 7 days of being placed in the brooder shed. There was subsequent 100% carriage rate of *Campylobacter* in all 5 brooder sheds tested by day 21 of the study (page 225). Biotyping of *Campylobacter* isolates showed that they were all *C. jejuni* (page 226).

1308. There is also some suggestion that turkeys may be preferentially colonized by *C. coli* rather than C.jejuni (Zhao et al., 2001) (Nielsen & Nielsen, 1999). Overall these

observations suggest that *Campylobacter* colonization in broilers and turkeys may have significant host-specific differences. [Newell (B-1908) P.4 L.7-12]

CVM CRITIQUE: This proposed finding is misleading, when taken out of context. Dr. Newell does state that on Page 4, lines 7-9, "There is also some suggestion that turkeys may be preferentially colonized by *C. coli* rather than *C. jejuni* (Zhao et al., 2001) (Nielsen & Nielsen, 1999)." However, this sentence closes with the following statement "though this is not confirmed by other studies (Wallace, et al., 1998) and may be reflection of regional differences and contact with animals, such as pigs, with *C. coli* infections (R. Meinsermann, personal communication)."

Additionally, Dr. Logue states in her testimony (G-1464) on Page 6, lines 7-10, that "Differences were observed with regards to prevalence of *Campylobacter* species recovered at each individual plant with 51.6% of isolates identified as *C. jejuni* and 40.5% identified as *C. coli* at plant A and 76.8% of isolates identified as *C. jejuni* and 14.6% identified as *C. coli* at plant B."

G-1712 is a study that described the distribution of serogroups of thermophilic *Campylobacters* isolated in Israel from human patients (2421 isolates), chicken (942), turkeys (158), cattle (398), wild birds (234) and other sources. Interestingly, *Campylobacter jejuni* accounted for 86.7% to 92.1% of the isolates from man, chickens, turkeys, cattle and most of the wild birds.

G-686 (Wallace et al., 1998) reported that colonization with *Campylobacter* by turkey chicks began within 7 days of being placed in the brooder shed. There was subsequent 100% carriage rate of *Campylobacter* in all 5 brooder sheds tested by day 21 of the study (page 225). Biotyping of *Campylobacter* isolates showed that they were all *C. jejuni* (page 226).

1309. Whilst there are many reports on *Campylobacter* colonization in chickens very little is known about this infection in turkeys. Few studies have been undertaken on the live birds. [Newell (B-1908) P.10 L.8-9]

CVM CRITIQUE: The proposed finding is misleading as it is taken out of context. The immediate sentence from Dr. Newell's testimony does discuss several studies and their outcomes with regards to *Campylobacter* colonization in turkeys "In some studies turkey poults appear to become infected earlier (at 1-7 days) than chicks (Wallace, et al., 1998). However, some flocks may remain negative for longer (Luechtefeld and Wang, 1981). Dissemination of infection throughout a turkey flock may take a longer time than in a broiler flock. Colonization in turkeys is also chronic and most birds are colonized at slaughter though shedding may be intermittent (Glunder, 1989) (Cox, et al., 2000)."

1324. The current label dose for enrofloxacin is 25 to 50 ppm for broiler chickens and turkeys. The safety and efficacy studies demonstrated that when medicating the drinking water with enrofloxacin, individual birds are dosed adequately, even at half the lowest

recommended dose. This study also indicates that a superior result could not have been obtained with the use of an individually dosed injectable product. [Terhune (B-1915) P.5 L.16 through P.6 L.5]

CVM CRITIQUE: See CVM's critique of Bayer's proposed finding of fact 891.

1325. Enrofloxacin is the most efficacious antibiotic available in the United States for treatment of *E. coli* infections in broiler chickens and *E. coli* and Pasteurella multocida infections in turkeys. The pharmacokinetics of the compound are such that high levels of enrofloxacin are reached in the respiratory tissues of treated birds, which is the desired site for effective treatment of both *E. coli* and P. multocida infections. This characteristic, coupled with the typical low Minimum Inhibitory Concentration (MIC) values of enrofloxacin against avian *E. coli* and P. multocida, (G-59, G-256) insures that levels reached at the site of infection are far higher than the MIC required for an effective outcome. This also minimizes the potential for resistance development in the target organism. [Glisson (B-1903) P.5 L.21 – P.6 L.7]

CVM CRITIQUE: The last sentence of this proposed finding is contradicted by Exhibit B-926 which states that the present dosing of enrofloxacin does not minimize bacterial resistance. CVM agrees with the rest of this proposed finding.

