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

In the Matter of: **Enrofloxacin for Poultry: Withdrawal of Approval of New Animal Drug Application NADA 140-828**	**FDA DOCKET: 00N-1571** **Date: April 14, 2003**

RESPONDENT BAYER CORPORATION'S AND PARTICIPANT ANIMAL HEALTH INSTITUTE'S JOINT RESPONSE TO THE CENTER FOR VETERINARY MEDICINE'S PROPOSED FINDINGS OF FACT

Pursuant to the April 10, 2002 Order and Schedule of Due Dates in this proceeding,. Respondent Bayer Corporation and Participant Animal Health Institute hereby jointly submit the following critique of the Proposed Findings of Fact (PFOF) submitted on Mach 17, 2003 by the Center for Veterinary Medicine.

Frank Aarestrup (G-1451)

1. Dr. Aarestrup is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI agree to this PFOF except as relates to the application of Dr. Aarestrup's testimony to the United States. Bayer/AHI agree that Dr. Aarestrup is an expert in microbiological and veterinary issues in Denmark, but do not agree that his expertise extends to treatment of microbiologically-based disease in the United States poultry industry. A-202 P.27 L.19-20; P.28 L.6-11, 12-15, 16-18.

2. The first antimicrobial agents were introduced in the 1930s and a number of new compounds were discovered in the following decades. However, shortly after their introduction, bacteria began to show resistance. Since then, resistance mechanisms have been identified in bacteria for all known antimicrobial agents. This includes both natural and synthetic compounds. In addition, bacteria frequently acquire several mechanisms for resisting drugs, making them highly resistant to antimicrobial therapy. Aarestrup WDT: p. 1, lines 45-49 and p. 2, lines 1-2

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Frank Aarestrup (G-1451)

1. Dr. Aarestrup is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI agree to this PFOF except as relates to the application of Dr. Aarestrup's testimony to the United States. Bayer/AHI agree that Dr. Aarestrup is an expert in microbiological and veterinary issues in Denmark, but do not agree that his expertise extends to treatment of microbiologically-based disease in the United States poultry industry. A-202 P.27 L.19-20; P.28 L.6-11, 12-15, 16-18.

2. The first antimicrobial agents were introduced in the 1930s and a number of new compounds were discovered in the following decades. However, shortly after their introduction, bacteria began to show resistance. Since then, resistance mechanisms have been identified in bacteria for all known antimicrobial agents. This includes both natural and synthetic compounds. In addition, bacteria frequently acquire several mechanisms for resisting drugs, making them highly resistant to antimicrobial therapy. Aarestrup WDT: p. 1, lines 45-49 and p. 2, lines 1-2

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Bayer/AHI Response: Bayer/AHI object to this PFOF on the grounds that it is a set of compound facts, some of which Bayer/AHI agree with and some of which Bayer/AHI disagree with. Bayer/AHI agree with the first two sentences. Bayer/AHI disagree with the 3rd and 4th sentence as being too broad and contradicted by the continued efficacy of all antibiotics against at least some bacteria. Additionally, the last sentence is incorrect as it applies to *Campylobacter* since *Campylobacter* do not "acquire mechanisms for resisting" fluoroquinolones, as *Campylobacter* resistance to fluoroquinolones occurs as a spontaneous point mutation. Joint Stipulation 1, and G-219 at P.68-69.

3. Antimicrobial agents have saved millions of lives and are the most important weapon against infectious diseases. The greatest threat against the use of antimicrobial agents is the development of resistance in pathogenic bacteria. In general the occurrence of resistance follows the consumption of antimicrobial agents closely. Aarestrup WDT: p. 2, lines 4-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being compound and as being inaccurate. Bayer/AHI do not dispute that antimicrobial agents have saved millions of lives. The claim that antimicrobial agents (as opposed to prevention via improved sanitation, hygiene, cooking, processing, etc.) "are the most important weapon against infectious diseases" is unsubstantiated and inaccurate, in part because antimicrobial agents do not work against viral infectious diseases. Bayer/AHI do not dispute that the development of resistance in pathogenic bacteria is a concern, but does not know whether it is "the greatest threat against the use of antimicrobial agents". The last sentence stating that "the occurrence of resistance follows the consumption of antimicrobial agents closely" ignores naturally occurring resistance prior to antibiotic use such as demonstrated in B-1851 and is also refuted by Joint Stipulation 1; CVM Response to Bayer Interrogatory 4 and 81; B-1851; A-201 P.14 L.9-11; G-1453 P.2 L.14-16; B-1908 P.15 L.12-13; B-1908 P.16 L.24 – P.17 L.6; B-609.

4. *Campylobacter* followed by *Salmonella* are the most common causes of bacterial gastro-intestinal infections in man worldwide. Aarestrup WDT: p. 2, lines 9-10

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to the current status in the United States, which is the relevant time and location for the issues in this hearing. As relates to the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates (27% between 1996 and 2001). This is the most recent information available on this subject.

5. Emergence of resistance in *Salmonella* and *Campylobacter* would have consequences for the possibilities to treat infections in man. Aarestrup WDT: p. 2, lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF as unsubstantiated speculation. Bayer/AHI specifically dispute this PFOF as it relates to the issues for this hearing (fluoroquinolone resistance and *Campylobacter*). For *Campylobacter* the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint

Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

6. Fluoroquinolones are the drug of choice for treatment of gastro-intestinal infections in humans in most countries. Thus, resistance to this group of antimicrobial agents would have the most severe consequences. Aarestrup WDT: p. 2, lines 12-14; p. 4, lines 5-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The majority of gastrointestinal infections in humans are viral, not bacterial and, therefore, antibiotics, including fluoroquinolones would not be effective for treatment. G-1485 P.4 L.36-37; B-1909 P.3 L.4-6. Moreover, for campylobacteriosis, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). This statement as applied to *Campylobacter* is further disputed because campylobacteriosis is in most instances a self-limiting disease, rarely with complications (G-1485 P.5 L.37-39; B-1909 P.3 L.4-5, L.16-17) and because in situations where antibiotic therapy is indicated, macrolides such as erythromycin or azithromycin are the preferred treatment for campylobacteriosis. B-1905 P.4. L.9-12.

7. Evolving resistant bacterial population does not respect traditional boundaries between countries. People travel and food of animal origin is traded worldwide. Thus, the development of resistance in any country is an impending problem for all countries. Aarestrup WDT: p. 2, lines 14-17

Bayer/AHI Response: Bayer/AHI dispute this PFOF as unsubstantiated, illogical and incorrect. The PFOF as written is not specific to any particular bacterial population, country, or food of animal origin. This PFOF is not relevant to the issue of whether domestic use of enrofloxacin has an adverse impact on human health in the U.S. It also assumes that "People travel and food of animal origin is traded worldwide" (with which we agree) implies "development of resistance in any country is an impending problem for all countries" (which we believe is untrue and is refuted by data on international resistance rates overtime). This embedded assumption has not been established as true; hence, we object to the PFOF as implicitly assuming that an unsubstantiated assumption is true.

8. Antibiotics are used for the treatment of infectious diseases caused by bacteria. To be effective, an antibiotic should show activity against the infecting bacteria and have the ability to reach the infected organ or tissue in sufficiently high concentrations to stop the infection. Aarestrup WDT: p. 3, lines 3-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

9. Fluoroquinolones have activity against a wide range of different organisms and have very good distribution in the body. There is a good chance that this antibiotic will have a

beneficial effect on almost all infections in all different organs/tissues. It is therefore a very easy antibiotic to use even in the absence of a proper diagnosis or accurate identification of the infectious agent. Aarestrup WDT: p. 3, lines 9-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that it combines multiple proposed facts, some of which Bayer/AHI agree with and some of which Bayer/AHI do not. Bayer/AHI agree with the first sentence. Bayer/AHI dispute the second sentence. For example, fluoroquinolones are not effective against anerobes and some gram positive bacteria.

10. The first fluoroquinolones were introduced in human medicine in Europe in 1984 and in 1985 in USA. Since that time there has been an increasing use of these antimicrobial agents especially in hospitals. Aarestrup WDT: p. 4, lines 6-14; G-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

11. The introduction of fluoroquinolones in veterinary medicine was followed by an emergence and increase in resistance among bacteria in food animals, including zoonotic bacteria such as *Campylobacter* and *Salmonella.* Aarestrup WDT: p. 4, lines 6-14; G-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

12. In several countries the introduction of fluoroquinolones for veterinary use was followed by an emergence among resistance in bacteria in food animals, including *Campylobacter.* Aarestrup, WDT: p. 4, lines 11-14 and 25; G-191

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Additionally, it is not clear which countries are being cited here. Bayer/AHI agree that CVM was aware before 1995 of reports of resistance in human *Campylobacter* isolates following the introduction of enrofloxacin in the Netherlands, but does not agree that there was a causal connection shown. B-1916 P.8 L.1-28.

13. The introduction of fluoroquinolones for veterinary use has been the driving force behind the emergence of fluoroquinolone-resistant *Campylobacter* giving infections in man. It can be observed that resistance emerged first in the countries that first approved fluoroquinolones for veterinary use. Aarestrup, WDT: p. 4, lines 31-32; G-191

Bayer/AHI Response: Bayer/AHI dispute this PFOF. It is refuted by publications such as Svedhem, 1981 (cited in B-1901) that showed resistance in animals and humans long before approval of fluoroquinolones for veterinary use Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. There is also evidence that in the U.S. there were high rates of resistant *Campylobacter* before approval of enrofloxacin (i.e., 21% in 1995; G-1517). This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. The PFOF is not a fact.

14. Dr. Aarestrup's Figure 1, depicts trends in fluoroquinolone resistance among *Campylobacter* isolated from humans in 10 countries as reported in several studies. The figure shows that resistance for these countries emerged after approval of fluoroquinolones for veterinary use in that country. Aarestrup WDT: p. 5, Figure 1; G-191

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. There is also evidence that in the U.S. there were high rates of resistant *Campylobacter* before approval of enrofloxacin (i.e., 21% in 1995; G-1517). This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

15. The fluoroquinolones have also become widely used agents in veterinary medicine. In the Netherlands water medication with the fluoroquinolone enrofloxacin in poultry production was followed by an emergence of fluoroquinolone-resistant *Campylobacter* species among both poultry and humans. Aarestrup WDT: p. 4, lines 17-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF, especially as relates to the United States. Bayer/AHI also object to this PFOF as combining two separate proposed facts. As relates to the first sentence, fluoroquinolones have <u>not</u> "become widely used agents in poultry veterinary medicine" in the United States. That portion of the PFOF is refuted by B-1914 P.25 L.20 – P.26 L.4; B-1903 P.11 L.20 – P.21 L.2; B-1915 P.6 L.11-14; B-1917 P.21 L.8-11; A-201 P.20 L.9; A-

54; A-192 and Joint Stipulations 15, 16, 17 and 46. As relates to the second sentence, evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

16. In Spain, an increase in the occurrence of fluoroquinolone-resistant *Campylobacter* infecting humans has been observed after the introduction of fluoroquinolones into veterinary medicine. More than half of the *Campylobacter* isolates from human infections were reported to be resistant two years after fluoroquinolones were licensed for animals compared to none before licensing. Aarestrup WDT: p. 4, lines 20-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by evidence in the record showing that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Also, Bayer/AHI dispute the applicability of this PFOF to the issues in this hearing. The conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, Bayer's Submission of Facts, Information and Analyses in Response to the Notice of Opportunity for Hearing (B-1(A)) P.10).

17. There is compelling evidence that the introduction of fluoroquinolones in veterinary medicine has lead to the emergence and increase in resistance among all different bacterial groups colonizing animals. This includes the zoonotic bacteria *Campylobacter* and *Salmonella.* Aarestrup WDT: p. 6, lines 3-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

18. A decreased usage of antimicrobial agents in food animals will lead to a decrease in resistance in the bacteria they carry to slaughter. Aarestrup WDT: p. 8, lines 4-5

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.86 (citing B-1020), P.27 (citing B-119 and B-29), P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. This PFOF is speculation, not fact.

19. Fluoroquinolones inhibit the activity of a bacterial enzyme called DNA gyrase. Aarestrup WDT: p. 8, line 8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

20. In *Campylobacter* (unlike other enteric pathogens) full resistance to fluoroquinolones can be obtained by a single mutation in the gyrA gene, making it very easy for these bacteria to acquire resistance. Aarestrup WDT: p. 8, lines 17-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the concept of "full resistance" is undefined and unknown. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). Bayer/AHI agree that fluoroquinolone resistance develops in *Campylobacter* as a spontaneous genetic mutation in the gyrA gene within a *Campylobacter* population and is not as a result of exposure to fluoroquinolones. (*See, e.g.* Joint Stipulation 1 and Bayer/AHI PFOF 36).

21. Resistance to fluoroquinolones in *Campylobacter* is most often mediated by a single point mutation, indicating that resistance in this bacterium arises much more rapidly than in other bacteria such as *Salmonella* and *E. coli*. Aarestrup WDT: p. 8, lines 26-28

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the concept of the relative speed with which resistance in a bacterium arises is undefined and unknown. Bayer/AHI agree that fluoroquinolone resistance develops in *Campylobacter* as a spontaneous genetic mutation in the gyrA gene within a *Campylobacter* population and is not as a result of exposure to fluoroquinolones. (*See, e.g.* Joint Stipulation 1 and Bayer/AHI PFOF 36).

22. The use of fluoroquinolones will select for resistance in all bacteria living in animals, including bacteria capable of transferring to and causing infections in humans, such as *Campylobacter* and *Salmonella*. Aarestrup WDT: p. 9, lines 24-26

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being too broad. The use of fluoroquinolones will not select for resistance in all bacteria living in animals; some bacteria such as *C. lari* are naturally resistant to fluoroquinolones. Bayer/AHI do not dispute that fluoroquinolones *can* select for resistance in bacteria living in animals, including *Campylobacter*.

23. Quinolone resistance has emerged in *Campylobacter* and *Salmonella* causing infections in man as a consequence of the introduction of fluoroquinolones for food animals. Aarestrup WDT: p. 9, lines 28-30

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

24. A more limited usage of fluoroquinolones will lead to a decrease in resistance. Aarestrup WDT: p. 9, line 32

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.86 (citing B-1020), P.27 (citing B-119 and B-29), P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

25. Fluoroquinolones are convenient drugs to use in veterinary medicine, but they are rarely important and never essential. Aarestrup WDT: p. 9, lines 34-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF generally, and specifically as it relates to the U.S. where enrofloxacin is the only effective alternative to treat poultry for the labeled indications. This PFOF is refuted by A-202 P.27 L.6 – P.28 L.11, P.30 L.13 - P.31 L.31; B-1912 P.26 L.15-17; B-1903 P.5 L.21 - P.6 L.7, P.14-25; B-1914 P.32 L.4-8; B-1915 P.8 L.13-14.

Frederick Angulo (G-1452)

26. Dr. Angulo is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination, except where Dr. Angulo testifies on matters related to causality and causal analysis.

27. Foodborne infections are an important public health challenge. Angulo WDT: p. 2, line 7 and 42-43; G-410.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

28. The CDC estimates that foodborne infections cause 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths each year. Angulo WDT: p. 2, line 42-43; G-410.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is outdated, misleading and not applicable to this proceeding. The figures cited are based on 1996 information and reveal nothing concerning *Campylobacter*. In fact, this publication estimated that *Campylobacter* only accounted for 3% of foodborne infections and the incidence of campylobacteriosis since then has decreased 27% from 1996 to 2001 according to CDC. G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10; B-1042; G-1391.

29. *Campylobacter* causes a significant burden of illness in the population of the United States. Angulo WDT: p. 7, line 5-8 and 10-14; p. 9, line 16; G-410; G-1452, Attachment 1.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Campylobacteriosis is usually self-limiting and the symptoms are often mild. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. This is often true even in cases of bactermia. B-1906 P.5 L.7-9. Many *Campylobacter* enteritis cases do not even get reported to the doctor. G-1452 P.6 L.22-45. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4.

30. Despite a decline in incidence, *Campylobacter* continues to present a significant burden of infection in the U.S. population. Angulo WDT: p. 5, line 21-23; p. 7, line 5-8 and 10-14; p. 9, line 16; G-410; G-1452, Attachment 1.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI dispute this PFOF. Campylobacteriosis is usually self-limiting and the symptoms are often mild. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. This is often true even in cases of bactermia. B-1906 P.5 L.7-9. Many *Campylobacter* enteritis cases do not even get reported to the doctor. G-1452 P.6 L.22-45. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4.

31. Many cases of foodborne diseases are not reported. Angulo WDT: p. 6, line 17-18; G-410.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

32. A large number of cases of campylobacteriosis are not reported to public health officials and therefore are not detected through routine public health surveillance. Angulo WDT: p. 6, line 22-45; G-410.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF; the likely reason that a large number of cases are not reported is that campylobacteriosis is self-limiting and the symptoms are

often mild. B-1909 P.3 L.16-17; G-240; G-530; G-622. This is often true even in cases of bactermia. B-1906 P.5 L.7-9.