1326. We have no viable alternatives to enrofloxacin in the United States poultry industry for treating *E. coli* infections in broiler chickens and turkeys. [Glisson (B-1903) P.12 L.3-4]

CVM CRITIQUE: This proposed finding is contradicted by Exhibit B-1832, which indicates that neomycin sulfate can be used to treat *E. coli* infections in turkeys.

1327. The CVM/Vose analysis explicitly considers only risks posed with respect to fluoroquinolone-resistant *Campylobacter* in chicken, and does not provide explicit consideration with respect to turkey. [Haas (B-1904) P.26 L.12-14]

CVM CRITIQUE: This proposed finding is not supported by the weight of the evidence.

1328. There is limited data with regard to the prevalence of food borne pathogens (Salmonella and *Campylobacter*) among turkey carcasses at slaughter. [Logue (G-1464) P.2 L.26-27]

CVM CRITIQUE: Dr. Logue states that there are limited data with respect to turkeys as a reason she she conducted her studies. However, her results add to the growing body of literature with respect to the prevalence of food borne pathogens among turkey carcasses.

1331. The isolation and detection of *Campylobacter* spp. from the carcass swabs and the chill water was carried out using modified methods that were lab-specific. [Logue (G-1464 P.4 L.18-20]

CVM CRITIQUE: This proposed finding of fact is misleading because it has been taken out of context. Dr. Logue's actually testimony states "The isolation and detection of *Campylobacter* spp. from the carcass swabs and the chill water was carried out using standard techniques (BAM 1998) and methods that were modified for use in our research labs (Logue et al. 2002 a,b)" (emphasis added).

1333. Results from the study show differences in the overall incidence of the pathogen detected between the two processing plants. [Logue (G-1464) P.5 L.27-29]

CVM CRITIQUE: This proposed finding is contrary to Dr. Logue's WDT. The portion of Dr. Logue's testimony cited as support for this finding by Bayer is referring to differences observed in the prevalence of *Campylobacter* spp. for the pre-chill carcass samples versus the post-chill carcass samples for each plant, not in the overall incidence at the two plants.

1338. The incidence of turkey carcass samples that tested positive for *Campylobacter* species was higher at plant A than plant B. Again, such noted differences may be related to the processing conditions used. Plant A used a batch chill process and did not add any additional chorine to their chill tanks, aside from city water which was used to make ice chips. In contrast, plant B hyperchlorinated their water supply to a level of 20 ppm and used a continuous chill process. [Logue (-1464) P.7 L.9-17]

CVM CRITIQUE: CVM disagrees that this proposed finding is supported by the cited record reference. Dr. Logue's testimony (G-1464) actually states in Table 1 on page 15 that indeed turkey carcass samples tested positive for *Campylobacter* overall (Plant A 39% vs. Plant B 31%), however, this is not the case when one looks at the pre-chill samples where more turkey carcass samples were positive from Plant B (42%) than Plant A (41%). Also, Dr. Logue indicates as well that "in both cases, the chlorine concentrations of the water in the chill immersion tanks was not established at the time of the study." [Logue (B-1464) P.7 L.6-7]

1343. According to Dr. Angulo, the largest population attributable fractions were for eating chicken in a restaurant and eating non-poultry meat in a restaurant. The population attributable fraction for eating chicken in a restaurant was 24 percent (95 percent confidence interval, 17 to 30 percent), and for eating non-poultry meat in a restaurant was 21 percent (95 percent confidence interval, 13 to 30 percent). The population attributable fraction suggests that, among non-travelers, 24 percent of sporadic cases of campylobacteriosis in the United States are due to eating chicken in a restaurant, 21 percent are due to eating non-poultry meat in a restaurant, and 4 percent are due to eating turkey in 3 restaurant in the seven days prior to illness onset. [Angulo (G-1452) P.10 L.36-44]

CVM CRITIQUE: CVM assumes that Bayer intended "3 restaurant" to be "a restaurant."

1350. Recently, our research team examined 35 caecal samples of 16 week-old turkeys. The average concentration of *Campylobacters* (per gram of caecal content) was estimated at $1.6x10^6$ CFUs {Nico Bolder, personal communication}. Our findings are in line with results of other studies, which found $1.2x10^4$ to $15x10^7$ (median: $2.7x10^5$) CFUs of C. fetus subspecies jejuni (*Campylobacter jejuni*) per gram of caecal content {Luechtefeld et al., 1981). [Jacobs-Reitsma (G-1459) P.3 L.4-9]

CVM CRITIQUE: CVM notes a typo in Bayer's proposed findng of fact. The correct number is $2.7x10^6$ not $2.7x10^5$.

1354. Antimicrobial resistance phenotypes of *Campylobacter* differ according to species of the organism and source of isolation. [Meng (G-1466) P.3 L.29-31]

CVM CRITIQUE: This proposed finding of fact is misleading because it is taken out of context. Dr. Meng makes this statement only as it pertains to his recent study from his laboratory which looked at *Campylobacter* contamination of retail raw meats (Meng WDT P.3 L.24, P.4 L.8).

1360. As early as 1981 the development of resistance to antimicrobials of therapeutic importance, including erthyromycin and nalidixic acid in both human and animal strains, was being reported (Goldstein et al., 1982) (Vanhoof et al., 1982). [Newell (B-1908) P.11 L.4-7]

CVM CRITIQUE: This proposed finding is attributed to two studies, neither of record.

1363. In late 1993 or early 1994 CVM became aware of foreign studies asserting that fluoroquinolone use in chickens or in turkeys can act as a selection pressure and result in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*. FDA was concerned that the slaughter, inspection and packaging process for poultry in the United States was such that if the chickens or turkeys are contaminated with the resistant pathogens at the time of slaughter, food products could transmit the resistant organisms to humans. If the resistant *Campylobacter* cause an illness in a consumer who needs treatment, medical therapy may be compromised. [Tollefson (G-1478) P.13 L.22-33]

CVM CRITIQUE: This proposed findng is a slight alteration of Dr. Tollefson's testimony. The wording in Dr. Tollefson's WDT is "demonstrating" not "asserting". (G-1478, P.13 L.23).

1391. A review of the scientific literature after the approval of enrofloxacin in 1996 does not reveal new evidence (i.e., evidence that was not already known prior to approval) to demonstrate that fluoroquinolone use in poultry acts as a selection pressure resulting in the emergence of fluoroquinolone-resistant *Campylobacter* in poultry. Indeed, information published since the time of approval merely confirms those conclusions known at the time prior to approval. [van den Bogaard (B-1916) P.7 L.12-16]

CVM CRITIQUE: This proposed finding of fact is contradicted by the tremendous volume of evidence on the docket that was published after the approval date. Moreover, NARMS did not exist prior to the approval of Baytril, so the data from NARMS, from the *Campylobacter* case-control study and the *Campylobacter* risk assessment are certainly new evidence. [Tollefson WDT (G-1478) P.4 L.41-47]

1392. The findings of Jacobs-Reitsma et al. (1994b) have been confirmed recently by others (McDermott et al, 2002 (B-868); Luo et al., 2001 (A-190); Stapleton et al., 2001; Ridley et al., 2002, but these studies have not revealed new premises to alter the conclusion that fluoroquinolone use in poultry does act as a selection pressure resulting in the emergence of fluoroquinolone-resistant *Campylobacter jejuni* in poultry. [van den Bogaard (B-1916) P.7 L. 17-21]

CVM CRITIQUE: This proposed finding of fact is contradicted by the evidence because the studies cited do add a new dimension to the Jacobs-Reitsma study of 1994 in the degree to which fluoroquinolone use in poultry acts as a selection pressure. For example, the McDermott study (B-868) found that 100% of poultry treated with fluoroquinolone resulted in fluoroquinolone-resistant *Campylobacter* whereas 0% of the poultry not treated with fluoroquinolone developed fluoroquinolone-resistant *Campylobacter*.

1394. In late 1993 or early 1994, before fluoroquinolones were approved for use in chickens and turkeys, CVM management understood and accepted that if fluoroquinolones were used in chickens and turkeys, the likelihood existed for fluoroquinolone-resistant *Campylobacter* strains to be transferred from chickens and turkeys to humans and contribute to the development of fluoroquinolone-resistant *Campylobacter* infections in humans. [Joint Stipulation 3]

CVM CRITIQUE: The proposed finding of fact is not supported by the citation to Joint Stipulation 3, and CVM strongly disagrees that Joint Stipulation 3 supports this proposed finding of fact. Bayer substituted a key word contained in the joint stipulation when proposing this finding. Joint Stipulation No. 3 states, "In late 1993 . . . CVM management understood . . . the potential existed for fluoroquinolone-resistant *Campylobacter* strains to be transferred . . . ."(emphasis added). Bayer conveniently (for them) substitutes the word "likelihood" in its proposed finding for the word "potential" in the joint stipulation. Therefore, Bayer's proposed finding is without any citation to an appropriate record reference, and at best mischaracterizes the proposed finding.