33. The number of laboratory-diagnosed *Campylobacter* cases reported to public health officials represents but a fraction of the many *Campylobacter* infections that occur in the United States. Angulo WDT: p. 6, line 22 through p. 7, line 2.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF; the likely reason that a large number of cases are not reported is that campylobacteriosis is self-limiting and the symptoms are often mild. B-1909 P.3 L.16-17; G-240; G-530; G-622. This is often true even in cases of bactermia. B-1906 P.5 L.7-9.

34. In 1999, the CDC estimated the degree of underreporting of *Campylobacter* to be approximately 38-fold. Angulo WDT: p. 7, line 4-5; G-410.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

35. Using FoodNet surveillance data from 1996-1997, and correcting for underreporting, researchers estimated that *Campylobacter* causes 2.4 million infections, 13,000 hospitalizations, and 124 deaths a year in the United States, where the frequency of foodborne transmission of *Campylobacter* was estimated to be 80 percent. Angulo WDT: p.. 7, line 5-8; G-410.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is outdated, misleading and not applicable to this proceeding. CDC estimates that campylobacteriosis incidence since 1996 has decreased 27% (1996 to 2001) and the estimate for *Campylobacter* infections in 1999 was 1.4 million. CVM proposed finding of fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10

36. Using *Campylobacter* incidence in 1999 from FoodNet surveillance data and a simulation procedure developed by FDA in a *Campylobacter* risk assessment, CDC estimated that in 1999 *Campylobacter* infected an estimated 1.4 million persons. Angulo WDT: p. 7, line 10-14; G-1452, Attachment 1.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

37. FoodNet is a collaborative project among the CDC, state health departments, the United States Department of Agriculture Food Safety and Inspection Service, and the United States Food and Drug Administration. Angulo WDT: p. 2, line 16-19.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

38. In 2001, FoodNet conducted population-based active surveillance for clinical laboratory isolations of *Campylobacter, Cryptosporidium, Cyclospora,* Shiga-toxin producing *Escherichia coli* including *E. coli* O157:H7, *Listeria, Salmonella, Shigella, Vibrio,* and

Yersina infections in Connecticut, Georgia, Maryland, Minnesota, and Oregon, and selected counties in California, Colorado, New York, and Tennessee. Angulo WDT: p. 2, line 34-38; G-1791.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, subject to the caveat that "population-based" does not mean, suggest, or imply "representative of the US population" (or of any other population outside the sample itself).

39. In 2001, the total population in the area under FoodNet surveillance was greater than 37 million persons, which was greater than 13 percent of the population of the United States. Angulo WDT: p. 2, line 38-39; G-1791.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, subject to the caveat that the FoodNet surveillance did not include the 37 million persons within its scope, but only the tiny fraction that were ultimately selected for sampling. Bayer/AHI dispute that the FoodNet surveillance area is representative of the U.S. population. Conclusions from the FoodNet database are therefore not typically representative of the U.S. population. G-1468 P.5 L.17-21; G-1452 P.4 L.2-22; A-200 P.17 L.23-24 – P.18 L.1-2; A-199 P.11 L.14 - P.13 L.24; A-199 P.44-76; A-52; B-1879.

40. The populations in the FoodNet surveillance area and the United States had similar age and gender distributions. Angulo WDT: p. 4, line 7-19.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, subject to the caveat that Bayer/AHI do dispute that the FoodNet surveillance area is representative of the U.S. population. Conclusions from the FoodNet database are therefore not typically representative of the U.S. population. G-1468 P.5 L.17-21; G-1452 P.4 L.2-22; A-200 P.17 L.23-24 – P.18 L.1-2; A-199 P.11 L.14 - P.13 L.24; A-199 P.44-76; A-52; B-1879.

41. FoodNet surveillance data are generalizable to the United States population for the purpose of understanding the epidemiology of foodborne illness. Angulo WDT: p. 4, line 21-26; G-769.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the

entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24.

42. The estimated incidence of laboratory-confirmed *Campylobacter* infections per 100,000 population in sites participating in FoodNet surveillance was 23.5 in 1996, 24.7 in 1997, 19.4 in 1998, 15.0 in 1999, and 15.4 in 2000. Angulo WDT: p. 4, line 44-46 and p.5, line 1-3; G-102; G-93; G-94; G-1791.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

43. Preliminary data for 2001 ascertained 4,740 laboratory-confirmed *Campylobacter* infections, which correlate to an incidence of 13.8 laboratory-confirmed infections per 100,000 population in sites participating in FoodNet surveillance. Angulo WDT: p. 5, line 6-9; G-1791.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

44. A log-linear Poisson regression model was used to estimate the effect of time on the incidence of *Campylobacter*, treating time (calendar year) as a categorical variable, with 1996 as the reference year to account for a near doubling between 1996 and 2001 in the number of sites and population under FoodNet surveillance and the variation in incidence among sites; in this model, the incidence of *Campylobacter* declined by 27 percent (95% CI: 19%, 35%) between 1996 and 2001. Angulo WDT: p. 5, line 15-21; G-1791.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, subject to the caveat that the log-linear Poisson regression model was not validated and may not have been appropriate for this application, and may have produced false and misleading results [Cox 2001, Chapter 3, cited in B-1901].

45. A review of the epidemiology of *Campylobacter* infections using FoodNet surveillance data from 1996-1999 showed that ten percent of persons with laboratory-confirmed *Campylobacter* infections were hospitalized, with the highest hospitalization rate (27 percent) among persons 60 years of age or older. Angulo WDT: p. 5, line 25-33; G-1452, Attachment 1; G-555.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

46. A review of the epidemiology of *Campylobacter* infections using FoodNet surveillance data from 1996-1999 showed that one person in every 3,000 persons with a laboratory-confirmed *Campylobacter* infection died. Angulo WDT: p. 5, line 25-33; G-1452, Attachment 1; G-555.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is misleading to the extent that it implies or suggests that people who die with laboratory confirmed cases of *Campylobacter* infection die as a result of the infection, when in fact these patients almost always are afflicted with a serious underlying disease. Kist (B-1906) P.14 L.18-19; Pasternack (B-1909) P.19 L.6-8; (G-1661) P.4

47. The vast majority of *Campylobacter* infections are not related to recognized outbreaks but occur as sporadic individual infections. Angulo WDT: p. 9, line 18-19.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

48. *Campylobacter* does not tend to multiply in foods left out for many hours unlike some other bacteria; indeed, it does not tolerate exposure to atmospheric oxygen or to drying. Angulo WDT: p. 9, line 29-31.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

49. Epidemiological investigations have been conducted in the United States and in other developed nations to determine risk factors for sporadic *Campylobacter* infections. Although these studies differed in location, technique, and sample size, they consistently indicate several dominant sources of infection, including contact with and consumption of chicken and turkey. Angulo WDT: p. 9, line 36-40; G-268; G-162; G-334; G-1718; G-10; G-182; G-1686.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major (let alone "dominant") source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44. Moreover, recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Recent studies in the United Kingdom also now question whether chicken is a major source of fluoroquinolone-resistant campylobacteriosis. B-1909 P.40 L.20-22. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a dominant source of *Campylobacter* infection.

50. Data from the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors demonstrate that the dominant domestic source of *Campylobacter* infections in humans is

poultry, particularly chicken but also turkey. Angulo WDT: p. 10, line 22 through p. 11, line 1; G-1452, Attachment 3; G-228.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record, specifically including analysis of data from the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors [B-1901], disputes the contention that chicken or turkey is a major source of campylobacteriosis, let alone "the dominant domestic source". Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. G-1452 P.10 L.36-44. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Recent studies in the United Kingdom also now question whether chicken is a major source of fluoroquinolone-resistant campylobacteriosis. B-1909 P.40 L.20-22. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is the dominant domestic source of *Campylobacter* infections in humans.

51. The 1998-1999 FoodNet *Campylobacter* case-control study on risk factors was population-based and conducted in seven FoodNet sites --Connecticut, Georgia, Minnesota, Oregon, and selected counties in California, Maryland, and New York. Angulo WDT: p. 9, line 46 through p. 10, line 1; G-1452, Attachment 3; G-228.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is incorrect and misleading. For example, in Connecticut, only residents in Hartford, New Haven and Fairfield counties were included in the study. G-1489 P.7.

52. The 1998-1999 FoodNet *Campylobacter* case-control study on risk factors determined that the largest population attributable fractions for *Campylobacter* infections were for eating chicken in a restaurant and eating non-poultry meat in a restaurant. Angulo WDT: p. 10, line 36-44.

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF. For example, "eating chicken or non-poultry meat in a restaurant" has a larger population attributable fraction for *Campylobacter* infections than either of the factors listed in the PFOF. The population attributable fractions for *Campylobacter* infections referred to were not calculated appropriately (using appropriate multivariate methods), did not correct for confounders (such as dining in restaurants), did not account for protective effects of chicken consumption overall, excluded relevant risk factors (such as consumption of contaminated drinking water), and lack any causal interpretation or predictive capability. B-1901 P.60-64.

53. The 1998-1999 FoodNet *Campylobacter* case-control study on risk factors used the following methods: (a) all selected cases with a culture-confirmed *Campylobacter* infection in the surveillance sites during the study period were attempted to be enrolled; (b) one age-matched well control was enrolled for each case; (c) 1316 *Campylobacter* cases and 1316 matched well community controls were enrolled; and (d) cases and controls were asked about foreign travel, food and water exposures, and food handling practices in the seven days prior to illness onset of the case. Angulo WDT: p. 10, line 1-5, 14-15; G-1452, Attachment 3.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

54. In the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors: (a) cases were 10.0 times more likely (95% CI: 6.0, 16.7) to have traveled internationally in the seven days prior to illness onset than controls (13% of cases traveled outside the United States in the seven days prior to illness onset compared with 1.5% of controls); and (b) the population attributable fraction for foreign travel was 12 percent, suggesting that 12 percent of sporadic cases of campylobacteriosis in the United States are due to travel outside the United States. Angulo WDT: p. 10, line 14-20; G-1452, Attachment 3.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

55. In the final multivariate logistic regression model used to determine risk factors for acquiring a *Campylobacter* infection among persons who did not travel outside the United States, the 1998-1999 FoodNet *Campylobacter* case-control study found that: (a) cases were 2.2 times more likely (95% CI: 1.7, 2.9) to have eaten chicken in a restaurant in the seven days prior to illness onset than controls (44% of cases ate chicken in a restaurant compared with 26% of controls); (b) cases were 2.5 times more likely (95% CI: 1.3, 4.7) to have eaten turkey in a restaurant in the seven days prior to illness onset than controls (6% of cases ate turkey in a restaurant compared with 3% of controls); and (c) cases were 1.7 times more likely (95% CI: 1.3, 2.2) to have eaten non-poultry meat in a restaurant in the seven days prior to illness onset than controls (52% of cases ate non-poultry meat in a restaurant compared with 35% of controls). Angulo WDT: p. 10, line 22-32; G-1452, Attachment 3.

Bayer/AHI Response: Bayer/AHI do not dispute that restaurant dining is a risk factor for a domestically acquired *Campylobacter* infection as pointed out by the PFOF. Bayer/AHI dispute the numbers in this PFOF as being inconsistent with CVM evidence showing risk ratios of 2.2 for resistant chicken, 1.7 for resistant turkey and 2.5 for resistant non-poultry meat, indicating less risk associated with poultry compared to non-poultry meat. Therefore this proposed finding of fact is misleading. G-1488 P.3 & 10.

56. In the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors, the population attributable fraction for eating: (a) chicken in a restaurant was 24 percent (95% CI: 17%, 30%); (b) non-poultry meat in a restaurant was 21 percent (95% CI: 13%, 30%); and (c) turkey in a restaurant was 4 percent (95% CI: 1%, 6%). Angulo WDT: p. 10, line 36-41; G-1452, Attachment 3.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, other than noting the caveats that the population attributable fractions for *Campylobacter* infections referred to were not calculated appropriately (using appropriate multivariate methods), did not correct for confounders (such as dining in restaurants), did not account for protective effects of chicken consumption overall, excluded relevant risk factors (such as consumption of contaminated drinking water), and lack any causal interpretation or predictive capability. B-1901 P.60-64. Bayer/AHI also note that these numbers differ from G-1452, Attachment 3.

57. The population attributable fraction determined in the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors suggests that, among persons who did not travel outside the United States, 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 a restaurant in the seven days prior to illness onset. Angulo WDT: p. 10, line 36-44; G-1452, Attachment 3.

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as assigning an inappropriate causal interpretation to population attributable fractions that were calculated based only on statistical associations, not causal ones. The population attributable fractions for *Campylobacter* infections referred to in the PFOF were not calculated appropriately (using appropriate multivariate methods), did not correct for confounders (such as dining in restaurants), did not account for protective effects of chicken consumption overall, excluded relevant risk factors (such as consumption of contaminated drinking water), and lack any causal interpretation or predictive capability. B-1901 P.60-64.

58. Several factors in addition to the high prevalence of *Campylobacter* on chickens and turkeys after processing contribute to the high number of human campylobacteriosis cases that occur each year in the United States. The high frequency that *Campylobacter*-contaminated chickens and turkeys are handled by food handlers and consumers contribute to the number of *Campylobacter* infections. Chickens and turkeys sold to restaurants are frequently contaminated with *Campylobacter* and are thereby handled by food handlers in restaurant kitchens during preparation. Chickens and turkeys sold in grocery stores are frequently contaminated with *Campylobacter* and therefore chicken or turkey contaminated with *Campylobacter* are commonly brought into consumer's kitchens in the United States. Once in a consumer's kitchen, *Campylobacter* on the chicken or turkey can easily contaminate other foods through routine kitchen activities. Angulo WDT: p. 12, line 37-48.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. There are no studies measuring prevalence of *Campylobacter* on chicken sold to restaurants. While it may be true that chickens and turkeys sold in grocery stores are frequently contaminated with *Campylobacter* and that chicken or turkey contaminated with *Campylobacter* are commonly brought into consumer's kitchens in the United States, evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent

epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Dr. Friedman found that eating chicken or non-poultry meat prepared in the home is protective. G-1488 P.23. Even 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. B-1901 P.29 (citing G-1644). The best, most recent epidemiological evidence in the record from the U.S. and elsewhere does not show or even merely suggest that poultry is a major source of campylobacteriosis. If people who prepare chicken in the home are protected (people who prepare and eat chicken at home are not as likely to become ill), then cross-contamination from chicken in the home is not associated with campylobacteriosis and cannot be accepted as fact.

59. Consumers can reduce, but not eliminate, the frequency of the occurrence of *Campylobacter* cross-contamination in kitchens by careful washing and disinfecting of hands and surfaces after handling uncooked chicken and turkey. Angulo WDT: p. 12, line 48 through p. 13 line 2.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that there is evidence that consumers are increasingly aware of the need to reduce the frequency of cross-contamination. A-204 P.10-12.

60. Because of the high prevalence of *Campylobacter* contamination of chickens and turkeys in grocery stores, and the high frequency that chickens and turkeys are purchased from stores and handled by consumers, it is likely that the incidence of *Campylobacter* infections in people would remain high even if all risky food handling practices in the United States were eliminated. Angulo WDT: p. 12, line 9-28; p. 12, line 37 through p. 13, line 2; p. 13, line 24-30; G-1528.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is inaccurate, taken out of context and speculative. Dr. Angulo states earlier that since risky (i.e. not washing hands after handling raw poultry) food handling practices increase the risk of acquiring a *Campylobacter* infection, reducing the frequency of risky food handling practices will reduce the incidence of *Campylobacter* infections. Dr. Angulo then goes on to speculate that risks would remain high even if all food handling risks were eliminated. G-1452 P.13 L.24-26. Dr. Angulo's speculation contradicts not only his own statement but the findings of Kassenborg. In the *Campylobacter* case-control study, Kassenborg found that many of the food preparation practices were associated with a decreased risk of campylobacteriosis. G-1452 P.88. Bayer/AHI also dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Recent epidemiological data, particularly in the U.S., demonstrate that retail chicken handled or prepared at home is associated with a statistically

significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, Bayer/AHI note that there is evidence in the record that consumers are increasingly aware of the need to improve food handling practices to reduce the frequency of cross-contamination. A-204 P.10-12.

61. A dominant source of *Campylobacter* infections in the U.S. population is poultry, particularly chicken, which is frequently contaminated with ciprofloxacin-resistant *Campylobacter*. Angulo WDT: p. 12, line 26-28; p. 17, line 22-24; G-1528.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a dominant source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data, particularly in the U.S., demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a dominant source of *Campylobacter* infections in the U.S. population.

62. The January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens was conducted in three FoodNet-participating state health departments (Georgia, Maryland, and Minnesota). Angulo WDT: p. 11, line 47-48; G-1528.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

63. The January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens used the following sample collection methods: (a) each participating state health department purchased ten whole broiler chickens each month from supermarkets located within the state; (b) the public health department laboratories at each site tested the chicken samples for *Campylobacter*; (c) carcass rinse samples were centrifuged and pellets were incubated in enrichment broth and plated onto *Campylobacter* blood agar plates; and (d) if available, one isolate from each carcass rinse was forwarded to the CDC for species identification and antimicrobial susceptibility testing. Angulo WDT: p. 11, line 48 through p. 12, line 6.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

64. The January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens used the following methods for species identification: (a) upon receipt at the CDC, isolates were tested for viability and purity; (b) isolates were confirmed as *Campylobacter* and then identified to species level by the hippurate test; (c) hippurate-positive isolates were classified as *C. jejuni*; (d) hippurate-negative isolates were additionally tested by a polymerase chain reaction to identify the presence or absence of the hippuricase gene; (e) isolates with the hippuricase gene were classified as *C. jejuni* and isolates without the gene were further tested to determine whether they are *C. coli*, *C. upsaliensas,* or another species of *Campylobacter*. Angulo WDT: p. 7, line 32-38; G-97; G-98; G-749.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

65. The January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens used the following methods for antimicrobial susceptibility testing: (a) all *Campylobacter* isolates were tested with the E-test system for minimal inhibitory concentrations for ciprofloxacin and several other antimicrobial agents; and (b) ciprofloxacin resistance was defined as a ciprofloxacin minimum inhibitory concentration of greater than or equal to four micrograms per milliliter. Angulo WDT: p. 7, line 38-41; G-97; G-98; G-749.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

66. In the January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens, 180 retail chicken products were purchased, representing multiple domestic brand names from over 20 grocery stores. Angulo WDT: p. 12, line 9-10; G-1528.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

67. In the January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens, *Campylobacter* was isolated from 80 (44%) of the samples. Angulo WDT: p. 12, line 10; G-1528.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

68. Among the 80 *Campylobacter* isolates in the January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens, 62 (78%) were *C. jejuni*, 16 (20%) were *Campylobacter coli*, and 2 were an unknown species. Angulo WDT: p. 12, line 10-12; G-1528.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Based on available information, this PFOF is inaccurate. The unpublished CDC data referenced in the testimony is not on the docket; abstracts relating to this study, G-541 and G-1528, do not publish these numbers. Dr. Rossiter published an abstract on the CDC web page of a presentation made at the 2nd International

Conference on Emerging Infectious Diseases in which she reported on only 61 *Campylobacter jejuni* isolates.

69. In the January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens, a ciprofloxacin-resistant strain of *Campylobacter* was identified in 11 percent of 180 retail chicken products tested, demonstrating the frequent contamination of chicken with ciprofloxacin-resistant *Campylobacter*. Angulo WDT: p. 12, line 26-28; G-1528.

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and potentially misleading. There are no official interpretive criteria for what constitutes "fluoroquinolone-resistant" for *Campylobacter* (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, asserting that 11% were "fluoroquinolone-resistant" uses a term that lacks any accepted definition to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that 11% of the isolates in question were resistant to clinically relevant doses of fluoroquinolones. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy WDT: P.10 L.1-4; Smith, G-1473 P.10 ¶ 22) Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant strain of *Campylobacter* was identified in 11 percent of 180 retail chicken products tested" is vague and misleading. It is also incorrect if "fluoroquinolone-resistant" is taken to mean, imply, or suggest "resistant to fluoroquinolone administered *in vivo*". While Bayer/AHI also dispute as vague and subjective the statement that finding 11% of the *Campylobacter* strains to be ciprofloxacin-resistant represents a "frequent contamination of chicken with ciprofloxacin-resistant *Campylobacter*".

70. Among the 62 *C. jejuni* isolates in the January – June 1999 FoodNet *Campylobacter* microbiologic survey of grocery store chickens, 15 (24%) were resistant to ciprofloxacin. Angulo WDT: p. 12, line 19; G-1528.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Based on available information, this PFOF is inaccurate. The unpublished CDC data referenced in the testimony is not on the docket; abstracts relating to this study, G-541 and G-1528, do not publish these numbers. Dr. Rossiter published an abstract on the CDC web page of a presentation made at the 2nd International Conference on Emerging Infectious Diseases in which she reported on only 61 *Campylobacter jejuni* isolates.

Bayer/AHI also dispute this PFOF as vague and potentially misleading. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, asserting that "ciprofloxacin-resistant *Campylobacter* was isolated from 18 products (20%)" uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant *Campylobacter*") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously

compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading.

71. Antibiotic resistance is a food safety problem. Angulo WDT: p. 3, line 9-12.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because as written it is too broad. If, for example, a certain foodborne bacteria becomes antibiotic resistant but the resistance does not confer any additional disease or complications compared to a susceptible strain of the same foodborne bacteria, that would not constitute a "food safety problem." Evidence in the record demonstrates that such is the case with *Campylobacter*. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P. 1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment #4, P.116-118; G-1489 P.10-11. 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. B-1901 P.78. Additionally, a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14.

72. As antibiotic resistance increases, resistance threatens the utility of antibiotics that are commonly used to treat serious human infections caused by bacteria commonly found in food, such as *Campylobacter*. Angulo WDT: p. 3, line 10-12.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because, as related to fluoroquinolones and *Campylobacter*, it is refuted by evidence in the record. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-

resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment #4, P.116-118; G-1489 P.10-11. Epidemiological data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness in patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. B-1901 P.78. Additionally, a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14.

73. The primary purpose of the human NARMS surveillance program is to monitor antimicrobial resistance among foodborne enteric bacteria including *Campylobacter, Salmonella,* and *Escherichia coli* O157:H7. Angulo WDT: p. 3, line 17-19; G-749.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

74. The human NARMS surveillance program is a collaborative project among the CDC, participating state health departments, the United States Food and Drug Administration, and the United States Department of Agriculture. Angulo WDT: p. 3, line 26-27; G-749.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

75. The human NARMS surveillance program testing of *Campylobacter* isolates began in 1997. Angulo WDT: p. 3, line 36; G-749.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

76. As part of the human NARMS surveillance program, clinical laboratories isolate foodborne enteric bacteria usually from diagnostic specimens collected from ill persons and forward the isolates to state public health laboratories; each of the state health departments participating in FoodNet sends selected *Campylobacter* isolates each week to the CDC for susceptibility testing. Angulo WDT: p. 3, line 32-33 and line 38-40; G-749.

Bayer/AHI Response: Bayer/AHI agree that the human NARMS surveillance program protocol called for the collection, selection and transport of samples in the manner described. Evidence in the record refutes that the protocol was followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

77. *Campylobacter* isolates in the human NARMS surveillance program exhibited two distinct populations with respect to their minimum inhibitory concentrations to ciprofloxacin: nearly all isolates either had a minimum inhibitory concentration of 0.5 or less micrograms per milliliter (susceptible isolates), or a minimum inhibitory concentration of 32 or more micrograms per milliliter (resistant isolates). Angulo WDT: p. 8, line 5-8; G-97; G-98; G-749.

Bayer/AHI Response: Bayer/AHI do not dispute that the human NARMS resistance program exhibit the bimodel distribution stated. Bayer/AHI dispute the characterization of 32 μg/ml as clinically "resistant." A National Committee for Clinical Laboratory Standards

(NCCLS) recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infection in humans. Joint Stipulation 14. Moreover, if a high enough concentration of antimicrobial relative to MIC of the infecting organism can be achieved not only will the parent organism be killed but also the "resistant" mutation. Given the high levels of ciprofloxacin in the GI tract, clinical cure can be demonstrated for a *Campylobacter* with an MIC of 32 μg/ml. B-1913 P.17 L.8 – P.18 L.15.

78. In the human NARMS surveillance program, the percent of *Campylobacter* isolates resistant to ciprofloxacin was 13 percent (28 of 217) in 1997, 14 percent (48 of 345) in 1998, 18 percent (58 of 319) in 1999, 14 percent (46 of 324) in 2000, and 19 percent (75 of 387) in 2001. Angulo WDT: p. 8, line 9-11; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI do not dispute that the human NARMS resistance program reported the rates cited. Bayer/AHI dispute that the rates cited are accurate or reflective of the U.S. populations due to limitations and problems in the human NARMS surveillance program. Evidence in the record demonstrates that human NARMS is not representative of or generalizable to the U.S. population. Selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12. Bayer/AHI also dispute "resistance" means "clinical resistance". B-1913 P.17 L.8 – P.18 L.15.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this

mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading.

79. In the human NARMS surveillance program, the percent of *C. jejuni* isolates resistant to ciprofloxacin was 12 percent (26 of 209) in 1997, 14 percent (45 of 330) in 1998, 18 percent (52 of 295) in 1999, 14 percent (43 of 306) in 2000, and 18 percent (67 of 366) in 2001. Angulo WDT: p. 8, line 13-16; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI do not dispute that the human NARMS resistance program reported the rates cited. Bayer/AHI dispute that the rates cited are accurate or reflective of the U.S. populations due to limitations and problems in the human NARMS surveillance program. Evidence in the record demonstrates that human NARMS is not representative of or generalizable to the U.S. population. Selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to

clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading

80. To account for the potentially confounding effects of the changing population base and the site variability in ciprofloxacin resistance, the human NARMS surveillance program used a multivariate logistic regression to analyze the change between 1997 and 2001 in the proportion of *Campylobacter* isolates that were resistant to ciprofloxacin. Angulo WDT: p. 8, line 27-29.

Bayer/AHI Response: Bayer/AHI do not dispute that the human NARMS surveillance program undertook such an analysis. We dispute that it is an appropriate analysis for time series or trend data or that the logistic regression model was able successfully "to account for the potentially confounding effects of the changing population base and the site variability in ciprofloxacin resistance" (see the Bayer/AHI response to CVM PFOF #81). Despite this analysis, there is extensive evidence in the record that the NARMS/FoodNet data are "artificial" (i.e., dependent on unvalidated and invalid modeling assumptions and techniques) and are not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24.

81. In the multivariate logistic regression model used in the human NARMS surveillance program, the proportion of *Campylobacter* isolates resistant to ciprofloxacin in 2001, controlling for site variation and age, was 2.5 times higher (95% CI: 1.4, 4.4) than the proportion of *Campylobacter* isolates resistant to ciprofloxacin in 1997. Angulo WDT: p. 8, line 35-38; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer cannot verify this as a fact since complete data sets are not in the docket and were not provided for review, notwithstanding a request made under the Freedom of Information Act. Bayer could not duplicate the Logistic Regression Model analysis since the data received contained numerous missing data on age. B-1900 P.43 L.13-15. Using the data provided, an independent logistic regression model clearly showed 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. A-200 P.54 L.2-4. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. In conducting the Logistic Regression Model to analyze the NARMS data, CDC not only failed to explore how the independent variables and outcome measured vary with respect to passage of time, but the analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. A-200 P.54 L.17 – P.55 L.4; B-1901 P.43. Bayer/AHI dispute that the rates cited are accurate or reflective of the U.S. populations due to limitations and problems in the human NARMS surveillance program. Evidence in the record demonstrates that human

NARMS is not representative of or generalizable to the U.S. population. Selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is also refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading

82. When restricting the analysis to only the *C. jejuni* isolates in the multivariate logistic regression model used in the human NARMS surveillance program, the proportion of *C. jejuni* isolates resistant to ciprofloxacin in 2001 was 2.2 times higher (95% CI: 1.2, 4.0) than the proportion of *C. jejuni* isolates resistant to ciprofloxacin in 1997. Angulo WDT: p. 8, line 41-44; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer cannot verify this as fact since complete data sets are not in the docket and were not provided for review, notwithstanding a request made under the Freedom of Information Act. Bayer could not duplicate the Logistic Regression Model analysis since the data received contained numerous missing data on age. B-1900 P.43 L.13-15. Using the data provided, an independent logistic regression model clearly showed 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. A-200 P.54 L.2-4. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. In conducting the Logistic Regression Model to analyze the NARMS data, CDC not only failed to explore how the independent variables and outcome measured vary with respect to passage of time, but the analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. A-200 P.54 L.17 – P.55 L.4; B-1901 P.43. Bayer/AHI dispute that the rates cited are accurate or reflective of the U.S. populations due to limitations and problems in the human NARMS surveillance program. Evidence in the record demonstrates that human NARMS is not representative of or generalizable to the U.S. population. Selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is also refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF

#408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading

83. No remarkable changes in the analysis were observed in either multivariate model when the cases from Connecticut were excluded from the multivariate logistic regression model used in the human NARMS surveillance program. Angulo WDT: p. 8, line 46-47.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, "remarkable" is not a defined term in statistics. We believe that excluding outlier data such as those from Connecticut makes a large difference and reverses some of CVM's conclusions, but we have no way to demonstrate what constitutes "remarkable changes". Second, Bayer cannot verify this as fact since complete data sets are not in the docket and were not provided for review, notwithstanding a request made under the Freedom of Information Act. Bayer could not duplicate the Logistic Regression Model analysis since the data received contained numerous missing data on age. B-1900 P.43 L.13-15. Using the data provided, an independent logistic regression model clearly showed 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. A-200 P.54 L.2-4. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. In conducting the Logistic Regression Model to analyze the NARMS data, CDC not only failed to explore how the independent variables and outcome measured vary with respect to passage of time, but the analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. A-200 P.54 L.17 – P.55 L.4; B-1901 P.43.

84. Data from the human NARMS surveillance program demonstrate that a high proportion (approximately one-fifth) of human *Campylobacter* isolates in the United States are resistant to ciprofloxacin. Angulo WDT: p. 8, line 11; p. 9, line 1-2; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Dr. Angulo states that overall, 16% of the isolates were resistant. G-1452 P.8. Bayer/AHI dispute that rates cited by NARMS are accurate or reflective of the U.S. populations due to limitations and problems in the human NARMS surveillance program. Evidence in the record demonstrates that human NARMS is not representative of or generalizable to the U.S. population. Selection of state health departments to participate in FoodNet was based upon written responses to a Request for Proposals published in the Federal Register; state health departments were not chosen specifically to be representative of the United States population. G-1452 P.4 L.2-5. Compared to the United States population, the population in the FoodNet surveillance area was more likely to be Asian G-1452 P.4 L.16-19, less likely to be Black G-1452 P.4 L.16-19, less likely to be Hispanic G-1452 P.4 L.16-19, more likely to include urban residents G-1452 P.4 L.16-19, more likely to include residents in counties with lower population density G-1452 P.4 L.16-19 and less likely to include persons living at or below poverty G-1452 P.4 L.16-19. Dr. Angulo acknowledges that there are demographic

differences between the populations residing in the FoodNet surveillance area and the United States. G-1452 P.4 L.21-22. This PFOF is refuted by CVM witness Dr. Molbak, who testified that although FoodNet data provide detailed information regarding *Campylobacter* infections, "the data do not reflect the entire U.S. population." G-1468 P.5 L.17-21. Additional evidence in the record shows that 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. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12. Bayer/AHI also dispute "resistance" means "clinical resistance". B-1913 P.17 L.8 – P.18 L.15.