1400. In Finland, a study on human *Campylobacter* collected in 1990 reported that 9% of the isolates were resistant to ciprofloxacin (Rautelin et al., 1991(B-625). Fluoroquinolones were not used in veterinary medicine in Finland at that time, and the authors concluded based on travel history that this quinolone resistance probably reflected the overall quinolone susceptibility of strains from other countries. [van den Bogaard (B-1916) P.9 L. 5-9]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support. Fluoroquinolones were not used in animals in Finland at that time, but the authors and Dr. van den Bogaard agree that these infections were probably from other countries. The travel histories that were listed in B-625 (page 2, last paragraph) are "Spain (12 patients), Turkey (9 patients), Portugal (5 patients), Soviet Union (5 patients), and France (5 patients)." Enrofloxacin was registered in Spain in October 1990 (Joint Stip. 63), in Turkey in March 1989 (Joint Stip. 73), and in the Russian Federation in October 1989 (Joint Stip. 74). Given the rapid development of resistance to fluoroquinolones by *Campylobacter* (G-1680), this travel-related resistance could easily be due to animal use of enrofloxacin.

1401. A 1993 study by Rautelin et al., reported that 17% of human isolates sampled in 1993 were resistant to ciprofloxacin, again in the absence of any fluoroquinolone use in Finnish poultry (Rautelin et al., 1993(B-881)). Subsequent analyses reported resistance rates among human isolates at 20% in 1995, 32% in 1996, and 35-37% in 1997 (see review Nachamkin et al., 2000) (B-44). [van den Bogaard (B-1916) P.9 L. 9-13]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the exhibits cited in support. Dr. van den Bogaard is ignoring travel and use of enrofloxacin in other countries. In B-44 (page 7, top of second column), Dr. Nachamkin wrote, " With the introduction of enrofloxacin (a derivative of ciprofloxacin) in veterinary medicine and, less important, fluoroquinolones in human medicine in mainland Europe, a rapid emergence of quinolone resistance in *Campylobacter* isolates from patients were registered."

1402. Observations as to the emergence and prevalence of fluoroquinolone resistance in *Campylobacter* isolates from humans were made prior to approval of enrofloxacin in the U.S. in several countries such as Austria (Feierl et al., 1993; 1994 (B-313), Italy (Crotti and Fonzo, 1991(B-264); Crotti et al., 1993), Japan (Itoh et al., 1995), United Kingdom (Bowler and Day, 1992 (B-223); McIntyre and Lyons,1993 (B-512)), Sweden (Sjögren et al., 1993 (B-932); Kaijser, 1994) or Canada (Harnett et al., 1995 (G-267)). [van den Bogaard (B-1916) P.9 L. 13-18]

CVM CRITIQUE: This proposed finding is contrary to the cited testimony and is misleading because it mischaracterizes the exhibits cited in support. Dr. van den Bogaard's testimony (B-1916, P. 9 L. 15) stated that the cited studies were made "in the early days", not that they were made "prior to approval of enrofloxacin in the U.S." Enrofloxacin had been registered in Austria in 1988 (Joint Stip. 51), in Italy in 1990 (Joint Stip. 59), in Japan in 1991 (Joint Stip. 70), in the United Kingdom in 1993 (Joint Stip. 65), in Sweden in 1989 (Joint Stip. 64), and in Canada in 1988 (Joint Stip. 76). In every case but the United Kingdom, this registration predates the papers that Dr. van den Bogaard cites.

1418. In 1992 it was reported that the clinical presentation for Guillain-Barre syndrome usually consists of a rapidly evolving generalized paralysis, frequently involving respiratory

musculature, rendering patients respirator-dependent in 20-35% of the cases. [Endtz (G-1457) P.3 L.11-14]

CVM CRITIQUE: This proposed finding omits the linkage to *Campylobacter jejuni*. Dr. Endtz actually states in his testimony "Others have reported that *C. jejuni* diarrhea is followed by the Guillain-Barre in 1/1000 cases. The clinical presentation usually consists of a rapidly evolving generalized paralysis, frequently involving respiratory musculature, rendering patients respirator-dependent in 20-35% of the cases."