Bayer/AHI also object to the use of the terms "high proportion" (as 20% is in line with some reported pre-enrofloxacin rates) and with use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to. clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading

85. Ciprofloxacin-resistant *Campylobacter* presents a substantial burden of infection in the U.S. population. Angulo WDT: p. 8, line 9-11; p. 17, line 9-10; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Campylobacteriosis is usually self-limiting and the symptoms are often mild regardless of whether organism is susceptible or resistant. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. This is often true even in cases of bactermia. B-1906 P.5 L.7-9. Many *Campylobacter* enteritis cases do not even get reported to the doctor. G-1452 P.6 L.22-45. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4. An overall resistance rate of 16%, even if true, cannot be interpreted as a "substantial burden" of infection.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, this PFOF uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of ciprofloxacin. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." Levy WDT: P.10 L.1-4. Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading

86. When using a multivariate model to account for the marked regional variation and increasing population size in the human NARMS surveillance program, 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. Angulo WDT: p. 8, line 23-38; p. 9, line 2-5; G-1452, Attachment 2.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer cannot verify this as fact since complete data sets are not in the docket and were not provided for review, notwithstanding a request made under the Freedom of Information Act. Bayer cannot verify this as fact since complete data sets were not provided for review. Bayer could not duplicate the Logistic Regression Model analysis since the data received contained numerous missing data on age. B-1900 P.43 L.13-15. Using the data provided, an independent logistic regression model clearly showed 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. A-200 P.54 L.2-4. The Logistic Regression Model used by CDC to analyze the NARMS data cannot be considered a true trend analysis. In conducting the Logistic Regression Model to analyze the NARMS data, CDC not only failed to explore how the independent variables and outcome measured vary with respect to passage of time, but the analysis also obliterated the sequential relationship among temporal identifiers which precluded analysis of trends because each year was considered in isolation. A-200 P.54 L.17 – P.55 L.4; B-1901 P.43.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

87. Ciprofloxacin-resistant *Campylobacter* infection in the U.S. population is increasing. Angulo WDT: p. 7, line 25 through p. 9, line 13; p. 17, line 17.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. What has been happening "in the U.S. population" is unknown, as no adequate sample representing the general U.S. population

has been used and as there is great variability among FoodNet sites, making any extrapolation outside the sampled locations (or even among them) invalid. Dr. Molbak shows that there was 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. (All 95% CIs pass through 1, indicating no statistical significance) G-1468 P.9. Drs. Angulo and Molbak both state that there was a high prevalence of ciprofloxacin-resistant *Campylobacter* found in Connecticut in 1999. Dr. Molbak suggested that the data analysis be done without Connecticut to see if the trend was in fact impacted by this one state. G-1452 P.8 L.30-31; G-1468 P.8 L.28-29 & L.21-23. Trend analysis does not support the PFOF's statement. Moreover, NARMS is not representative of the U.S. population and suffers from sampling problems. Evidence in the record shows that data collected for the Human NARMS program do not represent the general United States population G-1468 P.5 L.17-21. The program contains no means to correct its estimates for inherent sampling biases to make them representative of the general population. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 - P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

88. The trend between 1997 and 2001 of an increasing prevalence of ciprofloxacin resistance among human *Campylobacter* isolates is statistically significant. Angulo WDT: p. 9, line 3-6; p. 8, line 35-38.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Dr. Molbak shows that there was 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. (All 95% CIs pass through 1, indicating no statistical significance) G-1468 P.9. Drs. Angulo and Molbak both state that there was a high prevalence of ciprofloxacin-resistant *Campylobacter* found in Connecticut in 1999. To determine whether the higher Connecticut rates disportionally affected the trend analysis, Dr. Molbak conducted a trend analysis without Connecticut. G-1452 P.8 L.30-31; G-1468 P.8. L.28-29 & L.21-23. The trend analysis by Dr. Molbak in fact disputes this PFOF. For example, in 1999 and 2001, when Connecticut had elevated rates, removing Connecticut from the analysis shows no statistical increase in those years when compared to the 1997 base year. Moreover, NARMS is not representative of the U.S. population and suffers from sampling problems. Evidence in the record shows that data collected for the Human NARMS program do not represent the general United States population G-1468 P.5 L.17-21. The program contains no means to correct its estimates for inherent sampling biases to make them representative of the general population. A-200 P.17 L.23-24 – P.18 L.1-2. Finally, there is extensive evidence in the

record that Dr. Angulo has acknowledged in a public scientific meeting that the NARMS/FoodNet data are not population based, and not generalizable to, or representative of, the U.S. population. A-199 P.11 L.14 – P.13 L.24. Evidence in the record refutes that the protocol for the collection, selection and transport of human NARMS *Campylobacter* samples was even properly followed. A-200 P.27 L.5-24, P.30 L.1 – P.33 L.17, P.52 L.10-12.

Additionally, when Connecticut was left in the trend analysis, Dr. Molbak showed that the prevalence ratio between 1997 and 1998 to be not significant and the prevalence ratio between 1997 and 2000 to be not significant. G-1468 P.9. With this information, it cannot be stated as fact that the trend is increasing. The trend at best is variable from year to year.

Two major risk factors for fluoroquinolone-resistant *Campylobacter* in humans are foreign travel and prior fluoroquinolone use before culture. B-1900 P.8 L.43-44. The most glaring limitation of the NARMS data set is the absence of information on foreign travel and prior fluoroquinolone use. B-1900 P.44 L.42-43. Since a large proportion of the total number of resistant cases are not even germane to the question of interest, because of foreign travel or prior fluoroquinolone use, interpreting temporal trends in total reporting is dubious since increases in the total reporting of resistant cases could be attributable to foreign travel and prior fluoroquinolone use. B-1900 P.14 L.29-33. NARMS has no value in estimating the incidence or in determining if there has been a temporal decrease or increase in resistance. B-1900 P.55 L.8-10.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

89. Compared to persons with a ciprofloxacin-susceptible *Campylobacter* infection, persons with a ciprofloxacin-resistant *Campylobacter* infection are likely to have diarrhea for a longer duration, including in persons who have been treated with fluoroquinolones, which are commonly used to treat *Campylobacter* infections. Angulo WDT: p.15, line 12 through p. 16, line 7; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. (G-589) show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13. There is no statistically significant difference in duration of diarrhea between patients with a ciprofloxacin-susceptible *Campylobacter* infection and patients with a ciprofloxacin-resistant *Campylobacter* infection that are treated with a fluoroquinolone. G-1452, G-1367, G-1489, G-1679.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

90. Among persons treated with fluoroquinolones, persons with ciprofloxacin-resistant *Campylobacter* infections had a longer duration of diarrhea than persons with ciprofloxacin-susceptible *Campylobacter* infections. Angulo WDT: p.15, line 12 through p. 16, line 7; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. (G-589) show there is no significant difference in the mean duration of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13. There is no statistical difference, in duration of diarrhea, between patients with a ciprofloxacin-susceptible *Campylobacter* infection (6 days) and patients with a ciprofloxacin-resistant *Campylobacter* infection (8 days) that are treated with a fluoroquinolone (p value 0.08). G-1452, G-1367, G-1489, G-1679.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

91. It appears likely that fluoroquinolones are less efficacious against ciprofloxacin-resistant *Campylobacter*, thus prolonging the diarrheal illness. Angulo WDT: p. 15, line 12 through p. 16, line 7; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. (G-589) show there is no significant difference in the mean duration of diarrhea (i.e. no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13. There is no statistical difference, in duration of diarrhea, between patients with a ciprofloxacin-susceptible *Campylobacter* infection (6 days) and patients with a ciprofloxacin-resistant *Campylobacter* infection (8 days) that are treated with a fluoroquinolone (p value 0.08). G-1452, G-1367, G-1489, G-1679. There is substantial evidence that so called resistant organism readily respond to treatment. A National Committee for Clinical Laboratory Standards (NCCLS) recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infection in humans. Joint Stipulation 14. Moreover, if a high enough concentration of antimicrobial relative to MIC of the infecting organism can be achieved not only will the parent organism be killed but also the "resistant" mutation. Given the high levels of ciprofloxacin in the GI tract, clinical cure can be demonstrated for a *Campylobacter* with an MIC of 32 μg/ml. B-1913 P.17 L.8 – P.18 L.15.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

92. In the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences, 858 patients with culture-confirmed *Campylobacter* infections whose isolates had been susceptibility tested were asked about their medical treatment; persons who still had diarrhea at the time of interview, persons who were unable to give an estimated duration of diarrhea, and persons who reported not having diarrhea, were excluded from the analysis. Angulo WDT: p. 15, line 13-15, line 21-23; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

93. Of the 740 persons included in the analysis of data from the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences, the mean duration of diarrhea was 8 days (range, 2 to 21 days) for the 82 (11%) persons with ciprofloxacin-resistant *Campylobacter* infections and 7 days (range, 1 to 60 days) for the 658 persons with ciprofloxacin-susceptible *Campylobacter* infections (p=0.1). Angulo WDT: p. 15, line 26-29; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The above analysis was not adjusted for foreign travel and is therefore not valid. After correcting for confounding of foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30. Dr. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P.5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. B-1901 P.30. Dr. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P.59, P.57. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

94. In the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences, the mean duration of diarrhea among the 421 (57%) persons who did not take antidiarrheal medications (loperamide, diphenoxylate, or a prescribed antidiarrheal medication) for their illness was 9 days (range, 2 to 21 days) for the 39 patients with ciprofloxacin-resistant *Campylobacter* infections and 7 days (range, 2 to 60 days) for the 382 patients with ciprofloxacin-susceptible *Campylobacter* infections (p=0.05). Angulo WDT: p. 15, line 31-36; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The above analysis was not adjusted for foreign travel and is therefore not valid. After correcting for confounding of foreign

travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30. Dr. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P.5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. Dr. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P.59, P.57. Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

95. In the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences, the mean duration of diarrhea among the 67 of 421 (16%) persons not taking an antidiarrheal medication who also did not take an antimicrobial agent for their illness 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 WDT: p. 15, line 36-40; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The above analysis was not adjusted for foreign travel and is therefore not valid. After correcting for confounding of foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30. Dr. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P.5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. Dr. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P.59, P.57. Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e. no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

96. Of the 740 persons included in the analysis of data from the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences, 128 (17%), the mean duration of diarrhea among the 128 (17%) persons who took fluoroquinolones and no other antimicrobial agent or antidiarrheal medication for their illness was 8 days (range, 3 to 14 days) for the 17 patients with ciprofloxacin-resistant infections and 6 days (range, 2 to 31 days) for the 111 patients with ciprofloxacin-susceptible infections (p=0.08). Angulo WDT: p. 15, line 42-46; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The above analysis was not adjusted for foreign travel and is therefore not valid. After correcting for confounding of foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30. Dr. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P.5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. Dr. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P.59, P.57. Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

97. The multivariate analysis of variance (ANOVA) model used to analyze factors that were potentially associated with duration of diarrhea for the persons with *Campylobacter* infections and susceptibility results in the 1998-1999 FoodNet *Campylobacter* case-control study on medical consequences controlled for antimicrobial agent use, loperamide, diphenoxylate, or prescribed antidiarrheal medication use, having an underlying condition, and age; in this model, the mean duration of diarrhea was 9 days in persons with ciprofloxacin-resistant *Campylobacter* infections compared to a mean duration of diarrhea of 8 days in persons with ciprofloxacin-susceptible *Campylobacter* infections (p=0.05). Angulo WDT: p. 16, line 1-7; G-1452, Attachment 4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The above analysis was not adjusted for foreign travel and is therefore not valid. After correcting for confounding of foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30. Dr. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P.5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. Dr. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P.59, P.57. Bayer/AHI dispute this PFOF. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study show there is no significant difference in the mean duration of diarrhea (i.e., no "prolonged illness") for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

Bayer/AHI also object to the use of the term "resistant" in this PFOF. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). See our response to CVM's PFOF #85 on this point.

98. Ciprofloxacin-resistant *Campylobacter* may have some intrinsic factor or factors which make them more virulent than susceptible isolates. Angulo WDT: p. 16, line 27-28.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The PFOF presents unsubstantiated speculation. There is no evidence in the epidemiological experience available to date that there is an increase in virulence associated with fluoroquinolone-resistant *Campylobacter*. B-1900 P.3 L.17-18. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, L.12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment #4, P.116-118; G-1489 P.10-11. 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. B-1901 P.78.

Timothy Barrett (G-1453)

99. Dr. Barrett is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

100. Nalidixic acid was the first quinolone drug used to treat bacterial infections, beginning in the mid-1960s. Barrett WDT: page 2, lines 1 and 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

101. The fluoroquinolones, including ciprofloxacin and enrofloxacin, were created synthetically by adding one or two fluorine molecules to the basic quinolone ring structure. Barrett WDT: page 2, lines 3 to 5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

102. All of the quinolones physically interact with DNA gyrase, an enzyme essential for bacterial replication, and prevent it from functioning normally. Barrett WDT: page 2, lines 7 to 9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

103. Bacteria that have become resistant to fluoroquinolones (most often through mutation in the genes coding for subunits of the DNA gyrase molecule) are also typically resistant to nalidixic acid. The use of any fluoroquinolone can select for bacteria that are resistant to nalidixic acid as well as to the specific fluoroquinolone used and to other fluoroquinolones. It is not necessary that bacteria be exposed to nalidixic acid to become resistant to nalidixic acid. Barrett WDT: page 2, lines 9 to 15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

104. In any environment in which quinolones are present, bacteria that are resistant to those drugs will have a very large selective advantage over quinolone-susceptible bacteria. Barrett WDT: page 2, lines 16 to 18

Bayer/AHI Response: Bayer/AHI dispute this PFOF. In the first instance, whether "bacteria" that are resistant to fluoroquinolones will have a "very large selective advantage" over quinolone-susceptible bacteria, is inapplicable to this hearing. The only bacteria at issue in this hearing is *Campylobacter*, not all bacteria. Bayer has already agreed to PFOFs that address the selective pressure issue involving *Campylobacter*, see PFOFs #1421, 1430, 1431, 1577, so this PFOF is also repetitive and unnecessary.

105. *C. jejuni, C. coli,* and *C. lari* are sometimes referred to as the "thermophilic (heat liking) *Campylobacters*" because they grow well at 42° C, a temperature that inhibits the growth of

most bacteria of medical importance (most medically important bacteria prefer 37° C, normal body temperature). Barrett WDT: page 2, lines 29 to 32

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

106. Throughout the 1980s, susceptibility to nalidixic acid continued to be one of the primary criteria used to differentiate between the thermophilic *Campylobacters*, with *C. jejuni* and *C. coli* considered to be susceptible. Barrett WDT: page 3, lines 1 to 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

107. Up to 1988, Dr. Barrett considered *Campylobacter jejuni* resistance to nalidixic acid so rare that it could be used as a diagnostic criteria for distinguishing between *Campylobacter* strains. Barrett WDT: page 3, lines 10 to 12

Bayer/AHI Response: Bayer/AHI do not dispute that nalidixic acid was used as a diagnostic criteria for distinguishing between *Campylobacter* strains in the 1980s including 1988. The PFOF that resistance to fluoroquinolones was "rare" at that time is refuted by B-1901 P.79-80 and B-1851.

108. Dr. Barrett published a paper in 1988 describing finding only 2 of 42 *Campylobacter jejuni* resistant to nalidixic acid; and resistance to fluoroquinolones was even more unusual at that time. Barrett WDT: p. 3, lines 3-13; G-1609.

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Barrett found 2 of 42 (5%) fluoroquinolone resistance in 1988. The PFOF that resistance to fluoroquinolones was unusual at that time is refuted by B-1901 P.79-80 and B-1851.

109. As fluoroquinolone resistance emerged during the mid-1990s in *Campylobacter* isolates from human patients, nalidixic acid resistance emerged concordantly, making nalidixic acid-susceptibility a far less valuable test for speciation. During the 1990s, it was used by fewer and fewer researchers as a diagnostic criterion for identification of thermophilic *Campylobacters*. Barrett WDT: page 3, lines 20 to 24

Bayer/AHI Response: Bayer/AHI dispute that "As fluoroquinolone resistance emerged during the mid-1990s in *Campylobacter* isolates from human patients, nalidixic acid resistance emerged concordantly". First, "fluoroquinolone-resistance" (a term without a generally agreed on or clinically relevant definition for human patients) emerged in *Campylobacter* isolates from human patients long before the mid-1990s B-1901 P.79-80 and B-1851. Second, the statement "nalidixic acid resistance emerged concordantly" is incorrect B-1901 P.79-80 and B-1851. Finally, Bayer/AHI note that if this PFOF is true, NARMS, which added *Campylobacter* in 1997, was using a diagnostic criterion for identification of thermophilic *Campylobacter* that was outmoded.

110. The emergence of quinolone resistance in *C. jejuni* and *C. coli* may have incorrectly reduced the apparent incidence of these organisms (especially quinolone-resistant strains) in surveillance studies. Barrett WDT: page 3, lines 29 to 31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

111. Because *C. jejuni* and *C. coli* were originally considered to be nalidixic acid-susceptible, a researcher relying on this criterion to identify *C. jejuni or C. coli* would have excluded all quinolone-resistant isolates from surveillance for these two species. Barrett WDT: page 3, lines 31 to 34

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

112. In studies where a researcher relied on nalidixic acid susceptibility to identify *C. jejuni or C. coli*, the true incidence of fluoroquinolone-resistant *C. jejuni* and *C. coli* would have been drastically underreported. Barrett WDT: p. 3, lines 31-36.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

113. Despite the clinical use of nalidixic acid since the mid 1960s, nalidixic acid resistance was rare enough in *C. jejuni* that susceptibility to nalidixic acid was considered a critical characteristic in differentiating *C. jejuni* from *C. lari* throughout the 1980s. Barrett WDT: page 4, lines 4 to 7

Bayer/AHI Response: Bayer/AHI do not dispute that susceptibility to nalidixic acid was used to differentiate *C. jejuni* from the mid 1960s throughout the 1980s and later. Bayer/AHI dispute that nalidixic acid resistance was rare in the 1980s. B-1901 P.79-80 and B-1851.

114. The emergence of fluoroquinolone-resistant (and thus nalidixic acid-resistant) *C. jejuni* and *C. coli* in the mid-1990s has resulted in nalidixic acid-susceptibility being dropped as an identifying characteristic for these bacteria. Barrett WDT: page 4, lines 7 to 10.

Bayer/AHI Response: Bayer/AHI dispute that nalidixic acid-susceptibility was dropped as an identifying characteristic for *Campylobacter* in the mid-1990s since NARMS used it from 1996-2001. G-1478 P.9 L.31-46.

115. The emergence of quinolone-resistant *C. jejuni* in humans in the 1990s does not appear to be the result of nalidixic acid use in clinical medicine. Barrett WDT: p. 4, lines 10-12.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by G-1453 P.2 L.16-18; G-1478 P.2 L.29-32; and Joint Stipulations 6 and 8.

116. The purpose of bacterial subtyping is to take bacterial isolates that have already been characterized as belonging to a single species (*C. jejuni*, for example), and to further group them in some meaningful way. Barrett WDT: page 4, lines 19 to 21.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

117. By determining which bacterial isolates of the same species are most like each other, and thus most likely to have come from a common source, bacterial subtyping assists in finding links between patients and between patients and food or animal sources. Barrett WDT: page 4, lines 25 to 27.

Bayer/AHI Response: Bayer/AHI dispute this PFOF to the extent that it ignores indirect links between patients and food or animal sources. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

118. RAPD and PFGE are both techniques that enable scientists to compare strain similarity at the genetic level by examining large regions of the bacterial DNA. Barrett WDT: page 5, line 2 to 4.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

119. The purpose of molecular subtyping is to provide information that is useful to the type of investigation being conducted, not to identify the maximum number of types. Barrett WDT: page 5, lines 15 and 16.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

120. The data presented by Clow indicate that 77% of human *C. jejuni* isolates were types that were also seen in chickens. Barrett WDT: page 6, lines 40 and 41.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is misleading, incorrect and irrelevant. This statement refers to a study conducted in the south of England (B-250), therefore the findings of the study are not applicable to whether poultry is a source of campylobacteriosis in the United States. The study cited used fla-A & B PCR/RFLP typing to examine the relationship between chicken and human *Campylobacters*. Fla-A & B subtyping is not as highly discriminating as other subtyping methods. As a result, population overlaps will be

larger than more highly discriminating subtyping tests like PFGE, AFLP or MLST. Additionally, the most appropriate method of considering population overlaps is to assess how many clonal types are common to two populations. When this analysis is done the clonal overlap between chickens and humans in England using fla-A & B subtyping was found to be 23%. The isolate overlap cited here is an inappropriate method to consider coincidence of *Campylobacter* types in these two populations.

121. There is no universally accepted "gold standard" method for molecular subtyping of *C. jejuni.* Barrett WDT: page 7, lines 29 and 30.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. PFGE is validated for *Campylobacter.* G-1476 P.10 L.8.

Mary Bartholomew (G-1454)

122. Dr. Bartholomew is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination, except where Dr. Bartholomew testifies on matters related to causality and causal analysis and interpretation of data for microbial risk assessment. Dr. Bartholomew's background confirms has no experience in microbiological risk assessment except as it may relate to the CVM/Vose risk assessment.

123. Human food safety testing comprises a battery of toxicological studies, typically designed to look for chronic problems and cancers caused by long term exposures to trace amounts of chemicals in food or developmental problems in offspring of parents so exposed. The process of deciding on acceptable daily intakes (ADIs) from no observable effect levels (NOELs) based on these toxicology studies is a risk assessment activity. Bartholomew WDT: p. 2, lines 4-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The process of deciding on acceptable daily intakes (ADIs) is a risk management decision, not a risk assessment activity. Additionally, regardless of whether the activity constitutes "a risk assessment activity" such activity pertaining to chemical residues involves very different experience and expertise than those involved in characterizing the risks from living microorganisms such as *Campylobacter.*

124. The use of fluoroquinolones in chickens and the development of resistant *Campylobacter* in chickens were of concern to CVM for several reasons. First, chickens are reservoirs for many food borne pathogens including *Campylobacter* and *Salmonella.* For example, broiler carcass contamination measured in the processing plant estimates that 20% of broiler chickens in the United States are contaminated with *Salmonella* and over 80% are contaminated with *Campylobacter.* Consumption of food contaminated with these bacteria can lead to illness in susceptible. Second, *Campylobacter* is the most common known cause of bacterial food borne illness in the United States. Sporadic cases of *Campylobacter* account for approximately 99% of all *Campylobacter* cases. Epidemiological investigations

of sporadic infections have indicated that chicken is the most common source of human infection. Also, slaughter and processing of chickens may result in bacterial contamination on the carcass that can survive on retail product and result in human exposure during food preparation and consumption. Third, *Campylobacter* has been reported to develop resistance when fluoroquinolones are used. Finally, fluoroquinolones are used in human medicine empirically to treat gastrointestinal infections, such as campylobacteriosis and are important for use in many other therapeutic indications in human medicine. Increasing levels of resistance reduce the utility of fluoroquinolones in the empiric treatment of enteric illness. Bartholomew WDT: p. 3, lines 14-17, G-953

Bayer/AHI Response: Bayer/AHI object to this PFOF as containing compound proposed facts. Bayer/AHI dispute this PFOF. It is not an established fact that "Consumption of food [specifically, chicken] contaminated with these bacteria [specifically, *Campylobacter*] can lead to illness in susceptible [people]." Evidence in the record disputes the contention that chicken is a major source of campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record, particularly from the U.S., does not show or even merely suggest that poultry is a major source of campylobacteriosis. Finally, this PFOF ignores the declining campylobacteriosis rates in the U.S. (27% between 1996 and 2001). B-1042; G-1391.

125. Although some information on fluoroquinolone-resistant *Campylobacter* was available at the time that fluoroquinolones were approved, CVM approved fluoroquinolones for use in poultry as prescription only medication and prohibited its extra-label use. CVM expected that these measures would minimize the development of resistance. Bartholomew WDT: p. 3, lines 20-23; G-953

Bayer/AHI Response: Bayer/AHI object to this PFOF on the grounds that it is a set of compound facts, some of which Bayer/AHI agree with and some of which Bayer/AHI disagree with. Bayer/AHI agree with the first sentence. There was, in fact, a substantial amount of information on fluoroquinolone-resistant *Campylobacter* available at the time that fluoroquinolones were approved, including significant discussion about this issue at the Joint Advisory Committee in 1994, and nevertheless, CVM approved fluoroquinolones for use in poultry as prescription only medication and prohibited its extra-label use. Joint Stipulation 35; G-1478 P.4 L.26-38; B-1916 P.6 L.15-19; G-219 at P.53; B-1819 at P.96; B-1819 at P.99; B-1819 at P.165; B-1819 at P.61. However, Bayer/AHI disagree with the second sentence, in that what CVM "expected" to happen cannot be supported by the testimony of Dr. Bartholomew, since Dr. Bartholomew's testimony is only an unsupported opinion, and Dr. Bartholomew is not in a position to represent CVM in this capacity. Finally, this PFOF ignores the fact that the

information on fluoroquinolone-resistant *Campylobacter* that *was* available to CVM at the time that fluoroquinolones were approved in the U.S., particularly information from the Netherlands, involved the same conditions of use, i.e. as prescription only medication and prohibited extra-label use. B-1916 P.12 L.19 – P.13 L.3.

126. As part of its plans to address concerns about antimicrobial resistance, CVM decided to develop a risk assessment model that would be applicable to the general problem of antimicrobial resistance in food borne pathogens where that resistance is attributed to the use of an antimicrobial drug in animals. Bartholomew WDT: p. 3, lines 34-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

127. CVM became concerned about the potential public health impact of veterinary uses of the fluoroquinolones when, despite the precautionary use restrictions, emerging resistance to fluoroquinolones in *Campylobacter* was noted in humans. This concern was reinforced by scientific literature reporting the emergence of fluoroquinolone resistance in human campylobacteriosis after approval of poultry fluoroquinolones in several foreign countries, notably in the Netherlands and Spain. Bartholomew WDT: p. 3, lines 40-46; Exhibits G-190, G-320, G-491, G-505 and G-671.

Bayer/AHI Response: Bayer/AHI do not dispute that before enrofloxacin approval CVM became concerned about the potential public health impact of veterinary uses of the fluoroquinolones from scientific literature in the Netherlands, Spain and elsewhere. Bayer/AHI dispute that taken as a whole literature from foreign countries shows that resistance emerged "after approval of poultry fluoroquinolones in several foreign countries." Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Thus, describing resistance as "emerging" following the introduction of poultry fluoroquinolones and "despite the precautionary use restrictions" mischaracterizes the actual timing of its emergence.

128. A detailed description of the risk assessment model is given in the report document "The Human Health Impact of Fluoroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken" which was made available to the public on the CVM website in its final version on January 5, 2001. Bartholomew WDT: p. 4, lines 10-13; G-953

Bayer/AHI Response: Bayer/AHI do not dispute that a description of the CVM/Vose risk assessment model was described and made available as described in this PFOF. Bayer/AHI dispute the validity of the CVM/Vose model as a valid risk assessment model.

129. At the time the risk assessment was initiated, there were no food animal approvals for fluoroquinolones except those in poultry. Bartholomew WDT: p. 4, lines 21-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

130. Predictive microbiology is used in microbial risk assessments to model the increases or decreases in microbial load under varied conditions of food processing or storage. Bartholomew WDT: p. 4, lines 28-29

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

131. At the time CVM conducted its risk assessment, the data describing the complex exposure, host-pathogen interactions necessary to recreate an accurate dose-response relationship were lacking. Bartholomew WDT: p. 4, lines 33-34

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI disagree with the assumption embodied here that "data describing the complex exposure, host-pathogen interactions" are "necessary to recreate an accurate dose-response relationship". In fact, accurate dose-response models can be created without such detailed data.

132. In its *Campylobacter* risk assessment, CVM used an estimate using data collected by the Centers for Disease Control (CDC) FoodNet program of the annual number of people with campylobacteriosis as a starting point in its risk assessment modeling process. Bartholomew WDT: p. 4, lines 44-47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

133. The CDC had begun collecting prevalence data for campylobacteriosis in humans in FoodNet in 1996. FoodNet is an active surveillance system for food borne illness coordinated by the CDC with participating Health Departments reporting culture-confirmed cases. Bartholomew WDT: p. 5, lines 40-43

Bayer/AHI Response: Bayer/AHI dispute the first sentence in this PFOF. It is refuted by G-1452 P.3 L.36; A-200 P.3 L.8-10. Bayer/AHI do not dispute the second sentence.

134. Estimates used in the CVM *Campylobacter* risk assessment for the proportion of times persons with diarrhea sought care and submitted stool samples were obtained from a telephone survey conducted by CDC. Bartholomew WDT: p. 6, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

135. An estimate of the proportion of samples from persons with campylobacteriosis that actually yield *Campylobacter* was obtained from the literature. Bartholomew WDT: p. 6, lines 8-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

136. The CDC had begun collecting human *Campylobacter* isolates and testing for resistance in the National Antimicrobial Resistance Monitoring System (NARMS) in 1997. Bartholomew WDT: p. 6, lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

137. The amount of chicken consumed is available from the United States Department of Agriculture (USDA) Economic Research Service (ERS). As part of the NARMS program, USDA Agricultural Research Service (ARS) had in 1998 begun performing susceptibility testing on *Campylobacter* from chicken collected by the Food Safety Inspection Service (FSIS). Bartholomew WDT: p. 6, lines 17-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

138. The estimation used by CVM in its *Campylobacter* risk assessment of the number of campylobacteriosis cases seeking care who are prescribed a fluoroquinolone and who have fluoroquinolone-resistant campylobacteriosis attributed to the use of fluoroquinolones in chickens consists of four sub-component estimates. The estimates are for the total number of cases of campylobacteriosis; the number of campylobacteriosis cases attributed to chicken; the proportion of cases with resistant *Campylobacter* where the resistance is attributed to the use of fluoroquinolones in chickens; and the number of resistant cases attributed to chicken. that seek medical care and are treated with fluoroquinolones. Bartholomew WDT: p. 6, line 47- p. 7, line 2

Bayer/AHI Response: Bayer/AHI do not dispute that CVM's estimation was performed by this method, but do dispute that CVM's method of estimation is correct.

139. The total number of cases of campylobacteriosis contracted in the United States annually is estimated by the CDC from the total number of reported isolations in a year. The CVM used the process developed by the CDC and modeled the uncertainties in parameters used in the process of deriving the estimate. The CDC estimates the total number of cases by taking the observed number of culture-confirmed cases within FoodNet sites and multiplying it by factors that account for undercounting and under-reporting. Bartholomew WDT: p. 7, lines 5-10

Bayer/AHI Response: Bayer/AHI do not dispute that CVM's estimation was performed by this method, but do dispute that such a method of estimation is correct.

140. The CVM model derives the uncertainty distribution for the estimated mean number of cases of campylobacteriosis cases attributed to chicken. Two case-control studies from the literature were used for input values for determining the proportion of all campylobacteriosis cases attributable to chicken (Harris et al. 1986; Deming et al. 1987). In the Harris study, an attributable fraction of 45.2 percent was given; in the Deming study, the attributable fraction was 70 percent. Bartholomew WDT: p. 8, lines 12-16.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The numbers obtained by CVM from the Harris and Deming studies, of 45.2 and 70 percent, are *not* attributable fractions as defined and interpreted by CVM and its witnesses (namely, the fractions of campylobacteriosis cases caused by chicken consumption). Cox B-1901 P.38-39. Neither the Harris et al. nor the Deming et al. study isolated the portion of CP 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. Hence, the attributable fractions used in the CVM-Vose model cannot correctly be interpreted causally, as CVM has done. Cox B-1901 P.38-39. Moreover, Bayer/AHI disagree that "The CVM model derives the uncertainty distribution for the estimated mean number of cases of campylobacteriosis cases attributed to chicken." The uncertainty distribution in the CVM model does not include key uncertainties due to the model form selected, the attribution formulas used, the variables selected, the coding of those variables, or the studies selected. Cox B-1901 P.15. Hence, it does not quantify the full uncertainty distribution for the estimated mean number of cases of campylobacteriosis cases attributed to chicken. We also disagree that "Two case-control studies from the literature were used for input values for determining the proportion of all campylobacteriosis cases attributable to chicken (Harris et al. 1986; Deming et al. 1987)." These studies do not provide "input values for determining the proportion of all campylobacteriosis cases attributable to chicken" in the sense that CVM has defined "attributable to" (as "caused by"). They provide association-based risk measures that do not correct for all relevant confounders and that do not have the causal interpretations that CVM has given them. Cox B-1901 P.38-39. This part of the PFOF is refuted by (Cox B-1901 P.38-39). Bayer/AHI also disagree that using the Deming and Harris studies was appropriate since both were out dated and unrepresentative of the national population. B-1901 P.38-39, P.57-64.

141. Data from the *Campylobacter* case-control study assisted in the removal of proportions of resistance attributed to other sources. Bartholomew WDT: p. 9, lines 5-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bartholomew has stated in her direct testimony that all resistance (for domestically acquired non-treatment cases) was attributed to chicken. Bartholomew, G-1454 P.9 L.28, 29. The case-control data were not used to remove the "proportions of resistance attributed to other sources" such as drinking water, pet ownership, farm visits, restaurant dining, etc. This statement suggests that a needed correction (removal of proportions of resistance attributable to other sources) was made, when in fact it was omitted.

142. The proportion of resistance among domestically acquired cases was multiplied by the number of chicken-associated cases to estimate the mean number of cases resistant and attributed to resistance from chicken. Bartholomew WDT: p. 9, lines 29-31

Bayer/AHI Response: This embodies a false assumption that the product of "proportion of resistance among domestically acquired cases" and "number of chicken-associated cases" gives an estimate of "the mean number of cases resistant and attributed to resistance from chicken". This implicit assumption is mistaken. It is refuted by (Cox B-1901 P.38-39), especially bullet point on "Wrong quantity calculated".

143. To estimate the mean number of resistant cases who had infections attributed to consumption of chicken who seek care and are treated with a fluoroquinolone and its associated uncertainty distribution, the mean number of cases with resistant campylobacteriosis attributed to chicken is multiplied by the respective care-seeking proportions discussed in the Bartholomew written direct testimony. Bartholomew WDT: p. 10, lines 13-16

Bayer/AHI Response: Bayer/AHI do not dispute that CVM's estimation was performed by this method, but do dispute that such a method of estimation is correct. Cox B-1901 P.38-39.

144. The proportion of cases who receive antibiotics and the proportion who receive a fluoroquinolone were derived from the 1998-1999 CDC *Campylobacter* case control study. Bartholomew WDT: p. 10, lines 20-21.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

145. CVM's *Campylobacter* Risk Assessment included estimation of the quantity of chicken with fluoroquinolone-resistant *Campylobacter* consumed and modeling the uncertainties in the estimate. Bartholomew WDT: p. 11, lines 13-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

146. Inputs to estimate the quantity of consumed chicken were taken from USDA Economic Research Service (ERS) with product sent for rendering, product diverted for pet food, exports, water added during processing and imports subtracted. The proportion of chicken with *Campylobacter* and the portion of *Campylobacter* that were fluoroquinolone-resistant were determined from samples that FSIS and ARS analyzed as part of the NARMS project. Bartholomew WDT: p. 11, lines 14-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

147. The CVM *Campylobacter* risk assessment enables the estimation of the probability that a pound of chicken meat with fluoroquinolone-resistant *Campylobacter* will result in a case of fluoroquinolone-resistant campylobacteriosis in a specific year. Bartholomew WDT: p. 12, lines 22-24

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The probability that a pound of chicken meat with fluoroquinolone-resistant *Campylobacter* will result in a case of fluoroquinolone-resistant campylobacteriosis in a specific year depends on the microbial load of *Campylobacter* in the chicken meat. The CVM model does not quantify the microbial load distribution and does not provide any way to estimate how it changes from year to year. Cox (B-1901) P.55, P.83-87.