1422. Prior to 1996, it wsa reported that the persons at greatest risk for invasive bloodstream infection with *Campylobacter* are the elderly and the immunocompromised. In 1984 Tauxe reported that the laboratory-based surveillance for *Campylobacter* from 1982-1986, 102/29468 or 0.03% of the infections for which this information was reported, were diagnosed by blood culture (Tauxe 1988). The proportion of infection that were in bloodstream varied with age. It was lowest, 0.2%, among persons aged 0-39, somewhat higher, 0.3%, among persons 40-69 years of age, and highest, 1.2%, among persons 70 years old or older [Tauxe (G-1475) P.15 L. 4-11]

CVM CRITIQUE: This proposed finding misrepresents the cited testimony. Dr. Tauxe's WDT does not state "[p]rior to 1996, it was reported that" no state "[i]n 1984."

1428. In 1993, Skirrow et al. reported that the incidence of bacteremia is <1%, mainly in immunocompromised and elderly hosts, with an incidence in the latter reported as 0.59%. According to a 1995 report by Schonheyder et al., an incidence of 8 bacteremia cases per 1000 intestinal infections was found in Denmark. As of 1995, it was known that since most strains of *C. jejuni* and *C. coli* are susceptible to the bactericidal (killing) activity of serum, bacteremia is usually self-limited and often remains untreated; bacteremia is a prerequisite for spread of the pathogen to extraintestinal tissues; and thus, such focal infections are even rarer and are mostly presented in the literature as single case descriptions (Skirrow and Blaser, 1995). [Kist (B-1906) P.5 L.3-11]

CVM CRITIQUE: Bayer's proposed findng is contrary to the WDT of Pasternack ("unlike *Campylobacter* enteritis in normal hosts, where *C. jejuni* bacteremia is rare, there appears to be a heightened susceptibility to invasive infection and bacteria in HIV-infected individuals. In this population, bacteremia rates approach 10% and can lead to life- threatening illness and significant mortality rates." Pasternack WDT P.6 L.12-16). Further, in many case bacteremia is treated since most experts and treatment guidelines recommend treating patients who are immunocompromised (Ohl WDT P.11, L.11-20; P.13 L.1-18) and bacteremia occurs more often in this subset of patients.

1437. In 1987 it was reported that raw poultry meats are commonly contaminated with *Campylobacter*, with prevalence rates reported up to as high as 100%. [White (G-1484) P.2 L. 46 - P.3 L. 2]

CVM CRITIQUE: CVM notes that Dr. White's testimony does not state "in 1987". Additionally, of the five references cited in Dr. White's testimony only one of these five references is from 1987. Of the other four, two are from 1994 and two are from 2002.

The 1987 reference is not in the evidentiary record and therefore Bayer cannot rely on it to support the addition of the word "In 1987". CVM endorses a finding based on the actual words of Dr. White's testimony.

1443. [Since Approval Things Have Only Gotten Better]

CVM CRITIQUE: This appears to be an internal editorial note from Bayer's drafting process and not a proposed finding of fact. It is not specific, nor supported by any reference to the record.

1445. When more attention is paid to food-handling practices in restaurants and other venues outside the home, the number of fluoroquinolone-resistant *Campylobacter* infections are reduced substantially. [Kassenborg (G-1460) P.10 L.14-16]

CVM CRITIQUE: This proposed finding is misleading because it mischaracterizes the testimony in Kassenborg's WDT, P. 10 lines 14 – 16. Dr. Kassenborg's WDT states "our findings suggests that if more attention is paid to food-handling practices in restaurants and other venues outside the home, the number of fluoroquinolone-resistant *Campylobacter* infections could be reduced substantially." (emphasis added). The proposed finding is drafted as if the event has occurred, substituting the word "when" for "if" and "are" for "could be." Bayer has not provided a record reference to any showing that fluoroquinolone-resistant *Campylobacter* has decreased due to food handling practices in restaurants.