148. For the years for which the CVM *Campylobacter* risk assessment was done, the model indicates that there would be a case of human fluoroquinolone-resistant campylobacteriosis from chicken for every 7900 pounds of chicken contaminated with fluoroquinolone-resistant *Campylobacter*. Bartholomew WDT: p. 13, Figure 6 and lines 3-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. We disagree with the causal interpretation embodied in the words "from chicken". The CVM *Campylobacter* risk assessment contains no causal analysis or causal modeling. The assertion that it indicates cases "from chicken" (i.e., caused by consumption of chicken) is therefore unjustified.

149. In 1995 about 88 percent of chicken carcasses yielded *Campylobacter* in the slaughterhouse, as reported by the USDA FSIS. This compares to 1-4 percent found on beef at slaughter in 1993. Bartholomew WDT: p. 14, lines 8-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

150. The microbial load of *Campylobacter* is higher on chicken than on other food animal products. Bartholomew WDT: p. 14, lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. "On chicken" is vague. It has not been shown that the microbial load of *Campylobacter* is higher on chicken than on other food animal products *at the point of consumption,* which is the only point that is relevant for dose-response modeling and risk assessment.

151. The CVM risk assessment calculated that approximately 50 pounds of domestically produced chicken per person was consumed in 1998/1999. This value was derived by subtracting off water weight and amounts sent for rendering and export from the pounds of chicken produced as given by USDA ERS. The combined information about *Campylobacter* contamination levels on chicken and the substantial exposure through consumption provide further credence to the epidemiologic study findings. Bartholomew WDT: p. 14, lines 11-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. We disagree that "The combined information about *Campylobacter* contamination levels on chicken and the substantial exposure through consumption provide further credence to the epidemiologic study findings." In fact, no data have been provided on exposure through consumption. It has not been shown that such exposure is "substantial." But if it is "substantial", as claimed, then it provides further evidence that these exposures usually do not cause campylobacteriosis (since most people eat chicken and do not get sick with campylobacteriosis.)

152. The mean value for the distribution of the estimated proportion of cases that is attributed to chicken in the CVM *Campylobacter* risk assessment is 57%. The proportion of cases attributable to chicken was multiplied times the number of cases of campylobacteriosis to estimate the number of cases of campylobacteriosis attributed to chicken. Bartholomew WDT: p. 14, lines 19-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF. We disagree that 57% represents the estimated proportion of cases that is attributed to chicken, in the sense of "attributed to" (as "caused by") defined by CVM. (Cox, 2001, Chapter 4). We agree that this is what the CVM risk assessment states, but we disagree that 57% in fact represents the estimated proportion of cases that is attributed to chicken, in the sense of "attributed to" (as "caused by") defined by CVM.

Cox B-1901 P.38-39. The numbers obtained by CVM from the Harris and Deming studies, of 45.2 and 70 percent, are not attributable fractions as defined and interpreted by CVM and its witnesses (namely, the fractions of campylobacteriosis cases caused by chicken consumption) Cox B-1901 P.38-39. Neither the Harris et al. nor the Deming et al. study isolated the portion of CP 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. Hence, the attributable fractions used in the CVM-Vose model cannot correctly be interpreted causally, as CVM has done. Cox B-1901 P.38-39. Bayer/AHI also disagree that using the Deming and Harris studies was appropriate since both were out dated and unrepresentative of the national population. B-1901 P.38-39, P.57-64.

153. The mean value for the distribution of the estimated proportion of cases that is attributed to chicken in the CVM *Campylobacter* risk assessment is 57%. Bartholomew WDT: p. 14, lines 19-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF. We agree that this is what the CVM risk assessment states, but we disagree that 57% in fact represents the estimated proportion of cases that is attributed to chicken, in the sense of "attributed to" (as "caused by") defined by CVM. Cox B-1901 P.38-39. The numbers obtained by CVM from the Harris and Deming studies, of 45.2 and 70 percent, are not attributable fractions as defined and interpreted by CVM, and its witnesses (namely, the fractions of campylobacteriosis cases caused by chicken consumption). Cox B-1901 P.38-39. Neither the Harris et al. nor the Deming et al. study isolated the portion of CP 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. Hence, the attributable fractions used in the CVM-Vose model cannot correctly be interpreted causally, as CVM has done. Cox B-1901 P.38-39. Bayer/AHI also disagree that using the Deming and Harris studies was appropriate since both were out dated and unrepresentative of the national population. B-1901 P.38-39, P.57-64.

154. Dr. Bartholomew concluded that the reported proportions of resistance among isolates from poultry are likely to be underestimates, and that the estimates of resistance among humans in the CVM *Campylobacter* risk assessment obtained by subtraction of other sources of resistance are likely to be nearer to the real values. Bartholomew WDT: p. 15, lines 41-44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

155. The proportion of resistant cases attributed to domestically-produced chicken among all cases attributed to domestically-produced chicken was estimated to be about 14.2% in 1998 in the CVM *Campylobacter* risk assessment. Bartholomew WDT: p. 16, lines 29-31

Bayer/AHI Response: Bayer/AHI do not dispute that this is what the CVM risk assessment states, but disagree that it is a correct statement.

156. The CVM risk assessment used an epidemiological approach to estimate the mean number of individuals impacted by fluoroquinolone-resistant campylobacteriosis attributable to chicken consumption. Individuals considered to be impacted were those with campylobacteriosis, who had fluoroquinolone-resistant infections, had sought care, and were prescribed a fluoroquinolone antibiotic to treat the infections. Bartholomew WDT: p. 17, line 43 -p. 18, line 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI disagree that the CVM risk assessment estimated the mean number of individuals impacted by fluoroquinolone-resistant campylobacteriosis attributable to chicken consumption. This may have been CVM's intent, but Bayer/AHI dispute that the technical methods used actually produced an estimate of the mean number of individuals impacted by fluoroquinolone-resistant campylobacteriosis attributable to chicken consumption. Instead, evidence shows that CVM's assessment produced meaningless numbers, driven by arbitrary assumptions, that it now seeks to interpret as meaningful estimates of number of individuals impacted by fluoroquinolone-resistant campylobacteriosis attributable to chicken consumption.

157. In 1998, the mean number (the number of cases that would occur on average if 1998 were to be repeated many times) was estimated to be 8,678 between the 5th percentile, 4,758 and the 95th percentile, 14,369. This corresponds to a risk of one impacted individual in every 34,945 individuals in the United States. Bartholomew WDT: p. 18, lines 2-6

Bayer/AHI Response: Bayer/AHI do not dispute that this is what CVM claims. Bayer/AHI disagree that CVM has actually estimated the means or confidence percentiles correctly. Hence, Bayer/AHI dispute that the numbers it offers correspond to any real risk, including a risk of one impacted individual in every 34,945 individuals in the United States.

158. In 1999, the mean number was estimated to be 9,261 between the 5th percentile, 5,227 and the 95th percentile, 15,326. This corresponds to a risk of one impacted individual in every 32,912 individuals in the United States. Bartholomew WDT: p. 18, lines 6-8

Bayer/AHI Response: Bayer/AHI do not dispute that this is what CVM claims. Bayer/AHI disagree that CVM has actually estimated the means or confidence percentiles correctly. Hence, Bayer/AHI dispute that the numbers it offers correspond to any real risk.

John Besser (G-1455)

159. Dr. Besser is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

160. The use of antibiotics in food production has a number of potential impacts on human health, including facilitating the emergence of drug resistance and increasing the proportion

of drug-resistant bacteria transmitted to humans. Besser WDT: p. 2, line 45 through p. 4, line 29.

Bayer/AHI Response: Bayer/AHI dispute this PFOF especially as relates to the issues applicable to this hearing (fluoroquinolone use and resistant *Campylobacter*). Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone-resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

161. The chance that a resistant clone will emerge from antibiotic use is related to the amount of antibiotic used, and the manner in which it is used. Besser WDT: p. 3, line 8-24; G-366.

Bayer/AHI Response: Bayer/AHI do not dispute the facts of this PFOF, but dispute the PFOF on the ground that it is inapplicable to the issues of this hearing. This PFOF does not identify any bacteria when it uses the term "clone". The only bacteria at issue in this hearing is *Campylobacter*. In addition, Bayer/AHI has already agreed to PFOFs that address the selective pressure issue involving *Campylobacter*, see PFOFs 1421, 1430, 1431, 1577, so this PFOF is also repetitive and unnecessary.

162. Evidence for the role that fluoroquinolone use in poultry plays in the emergence of fluoroquinolone resistance in humans includes: (a) temporal and epidemiologic association between the approval of fluoroquinolones for use in animals and the emergence of fluoroquinolone-resistant disease in humans in multiple countries; (b) experimental feeding experiments in poultry showing the rapid emergence of fluoroquinolone resistance in *Campylobacter* following fluoroquinolone treatment; and (c) biologic plausibility, i.e. that the observations in (a) and (b) above fit with what is known about the molecular mechanisms of fluoroquinolone resistance and the relative rapidity with which the mutations leading to fluoroquinolone resistance would be expected to occur. Besser WDT: p. 3, line 10-24; G-586; G-403; G-315; G-1350.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone-resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there

is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

163. The proportion of drug-resistant bacteria transmitted from food animals to humans is likely to increase as a result of antibiotic use in the animal source. Besser WDT: p. 3, line 26 through p. 4, line 22; G-1350.

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that it is inapplicable to the issues of the hearing as it is unsupported and overly general. The only bacteria at issue in this hearing is *Campylobacter*. With respect to *Campylobacter* it is clear that there are other sources than food animals. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Predominant routes of fluoroquinolone resistant *Campylobacter* infection in humans are other than associated with poultry. B-1910 P.7 L.20-22. It is clear that there exist important sources of *Campylobacter* infection other than food animals. *See also*, Joint Stipulation 32.

164. The use of antibiotics in a food animal population where resistant clones have already emerged increases the proportion of resistant bacteria in the food animals, which increases the probability that a human who becomes ill directly or indirectly (via cross-contamination of other material) from that food animal source will acquire a resistant infection. Besser WDT: p. 3, line 26 through p. 4, line 22; G-1350.

Bayer/AHI Response: Bayer/AHI dispute this PFOF especially as relates to the issues applicable to this hearing (fluoroquinolone use and resistant *Campylobacter*). Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone-resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. This PFOF is not applicable to the issues in this hearing in that it does not address the specifics regarding *C.*

jejuni and *coli*, fluoroquinolone susceptibility and poultry. *Campylobacter jejuni* and *coli* are weakly clonal and representatives of the few clones identified to date are infrequent causes of infection in either humans or poultry. B-1908 P.29, 31, 35-36.

165. Increasing antibiotic use in the food source increases the number of resistant infections in humans. Besser WDT: p. 3, line 26 through p. 4, line 22.

Bayer/AHI Response: Bayer/AHI dispute this PFOF especially as relates to the issues applicable to this hearing (fluoroquinolone use and resistant *Campylobacter*). Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone-resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

166. Control of antibiotic resistance spread relies both on limiting the emergence of resistance and limiting its spread. Besser WDT: p. 2, line 45 through p. 4, line 29.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF as a general proposition. The same can be said for preventing any disease of bacterial or viral origin. Moreover, certain control measures, such as irradiation or proper cooking could eliminate susceptible (as well as resistant) organisms from food products.

167. Withdrawal of fluoroquinolones for animal use should reduce the proportion of fluoroquinolone-resistant bacteria in the animals, and hence reduce fluoroquinolone-resistant infections in humans. Besser WDT: p. 2, line 45 through p. 4, line 29.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The reverse statement cannot be accepted if the forward statement (#165) is not accepted.

168. Antimicrobial susceptibility testing is used to determine if a given bacterium is likely to be inhibited or killed by antibiotics used to treat the infections that they cause. Besser WDT: p. 4, line 34-36.

Bayer/AHI Response: Bayer/AHI agree to this PFOF. However, to provide useful information, the test must be validated for the specific organism and drug combination and related to clinical outcome. For fluoroquinolones and *Campylobacter*, a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14) and the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

169. The most common way to measure antibiotic resistance is by reporting a "minimal inhibitory concentration," or "MIC." Besser WDT: p. 4, line 36-37.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

170. MIC is a laboratory test designed to predict the minimum amount of antibiotic needed to inhibit or kill the bacterium in question. Besser WDT: p. 4, line 37-39.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As indicated by PFOF 169 and 174, MIC is not a test, it is the outcome or result of a test.

171. The higher the MIC, the more antibiotic is needed to kill the organism or inhibit its growth. Besser WDT: p. 4, line 39-40.

Bayer/AHI Response: Bayer does not dispute this PFOF as a general proposition when performing *in vitro* testing. As relates to the issues in this case (fluoroquinolone resistance in *Campylobacter*), "high" MIC may have no clinical significance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. Substantial evidence demonstrates that *in vitro* resistance of *Campylobacter* to fluoroquinolones does not correlate to treatment failure or other clinical impact. B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean duration of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

172. In general, very high MIC values correspond to "resistant" bacteria (unaffected by treatment with the antibiotic), and very low MIC values correspond to "susceptible" bacteria (easily treated with the antibiotic). Besser WDT: p. 4, line 40-42.

Bayer/AHI Response: Bayer does not dispute this PFOF as a general proposition when performing *in vitro* testing. As relates to the issues in this case (fluoroquinolone resistance in *Campylobacter*, "high" MIC may have no clinical significance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-

23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "affect treatment."

173. Standardized antimicrobial susceptibility testing methods are available for a number of infection-causing bacteria and antibiotics commonly used to treat them. Besser WDT: p. 4, line 43-44.

Bayer/AHI Response: Bayer/AHI agree to this PFOF. However, a NCCLS recognized breakpoint indicating loss of clinical effectiveness for fluoroquinolone drug use in *Campylobacter* infections in humans has not been established. Joint Stipulation 14.

174. The term "breakpoint" refers to an MIC value (or the diameter of a zone of growth inhibition with some methods) used to indicate susceptible, intermediately susceptible, or resistant bacteria. Besser WDT: p. 4, line 46 through p. 5, line 2.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

175. Antimicrobial susceptibility testing standards, MIC values and established breakpoints do not exist for many disease-causing bacteria and associated antibiotics. Besser WDT: p. 5, line 8-9.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

176. When the Smith study of fluoroquinolone resistance in *Campylobacter jejuni* was conducted, there existed neither standardized methods nor established breakpoints. Besser WDT: p. 5, line 15-16.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

177. The Smith study of fluoroquinolone resistance in *Campylobacter jejuni* chose a commonly used antimicrobial susceptibility testing method called the E-test, and used breakpoints for the most similar bacterial family for which standards have been established, *Enterobacteraceae*. Besser WDT: p. 5, line 16-19.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. *Campylobacter* and genera in the family Enterobacteraceae are not similar. The use of breakpoints established for Enterobacteriacae is not relevant as the genera within the Family Enterobacteriacae differ significantly in many characteristics from *Campylobacter*, including resistance mechanism for fluoroquinolones. The NCCLS breakpoint for two different bacteria to the same antimicrobial may be very different. G-1481 P.5 ¶ 10; B-1913 P.19 L.15-19. Additionally, the E-test is not the NCCLS standard for susceptibility testing for *Campylobacter* resistance to ciprofloxacin and it tends to yield much higher resistant MICs than those measured by agar dilution (the NCCLS standard) at the resistant end of the MIC ranges. B-1913 P.20 L.12-22.

178. In the Smith study of fluoroquinolone resistance in *Campylobacter jejuni*, most isolates (96%) had MICs of >32 μg/ml, or 8 times the breakpoint level of 4.0 μg/ml specified in the NCCLS standards for *Enterobacteraceae*. Besser WDT: p. 5, line 29-31.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The breakpoint level for *Enterobacteracea* is not applicable for *Campylobacter*. The E-test, used in this study (G-589) is not a NCCLS approved method for determination of MIC's *in vitro* for *Campylobacter*. The NCCLS breakpoint for two different bacteria to the same antimicrobial may be very different. G-1481 P.5 ¶ 10; B-1913 P.19 L.15-19. Additionally, the E-test is not the NCCLS standard for susceptibility testing for *Campylobacter* resistance to ciprofloxacin and it tends to yield much higher resistant MICs than those measured by agar dilution (the NCCLS standard) at the resistant end of the MIC ranges. B-1913 P.20 L.12-22.

179. Given the broad bimodal nature of MIC values (i.e., very high or very low levels) in the Smith study of fluoroquinolone resistance in *Campylobacter jejuni*, the basic interpretations, i.e., "resistant" or "susceptible," are valid. Besser WDT: p. 5, line 35-37.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The distribution of *in vitro* MICs which is referred to here constitutes a basis for the determination of microbiological susceptibility and resistance. The determination of clinical breakpoints warrants inclusion of clinical, pharmacokinetic and pharmacodynamic data. Such data has not been included in setting the breakpoints used by Smith. B-1913 P.17 L.12-17. There are no NCCLS approved clinical breakpoints for fluoroquinolones and *Campylobacter*. Joint Stipulation 14. Moreover, The NCCLS breakpoint for two different bacteria to the same antimicrobial may be very different. G-1481 P.5 ¶ 10; B-1913 P.19 L.15-19, P.20 L.3-11.

180. DNA fingerprinting tells us whether a group of disease-causing bacteria with identical DNA fingerprints is more likely to have a common origin than a group with different DNA fingerprints. Besser WDT: p. 6, line 23-25.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

181. DNA fingerprinting serves to strengthen statistical associations that may already be present by removing from consideration cases less likely to be associated. Besser WDT: p. 6, line 28-30.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is misleading because it is taken out of context. The context is that DNA fingerprinting cannot be interpreted independently of an epidemiologic analysis. G-589.

182. DNA fingerprinting of bacteria allows patterns of disease in the population to be seen that might otherwise be too difficult to differentiate from background disease activity. Besser WDT: p. 6, line 41-43.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is misleading because it is taken out of context. The context is that one still has to prove that the revealed pattern has

meaning. This is usually done in the context of epidemiological studies such as a case control study. G-589.

183. DNA fingerprinting works by facilitating recognition of "clusters" of disease. Besser WDT: p. 7, line 1-3.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is misleading. It is misleading because it is taken out of context. The context is that one still has to prove that the revealed patterns or clusters have meaning. This is usually done in the context of epidemiological studies like the case control study. G-589.

184. DNA fingerprinting involves the use of "restriction" enzymes that cut the bacterial DNA into different sized fragments, which, when electrically separated from each other, form a pattern; the locations of bacterial DNA sequences that the enzymes recognize determine the sizes of the fragments. Besser WDT: p. 7, line 13-43.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

185. By using more enzymes in DNA fingerprinting, one can essentially examine more locations, identify more patterns, and find more differences between bacteria, thus increasing the "resolution" of the test. Besser WDT: p. 7, line 45 through p. 8, line 1.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

186. Since bacteria are constantly multiplying and changing, it is always possible to find differences between samples in DNA fingerprinting. Besser WDT: p. 8, line 1-2.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

187. The "right" level of resolution in DNA fingerprinting is achieved when cases cluster in a manner that proves to be meaningful after epidemiologic analysis. Besser WDT: p. 8, line 12-13.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

188. In DNA fingerprinting, the most useful classification level is one where meaningful relationships can be drawn from the associated epidemiologic analyses. Besser WDT: p. 9, line 5-7.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

189. No test method for DNA fingerprinting measures all of the differences between the DNA of the samples; rather, each method examines differences in selected "markers," which are used to reflect broader differences. Besser WDT: p. 9, line 12-15.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is erroneous. Many frequently used subtyping methods do not use "markers" at all.

190. The polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method examines differences in the gene that codes for the bacterial flagellum, which is an appendage of the bacterium that gives it motility. Besser WDT: p. 9, line 23-27.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

191. Since the flagellum is exposed to the immune system of animal hosts, it is thought that selective pressure would cause this gene to change at a rate which would make it a good indicator of short-term epidemiologic linkage. Besser WDT: p. 9, line 27-30.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

192. The flagellar gene ("*fla*A") is not in any way associated with the genes that cause resistance to ciprofloxacin or any other antibiotic, and one would not expect the method to reflect differences in susceptibility. Besser WDT: p. 9, line 30-33.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

193. The polymerase chain reaction restriction fragment length polymorphism method was chosen for the Smith study of fluoroquinolone resistance in *Campylobacter jejuni* since it was being considered as a national subtyping standard at that time, and is relatively fast and simple to perform. Besser WDT: p. 9, line 33-35.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

194. The pulsed-field gel electrophoresis (PFGE) method measures gene sequences, which could occur on any part of the bacterial DNA. Besser WDT: p. 9, line 37-44.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

195. Pattern differences in the pulsed-field gel electrophoresis (PFGE) method *may* reflect differences in antibiotic susceptibility, or any other factor. Besser WDT: p. 9, line 41-46.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is speculation. There is no evidence relating to any accounts genome regions impacted by restriction enzymes used in PFGE.

196. The Smith study of fluoroquinolone resistance in *Campylobacter jejuni* found a high degree of concordance between fluoroquinolone-resistant subtypes found in domestically acquired human infections and domestically produced chicken (92.3%), which implicates chicken as a likely source for fluoroquinolone-resistant human infections. Besser WDT: p. 10, line 7-10; G-589.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Smith did not identify a "high" degree of association, but only identified "an association." G-589 P.6-7. Additionally, this statement is scientifically unjustified and inconsistent with the reported data of study G-589. Conditional probability associations establish that the biological plausibility of finding fluoroquinolone-resistant associations before finding fluoroquinolone-sensitive associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that a fluoroquinolone-resistant chicken strain will cause a fluoroquinolone-resistant human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a *C. jejuni* from chicken is fluoroquinolone-resistant X probability that a domestically acquired human case is fluoroquinolone-resistant for 1998). Conversely, the same conditional probability for a chicken fluoroquinolone-sensitive strain causing a human fluoroquinolone-sensitive infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that fluoroquinolone-sensitive associations would be found over fluoroquinolone-resistant associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). Moreover, genetic typing analysis showing overlapping *Campylobacter* genotypes or "a high degree of concordance" between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

197. The association between fluoroquinolone-resistant subtypes in domestically acquired human infections and domestically produced chicken found in the Smith study of fluoroquinolone resistance in *Campylobacter jejuni* was further strengthened by the observation that other groups of infected humans, such as those with fluoroquinolone-sensitive infections or those who likely acquired their infections through foreign travel, did not share the same high proportion of common subtypes with fluoroquinolone-resistant domestic chicken isolates (44.4% and 35% shared subtypes, respectively). Besser WDT: p. 10, line 10-15; G-589.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is scientifically unjustified and inconsistent with the reported data of study G-589. Conditional probability associations establish that the biological plausibility of finding fluoroquinolone-resistant associations before finding fluoroquinolone-sensitive associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that a fluoroquinolone-resistant chicken strain will cause a

fluoroquinolone-resistant human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a *C. jejuni* from chicken is fluoroquinolone-resistant X probability that a domestically acquired human case is fluoroquinolone-resistant for 1998). Conversely, the same conditional probability for a chicken fluoroquinolone-sensitive strain causing a human fluoroquinolone-sensitive infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that fluoroquinolone-sensitive associations would be found over fluoroquinolone-resistant associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

John Carey (G-1456)

198. Dr. Carey is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

199. Young chickens that are produced for meat are called broilers. Carey WDT: page 2, line 4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

200. Male turkeys are called Toms and female turkeys are called Hens. Carey WDT: page 2, line 6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

201. Cleanout frequency (for poultry raising facilities) varies depending on the operation and owner husbandry practice but broiler facilities are typically cleaned out every 12-18 months. Broiler facilities may have as many as 5-7 successive flocks per year and turkey facilities 4 successive flocks per year, depending on final body weight and market considerations. Carey WDT: p. 3, lines 3-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

202. In all poultry housing facilities except all-slat broiler breeder facilities, birds are in contact with fecal material. Since it is normal behavior for birds to scratch and peck at the ground, they ingest fecal material (coprophagy) and related contamination from other birds in the facility. Carey WDT: p. 3, lines 18-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

203. Feeding, environmental and all other husbandry practices are largely applied to the flock as a whole. Individual birds are observed and care for if necessary; but generally, individual bird management or treatment is not feasible and is seldom necessary. Carey WDT: page 4, lines 27-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

204. Since birds are housed in large common groups, with common disease threats, health related care is typically administered on a flock basis via the water or feed. In such cases, all birds receive medicated feed or water. This is viewed as the most practical manner to treat poultry health episodes since the entire flock has exposure to the challenge due to their common housing, feeding, drinking, and litter exposure. Carey WDT: page 4, lines 31-37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

205. CVM did not proffer a PFOF #205.

Hubert Endtz (G-1457)

206. Dr. Endtz is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

207. Although many subspecies of *Campylobacter* have been described in the last 20 years, *Campylobacter jejuni* is by far the most frequently isolated as it is responsible for >90% of clinical infections. Endtz WDT: page 2, lines 17-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

208. Three distinct forms of infections caused by *C. jejuni* are known: (a) acute diarrhea; (b) extra-intestinal infections; and (c) non-supurative post-infectious complications. Endtz WDT: page 2, lines 22-23

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Many persons with *Campylobacter* infections - perhaps as many as 25% of all persons infected - do not exhibit clinical symptoms and are therefore "asymptomatic". B-1909 P.3 L.23, P.4 L.1-3, G-70 P.3. In addition, only a very small fraction of persons with *Campylobacter* enteritis seek treatment and are evaluated by a physician; e.g., based on FoodNet data, it was estimated that only 1 in 18 persons with *Campylobacter* seek treatment. G-615 P.3, B-1909 P.R L.4-6. The vast majority of *Campylobacter* cases, therefore, would fail to fall within the three categories set forth by the witness in this PFOF.

209. The most common manifestation of *C. jejuni* is an acute diarrhea. The incubation period ranges from 1 to 7 days. There is a so-called prodromal phase preceding the diarrhea of 12-48 hours with fever, headache and abdominal pain. Endtz WDT: page 2, lines 31-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is inaccurate. While Bayer/AHI agree that a so-called prodromal phase and acute diarrhea are common manifestations

of *C. jejuni* enteritis, not all persons infected with *C. jejuni* exhibit the prodromal phase (G-70 P.4; G-1616 P.3) or acute diarrhea (G-70, P.4). As noted in the response to PFOF 208, perhaps as many as 25% of all persons infected with *Campylobacter* are asymptomatic. B-1909 P.3 L.21-23, P.4 L.1-3.

210. Diarrhea associated with *Campylobacter jejuni* varies from very mild to massive, watery or grossly, bloody stools. Fifteen or more stools may pass on the worst day of illness. Endtz WDT: page 2, lines 35-36

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness has misquoted the reference for the statement that "fifteen or more stools may pass on the worst day of illness". The reference, G-1616, does not make that statement.

211. The mortality associated with *Campylobacter* diarrhea in the United States has been estimated at 8/10,000 and 24/10,000, respectively, cultured-confirmed cases in two different studies. Endtz WDT: page 2, lines 44-46; G-1644 and G-1783.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The mortality rates cited in this statement do not refer to current data. The literature cite many figures on the estimated mortality attributed to *Campylobacter* in the United States. A recent publication gives a mortality rate of *Campylobacter* infections in the United States of 0.5 per 10,000 infections. Kist DWT B-1906. P.3 L.19-22, P.4 L.1-16, P.4 L.1-16. In any event, deaths are rare and almost always related to serious underlying disease in developed countries. B-1906 P.3 L.19-20; B-1909 P.7 L.8-13; G-1B-44 P.1; G-580 P.4; G-1644 P.4.

212. The most important non-suppurative infective complications of *Campylobacter* infections include reactive arthritis and the Guillain-Barre syndrome (GBS). Endtz WDT: page 3, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to the proposed finding of fact; however, it is misleading and not relevant to this proceeding since there are no data associating complications such as reactive arthritis and Guillain-Barre with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2; CVM Answer to Bayer Interrogatory 60.

213. The DALY (Disability Adjusted Life Year) is a measure to assess the global health burden of a disease in a standardized manner. This integrated measure combines years of life lost by premature mortality with years lived in disability. Endtz WDT: page 3, lines 28-31

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

214. The total health burden of *Campylobacter* infection is similar to diseases as meningitis, sepsis, upper respiratory infections and stomach and duodenal ulcers. This underscores the impact of *Campylobacter* in society and the importance as a primary Public Health problem. Endtz WDT: page 3, lines 35-38

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because it attempts to equate such conditions with campylobacteriosis, which in the vast majority of cases is mild and not even reported to a physician, which usually resolves without treatment in less than 5 days, which rarely results in complications or death, and the incidence of which declined by 27% in the United States during the period 1996-2001. See Bayer/AHI responses to PFOF 1286, 1291, 1297, 1304, 1305. Moreover, this proceeding relates to the health impact of domestically acquired fluoroquinolone-resistant *Campylobacter* in the United States, which is not a significant health concern for the reasons given in Bayer/AHI's responses to PFOF 1342, 1350, 1307. Lastly, the witness has failed to clarify that the PFOF refers to statistics on *Campylobacter* infections, meningitis, sepsis, upper respiratory infections, and stomach and duodenal ulcers from The Netherlands. The scope of this hearing is limited to the United States and therefore this information is entirely irrelevant to the proceeding.

215. *Campylobacter* are zoonotic bacteria (i.e. they are transmitted from animals to humans and cause disease in humans). Endtz WDT: page 3, lines 43-44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

216. *Campylobacter* and *Salmonella* are the two most common causes of foodborne illness in the developed world. Endtz WDT: page 3, lines 44-45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

217. The great majority of *Campylobacter* infections are sporadic infections. Endtz WDT: page 3, lines 45-46

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

218. Human-to-human transfer of *Campylobacter* is very rare and probably of no epidemiological importance. Endtz WDT: p. 4, lines 1-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214. Human-to-human transfer of *C. jejuni* and *C. coli*, either by direct or indirect pathways, has been well-documented. For example, G-1697 describes an outbreak of *C. jejuni* infections associated with food handler contamination, G-1692 describes the intrafamilial spread of *Campylobacter* in five separate households, G-580 describes a "persistent" outbreak of *Campylobacter* infection in a day care nursery in Israel, and B-213 reviews nine different studies that point to person-to-person contact as being the main transmission route. The rate of human-to-human transmission in the United States is unknown, but such transmission is not necessarily as uncommon as has been supposed. G-1452 P.9 L.28-29. In addition, sewage treatment plants which process domestic, commercial, and industrial wastewaters that received human waste discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of bacteria, including fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4 L.4-9.

219. In developed countries poultry is often considered to be the most important reservoir of *C. jejuni.* Endtz WDT: page 4, lines 6-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. It is clear that there exist important sources of *Campylobacter* infection other than poultry. *See also*, Joint Stipulation 32.

220. Live poultry are often colonized by large numbers of *Campylobacters* without showing any signs of clinical illness. Colonization levels in the small intestine and ceca usually ranges from 10^5 - 10^9 CFU/g feces. Endtz WDT: page 4, lines 7-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

221. Several epidemiological studies suggest that the handling and consumption of poultry meat (either home or commercially prepared) is a dominant sources of sporadic infection. Endtz WDT: page 4, lines 12-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9 L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human

health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644, G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18. Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that the handling and consumption of poultry meat (either home or commercially prepared) is a dominant sources of sporadic infection.

222. In many studies handling and/or consumption of poultry have been found to be independent risk factors and may account for up to approximately 70% of the sporadic cases. Endtz WDT: page 4, lines 15-17

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The studies Endtz refers to (G-268 (Harris 1986) and G-162 (Deming 1987)) that purportedly support handling and/or consumption of poultry having a campylobacteriosis risk factor of 70% are outdated and epidemiologically flawed. The populations in the Harris (G-268) and Deming (G-162) studies were not representative of the current U.S. population in terms of age, income, travel habits, dietary habits, and other relevant risk factors. B-1901 P.38, P.57-64. The attributable fractions calculated in the Harris (G-268) and Deming (G-162) studies cannot correctly be applied to U.S. population case rates. B-1901 P.38, P.57-64. 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. B-1901 P.39, P.57-64. 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. B-1901 P.38-39, P.57-64. Bayer/AHI also dispute this PFOF because evidence in the record refutes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644, G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18. Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that the handling and consumption of poultry may account for up to approximately 70% of the sporadic cases.

223. Foreign travel is also a risk factor for acquiring *Campylobacter* infection. These cases likely result from consumption of contaminated food or water in the countries visited. Endtz WDT: page 4, lines 17-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

224. It is important to note that in a few studies, the consumption of chicken has been found to protect against *Campylobacter* infection. This paradox can be explained on the basis of acquired immunity after repeated challenges with contaminated meat. Endtz WDT: p. 4, lines 23-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

225. In 1999, Belgium had a dioxin crisis caused by dioxin-contaminated feed being fed to livestock. The contamination led to the withdrawal of all Belgian chicken and eggs from the market for a period of four weeks. Belgium has had a *Campylobacter* surveillance network of sentinel and reference laboratories since 1983, which provided an unique opportunity to investigate the effect of withdrawal of particular food products from the market on the prevalence of campylobacteriosis. Based on a model that was generated with reports from preceding years, they observed a significant decline of 40% of the number of *Campylobacter* infections upon this intervention. One has to stress that only Belgian poultry was withdrawn from the market and that foreign poultry remained on the market. In 1999, 41% of the poultry available for consumption has been imported. Thus, non-Belgian-poultry-related *Campylobacter* infections were still present in the reported numbers. The total percentage of poultry-related *Campylobacter* infections in Belgium in 1999 is likely to have exceeded the reported figure of 40%. Endtz WDT: page 4, lines 29-41; G-672

Bayer/AHI Response: Bayer/AHI object to this PFOF because it is a compound set of proposed findings of fact, some of which Bayer/AHI agree with and some of which Bayer/AHI do not. Bayer/AHI do not dispute that Belgium had a dioxin crisis in 1999 caused by dioxin-contaminated feed being fed to livestock, that the contamination led to the withdrawal of all Belgian chicken and eggs from the market for a period of approximately four weeks or that Belgium has had a *Campylobacter* surveillance network of sentinel and reference laboratories since 1983. The conclusions about the Belgian dioxin crisis as set forth in this PFOF are refuted by B-1901 P.36; B-1908 P.23 L.18-21.