1447. To the extent that CVM recognized the risk of development of fluoroquinolone-resistant *Campylobacter* in poultry, and the risk of transfer to humans prior to the 1996 approval of enrofloxacin, the risk is clearly less now than at the time of approval. [Tompkin (A-204) P.10 L.1-3]

CVM CRITIQUE: This statement is not supported by the record. Other WDT have been submitted concerning the rise in the level of fluoroquinolone resistant *Campylobacter* infections in humans (see WDTs Kassenborg, Smith, Angulo) since Baytril was approved.

1471. *C. coli* is more often recovered from retail turkey samples than *C. jejuni*. [Meng (G-1466) P.3 L.17-18]

CVM CRITIQUE: CVM notes that Dr. Meng was referring to one study in which *C. coli* was more often recovered from retail turkey samples than was *C. jejuni*. (G-727). In fact, Dr. Meng qualifies his statement with the word "Interestingly." If Bayer's proposed findings were indeed universally true, Dr. Meng would not have included the qualifier "Interestingly" in his testimony (G-1466 P.3 L.17). (also see G-686 and B-675, P.7).

1478. CVM does not have any facts or data demonstrating any increase in the rate or extent of complications (including but not limited to Guilian- Barre syndrome) from infections caused by fluoroquinolone- resistant *Campylobacter* as compared to infections caused by

fluoroquinolone- susceptible (non- resitant) *Campylobacter*. [CVM Response to Bayer's Interrogatory 60]

CVM CRITIQUE: This proposed finding is contradicted by Dr. Molbak's WDT, P.16 L. 29-P.22 L. 6.

1480. CVM does not have any facts or data to demonstrate that there was little to no fluoroquinolone-resistance in humans *Campylobacter* isolates prior to the approval of fluoroquinolones for use in poultry. [Burkhart (B-1900) P.8 L.4-28]

CVM CRITIQUE: This proposed finding is contradicted by Tollefson (G-1478) P.15 L.16-32 and the K. Smith study (G-589) P.3.

1482. Chlorine/Hypochlorite/Chloramines are compounds which are unproven, yet suspect as agents able to select for gyr-A spontaneous mutants. [Silley (B-1913) P.9 L.1-3]

CVM CRITIQUE: This proposed finding is not of fact, but of a suspicion.

1484. The frequency of occurrence of resistant *Campylobacter* sps may be overestimated and this erroneous data may lead FDA to conclude that certain veterinary antibiotics have a greater impact on human health than they actually do. [Silley (B-1913) Attachment 1 P.40 ¶ 2]

CVM CRITIQUE: This proposed finding is contradicted in the record. The study by Ge et al (G-763) comparing the method used by NARMS with the NCCLS reference method showed that the NARMS method (Etest) may actually underestimate the degree of fluoroquinolone resistance in Campylobacte

1485. The vast majority of authors have not even considered the principles laid down in the NCCLS Guideline M37-A2 with regard to how one evaluates for *Campylobacter* the utility of an appropriate method for determining its utility to a test antimicrobial compound. [Silley (B-1913) Attachment 1 P.45 ¶ 4]

CVM CRITIQUE: This proposed finding of fact is an unsupported opinion. No survey data as to "authors" understanding of NCCLS principles and documents is cited. In addition, those who do understand the principles of the M37-A2 would note that there is no guidance which can be described as "how one evaluates for *Campylobacter* the utility of an appropriate method for determining its utility to a test antimicrobial compound" as that document contains no such unintelligible language.

1486. There are no recommended antibiotic breakpoint concentrations (or an agreed susceptibility testing method) for *Campylobacter* spp." [Silley (B-1913); citing Piddock et. al., 2000, Attachment 1 P.46 ¶ 2]

CVM CRITIQUE: As has been pointed out in numerous variations on this proposed finding, this proposed finding is contradicted in the record in B-886 and G-776, among other places.

1488. For fluoroquinolones, the best clinical outcomes are associated with peak/MIC ratios >/= 10. [Silley (B-1913) Attachment 1 P.50 2]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1489. If a high enough peak to MIC ratio can be achieved then not only will the parent organism be killed but also the "resistant" mutant. [Silley (B-1913) Attachment 1 P.51 ¶ 1]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1490. Peak to MIC ratios can easily exceed 10 in the gastrointestinal tract of patients with *Campylobacters* that have an MIC of 32 when patients are treated with 500mg ciprofloxacin BID. [Silley (B-1913) Attachment 1 P.51 ¶ 1, 2]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1492. Given the high levels of ciprofloxacin reported in the gastro-intestinal tract it is not surprising that clinical cure can be demonstrated for organisms with an MIC of 32 ug/ml. [Silley (B-1913) Attachment 1 P.52 ¶ 1]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1493. A proportion of the isolates tested in the NARMS program have been shown to be impure cultures, this will lead to a degree of misinterpretation of the data. [Silley (B-1913) Attachment 1 P.55 ¶ 4]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1494. It is highly inappropriate to consider that *Campylobacter* spp. With an MIC of 4 ug/ml will be clinically resistant to ciprofloxacin. [Silley (B-1913) Attachment 1 P.55 ¶ 6]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1495. Available data supports a breakpoint of 64 ug/ml. Such a breakpoint would need to be substantiated in accordance with NCCLS guidelines. [Silley (B-1913) Attachment 1 P.56 ¶ 2]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1496. The NCCLS breakpoint for two different bacteria to the same antimicrobial may be very different. [Walker (G-1481) P.5 10]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1497. Testing methods not endorsed by NCCLS and interpretive criteria that are not set by NCCLS may be of questionable value. [Walker (G-1481) P.9 ¶ 13]

CVM CRITIQUE: The proposed findings for #s 1488- 1497 are identical to proposed findings 734- 743 so CVM's critiques are also identical.

1506. The articles listed in Appendix A were all published prior to the approval of enrofloxacin in October 1996.

CVM CRITIQUE: The proposed finding is not supported by and in several cases is contradicted by Appendix A to Bayer's proposed findings of fact, and CVM strongly disagrees with Bayer's proposed finding. Appendix A includes several exhibits that post-date the approval of Baytril, including G-589, Kirk Smith's powerful research published in the New England Journal of Medicine on May 20, 1999. In addition, the very first document listed on Appendix A, A-73 was submitted on February 10, 2000, and Attachment 2 to that document had to have been first prepared subsequent to CVM's risk assessment (after the approval date of Baytril).
Other "mistakes" include:

- A-169: There is no indication when in 1996 this article was published, the article and the book in which it appears only provide the year of publication, not the month or day.
- G-387: Bayer claims this abstract was published in May 1984 when, in reality the abstract indicates that the article was published in the Journal of Applied Microbiology in 1998.
- B-337: Bayer claims this article was published in 1988 when, in reality, the article was published in 1998.
- B-1724 and B-1725: Bayer claims these Exhibits were published in 1989; they are USDA, Bureau of Labor Statistic website searches for occupational injuries and illness from 1989- current and the data were abstracted on Nov. 26, 2002.

1507. The following witnesses are experts in their respective fields as described in their Written Direct Testimony and are qualified as experts to testify as to the matters set forth in their Written Direct Testimony submitted on December 13, 2002:

* Gregory Burkhart

* Tony Cox

* Roger Feldman

* John Glisson

* Charles Haas

* Paul Iannini

* Manfred Kist

* Tom Martin

* Diane Newell

* Mark Pasternack

* James Patterson

* Michael Robach

* Scott Russell

* Peter Silley

* John Smith

* Terry TerHune

* Anthony van den Bogaard

* Dennis Wages

* Steven Woodruff

* Robert Harris

* Richard Carnevale

* Bardley DeGroot

* Eric Gonder

* Charles Hofacre

* Ronald Prucha

* Bruce Tompkin

CVM CRITIQUE: CVM notes that Mr. Martin, Mr. Woodruff and Mr. Harris' WDTs have been stricken from the evidentiary record of this proceeding in their entirety, and a finding that each of them is an expert in his respective field is unnecessary.

Respectfully submitted by:

Nadine Steinberg

Robert M. Spiller, Jr.

Claudia J. Zuckerman

Candace Ambrose
Counsel for the Center for
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5600 Fishers Lane (GCF-1)
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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 Critique of Bayer's and AHI's Joint Proposed Findings of Fact was hand delivered this 14th day of April, 2003 to:

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

I also certify that a copy of CVM's Critique of Bayer's and AHI's Joint Proposed Findings of Fact has been hand delivered and e-mailed, this 14th day of April, 2003 to:

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

I also certify that a copy of CVM's Critique of Bayer's and AHI's Joint Proposed Findings of Fact was e-mailed and mailed by First Class U.S. mail, this 14th day of April, 2003, to:

Robert B. Nicholas
McDermott, Will & Emery
600 13th Street, NW
Washington, DC 20005

Kent D. McClure
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1325 G Street, NW, Suite 700
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