226. In rural areas in the developing world, close direct contact with animals, in particular poultry, is the most important risk factor for cases of campylobacteriosis in humans. Endtz WDT: page 4, lines 43-44

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and

domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. It is clear that there exist important sources of *Campylobacter* infection other than poultry. *See also*, Joint Stipulation 32.

227. A study from Denmark studied the serotype distribution, using the Penner scheme, of *Campylobacter* isolates from Danish patients and from major food production animals. The most commonly observed human serotypes showed large overlap with the distribution of *Campylobacter* serotypes in cattle and broilers, thereby suggesting that these food animals could be a major source of human campylobacteriosis. Endtz WDT: p. 5, lines 17-21; G-459

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

228. Serotyping studies in the Netherlands in the late eighties have observed that the five most prevalent human serotypes were also frequently found in isolates from poultry. Endtz WDT: p. 5, lines 23-26

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but dispute its applicability to the issues in this proceeding. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458 P.7 ¶ 11).

229. A study in Taiwan investigated the relatedness of quinolone-resistant *Campylobacters* from poultry products and from humans with PFGE and *flaA* RFLP (Restriction Fragment Length Polymorphism of the *flaA* gene). They found that 40% of the human types were shared with the populations isolated from poultry products. They concluded that domestic poultry is an important source of quinolone-resistant *Campylobacters*. Endtz WDT: page 5, lines 26–32; G-1775

Bayer/AHI Response: Bayer/AHI dispute this PFOF. G-1775 examined resistant isolates from poultry farms (comprising nearly 30% of their total samples) and included them in the poultry samples. Clearly, live birds were not eaten by the patients in question. They also found a large number of *C. coli* isolates that were resistant to nalidixic acid in their samples. The authors further state in this report that "other farms animals, such as pigs and cattle also played a role as the reservoirs for this bacterium" and that in their report that poultry products are "in part" related to human infections. Reports from Taiwan are not relevant to the U.S. situation because fluoroquinolones are widely used in many animal species in an unregulated fashion, and the Taiwanese poultry industry is not regulated under performance standards as the U.S. poultry industry. Moreover, genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458 P.7 ¶ 11).

230. In a comparable study in Canada using PFGE, 20% of the human *Campylobacter* isolates were genetically related to genotypes found in poultry indicating a potential important source of human infections. Endtz WDT: page 5, lines 33-35; G-1684

Bayer/AHI Response: Bayer/AHI object to this PFOF in that it purports to be making a comparison but no frame of reference is given. Bayer/AHI do not dispute this PFOF. Bayer/AHI note, however that genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458 P.7 ¶ 11).

231. Treatment of bacterial diarrhea is often empirical and antimicrobial therapy has to be initiated before the results of fecal cultures become available. Endtz WDT: page 6, lines 46-47

Bayer/AHI Response: Bayer/AHI disagree with this PFOF for the reasons stated in their responses to PFOF 1305, 1320, 1322, 1330, 1339, 651, 921.

232. To cover causes of bacterial diarrhea other than *Campylobacter,* like *Salmonella* and *Shigella*, where macrolides are not effective, the fluoroquinolones are the preferred agents since they are active against all major causes of bacterial diarrhea. Endtz WDT: page 6, lines 47 – p. 7, line 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF for several reasons: (1) this hearing is not concerned with *Salmonella, Shigella,* and other enteric pathogens; (2) it is not clear whether this PFOF is discussing empiric treatment or specific therapy once the results of a stool culture are known, although it appears to relate to empiric therapy, in the context of the witness's testimony; (3) fluoroquinolones are never preferred for the treatment of *Campylobacter* enteritis in infants and children, who account for a significant percentage of campylobacteriosis cases (4) fluoroquinolones are never preferred for the treatment of *Campylobacter* enteritis in pregnant women and lactating women; and (5) azithromycin, a macrolide, is a well-tolerated, effective, broad-spectrum antibiotic. B-1905 P.4 L.9-16; JS 25; B-1909 P.3 L.9-21; P.4 L.19; G-529 P.3; B-121 P.2; G-261 P.11-13.

233. With the introduction of quinolone resistance in *Campylobacter* species empirical treatment of patients with quinolones may result in treatment failures. Endtz WDT: page 7, lines 3-5

Bayer/AHI Response: Bayer/AHI disagree with the proposed finding of fact because resistance to erythromycin and azithromycin remain low, fluoroquinolone resistance is not a significant treatment problem in the United States because the mean durations for domestically acquired susceptible and resistant *Campylobacter* are not statistically different, and the occurrence of "treatment failures" for susceptible and resistant *Campylobacters* is similar. Pasternack WDT: P.12 L.20-22, P.13 L.1, 11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16; P.6 L.1-15; Burkhart WDT: P.36 table 8; B-50 P.2; B-1920 P.4; B-20 P.2; G-354 P.3; Cox WDT: P.78.

234. With increasing levels of fluoroquinolone resistance, empirical treatment with these drugs will become hazardous. Most patients with *Campylobacter* diarrhea are not hospitalized and one has therefore to rely on oral drugs. No other oral drug with comparable activities and toxicity profile is currently available as an alternative treatment. Endtz WDT: p. 7, lines 5-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The routine empiric treatment of gastrointestinal illness is already frowned upon and the prudent physician already minimizes empiric treatment to the extent possible. The second sentence is a *non sequitur*; most patients with *Campylobacter* enteritis are not hospitalized because they are not ill enough to be hospitalized and those that are ill enough to be hospitalized, will be hospitalized, regardless of whether an antibiotic is prescribed or not. *Campylobacter* enteritis is a self-limiting disease, up to 25% of patients with *Campylobacter* infections are asymptomatic, and approximately 17 out of 18 persons with *Campylobacter* enteritis do not seek medical assistance. For those that will require an antibiotic, whether hospitalized or not, there are effective alternatives to fluoroquinolones, contrary to the witness's assertion. Azithromycin is an effective, broad-spectrum alternative that is well-tolerated and to which resistance is low. Rifaximin may also become an alternative, and erythromycin is still an option. It is very important to point out that the need for empiric therapy will be obviated by availability of the new ProSpecT test that enables clinicians to identify *Campylobacter* within 2 hours and prescribe an antibiotic, if prudent, on that basis. B-1905 P.3 L.15-18, P.4 L.8-16, P.6 L.1-7; B-1909 P.3 L.16-17, P.3 L.21-23, P.4 L.1-3, P.4 L.4-6, P.4 L.10-21, P.13 L. 11-21, P.14 L.1-16, P.18 L.21-22, P.19 L.1-22, P.20 L.1-2; G-1457 P.6 L.44-45; G-1469 P.5 L.3-5; G-1477 P.2 ¶ 4; G-1485 P.9 L.36-46, P.10 L.1-7; G-557 P.3; B-816 P.2; B-857 P.2; G-253 P.5; G-707 P.9; B-50 P.2; B-1920 P.4; B-20 P.2; G-354 P.3, G-261 P.11; G-250 P.1; B-1143 P.1-3; G-615 P.3

235. Twenty-five years of study of the epidemiology of *Campylobacter* infections in the US and Europe has not come up with data that refute the hypothesis that epidemiology of *Campylobacter* in the two continents is in essence very comparable. Therefore, data from outside the US include valuable information that may be extrapolated to the US situation. Endtz WDT: p. 7, lines 14-17

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Campylobacteriosis is increasing in Europe and decreasing in the U.S. Moreover, this PFOF is refuted by CVM witness Nachamkin who testified that the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. The witness's point is moot anyway because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44. Moreover, recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Recent studies in the United Kingdom also now question whether chicken is a major source of fluoroquinolone-resistant campylobacteriosis. B-1909 P.40 L.20-22. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a dominant source of *Campylobacter* infection.

236. Fluoroquinolone resistance in *Campylobacter* from poultry must be the result of the use of these drugs in animal husbandry. Endtz WDT: p. 8, lines 6-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The presence of fluoroquinolone resistance in untreated flocks refutes the contention that fluoroquinolone resistance does not emerge in the absence of direct selection pressure by fluoroquinolone use. B-36 P.2-3; G-62 1-2; G-1458 P.4, ¶ 3; G-1459 P.6 L.36-37; B-1908 P.17 L.1-6. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. B-1908 P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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.

237. It is unlikely that the use of norfloxacin (in human medicine) alone may have led to the development of fluoroquinolone resistance in strains isolated from humans. It seems more probable that the use of enrofloxacin in poultry contributed significantly to the resistance problems in humans. Endtz WDT: p. 8, lines 7-10

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by G-1453 P.2 L.16-18; G-1478 P.2 L.29-32; and Joint Stipulations 6 and 8.

238. In Spain, before licensing of enrofloxacin for veterinary use in 1990, the prevalence of fluoroquinolone-resistant *Campylobacter* in human ranged from 0 to 3%. After licensing, fluoroquinolone resistance percentages in human *Campylobacter* increased dramatically to 39-88%. The sharpest increase occurred from 1990 to 1991, the first year following introduction of enrofloxacin. Endtz WDT: p. 8, lines 16-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by evidence in the record showing that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Also, Bayer/AHI dispute the applicability of this PFOF to the issues in this hearing. The conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, Bayer's Submission of Facts, Information and Analyses in Response to the Notice of Opportunity for Hearing (B-1(A)) P.10).

239. In the U.S., sarafloxacin was licensed in 1995 and enrofloxacin in 1996 for use in poultry. Endtz WDT: p. 8, lines 32-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF. SaraFlox WSP was approved in the United States on August 18, 1995 (Revised Joint Stipulation No. 47); SaraFlox Injection was approved in the United States on October 12, 1995 (Revised Joint Stipulation No. 48); and Baytril 3.23% concentrate oral solution was approved in the United States on October 4, 1996 (Revised Joint Stipulation No. 39). These dates are not the same as the date of first sale in the United States.

240. Smith observed an increase of fluoroquinolone-resistant *Campylobacter* infecting humans from 1.3% in 1992 to 10.2% in 1998. 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. Endtz WDT: p. 8, lines 33-38; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Smith provides no scientific evidence that domestically acquired fluoroquinolone-resistant *Campylobacter* is acquired from poultry. Evidence in the record disputes the contention that poultry is a source of domestically acquired *Campylobacter* infections, either fluoroquinolone-resistant or susceptible. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44. Moreover, recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a

statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Recent studies in the United Kingdom also now question whether chicken is a major source of fluoroquinolone-resistant campylobacteriosis. B-1909 P.40 L.20-22. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a source of domestically acquired *Campylobacter* infections, either fluoroquinolone-resistant or susceptible.

241. In another study conducted between 1982 and 1992, no *C. jejuni* or *C. coli* isolated from humans were resistant to the fluoroquinolones, thereby strengthening the hypothesis that prior to the licensing of fluoroquinolones in poultry, the prevalence of fluoroquinolone-resistant *Campylobacter* was very low. Endtz WDT: p. 8, lines 38-41

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that any *Campylobacter* isolation, speciation and susceptibility testing protocol relying on nalidixic acid susceptibility as a criterion to identify *C. jejuni* or *C. coli*, such as would have been used from 1982 to 1992 (G-1453 P.3 L.1-12) would have excluded all quinolone-resistant isolates from surveillance and therefore underreport resistance in *C. jejuni* and *C. coli*. G-1453 P.3 L.31-36.

242. Fluoroquinolones are not registered for use in the food-producing animals but they are registered for use in human medicine in Australia. Endtz WDT: p. 8, lines 45-47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

243. Very few Australian patients with diarrhea with fluoroquinolone-resistant *Campylobacter* have been reported in the English-language literature. The cases that have been reported acquired the infection abroad. Endtz WDT: p. 8, line 47 – p. 9, line 2; B-225; B-421

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the hearing pertains to the United States, not Australia.

244. In the absence of animal use, fluoroquinolone resistance in *Campylobacter* in Australia remains extremely low. Endtz WDT: p. 9, lines 3-4

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but dispute the implication that the absence of animal use is related to low fluoroquinolone resistance. Evidence in the record shows that in many countries, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable

in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Furthermore, the human use of fluoroquinolones is relatively low in Australia (B-255 P.2) as well, and this could account for the low levels of fluoroquinolone-resistant *Campylobacter*. For example, only four fluoroquinolones are approved (ciprofloxacin, norfloxacin, moxifloxacin, and gatifloxacin), and in contrast to many countries, urinary tract infections is not an indication for which fluoroquinolone use is authorized in Australia. In addition, if a fluoroquinolone treatment is to extend beyond 7 days, the doctor must receive approval from the Pharmaceutical Benefits Scheme (PBS) to prescribe the additional fluoroquinolones.

245. *Campylobacter* is an important pathogen in terms of prevalence, morbidity, mortality and total health burden. Endtz WDT: page 9, lines 12-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Campylobacteriosis is usually self-limiting and the symptoms are often mild. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. This is often true even in cases of bacteremia. B-1906 P.5 L.7-9. Many *Campylobacter* enteritis cases do not even get reported to the doctor. G-1452 P.6 L.22-45. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4. In addition, Bayer/AHI disagree with the proposed finding of fact because resistance to erythromycin and azithromycin remain low, fluoroquinolone resistance is not a significant treatment problem in the United States because the mean durations for domestically acquired susceptible and resistant *Campylobacter* are not statistically different, and the occurrence of "treatment failures" for susceptible and resistant *Campylobacters* is similar. Pasternack WDT: P.12 L.20-22, P.13 L.1, 11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16; P.6 L.1-15; Burkhart WDT: P.36 table 8; B-50 P.2; B-1920 P.4; B-20 P.2; G-354 P.3; Cox WDT: P.78.

246. Treatment options for acute bacterial diarrhea, including *Campylobacter*, are greatly compromised by the emergence of fluoroquinolone resistance. Endtz WDT: page 9, lines 15-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "compromise treatment options In addition, Bayer/AHI disagree with the proposed finding of fact because resistance to erythromycin and azithromycin remain low, fluoroquinolone resistance is not a significant treatment problem in the United States because the mean durations for domestically acquired susceptible and resistant *Campylobacter* are not statistically different, and the occurrence of "treatment failures" for susceptible and

resistant *Campylobacters* is similar. Pasternack WDT: P.12 L.20-22, P.13 L.1, 11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16; P.6 L.1-15; Burkhart WDT: P.36 table 8; B-50 P.2; B-1920 P.4; B-20 P.2; G-354 P.3; Cox WDT: P.78.

247. Poultry is an important source of *Campylobacters* causing infections in humans. Endtz WDT: page 9, lines 18-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that poultry is an important source of *Campylobacters* causing infections in humans, particularly in the U.S. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is an important source of *Campylobacters* causing infections in humans.

248. There is substantial evidence that the use of fluoroquinolone in poultry leads to fluoroquinolone resistance in *Campylobacter* from poultry. Endtz WDT: page 9, lines 21-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence of fluoroquinolone-resistant ciprofloxacin in poultry and other birds absent fluoroquinolone use refutes this PFOF. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of poultry flocks. B-1908 P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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.

249. In the absence of significant person-to-person transmission, one may deduce that a significant proportion of fluoroquinolone-resistant *Campylobacter* is reaching people via poultry. Endtz WDT: page 9, lines 24-26

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and

domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. It is clear that there exist important sources of *Campylobacter* infection other than poultry. *See also*, Joint Stipulation 32.

Marja-Liisa Hanninen (G-1458)

250. Dr. Hanninen is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

251. Baytril has been used for treatment of infections caused by *E. coli* or *Mycoplasma pneumoniae* in poultry since the early 1990s in various countries. Hanninen WDT: p. 1, ¶ 2

Bayer/AHI Response: The parties have entered into numerous stipulations as to when Bayer's enrofloxacin product was approved (See Revised Joint Stipulations 51-78). Said stipulations speak for themselves.

252. In most countries the use of fluoroquinolones in human medicine started in the 1980s. Hanninen WDT: p. 1, ¶ 2

Bayer/AHI Response: The parties have entered into numerous stipulations as to when Bayer's ciprofloxacin product was approved (See Revised Joint Stipulations 51-78). Said stipulations speak for themselves.

253. In veterinary medicine, fluoroquinolone use has been regulated and restricted for the treatment of poultry and other animal illnesses, but in some countries it has also been used extensively for prophylaxis. Hanninen WDT: p. 1-2, ¶ 2

Bayer/AHI Response: Bayer/AHI does not dispute this PFOF.

254. Spain was one of the first countries where Baytril was used in veterinary medicine, beginning in 1987. Hanninen WDT: p. 2, ¶ 2

Bayer/AHI Response: This PFOF is refuted by Revised Joint Stipulations 51, 52, 58, 61, 63, 64, 73, 74 and 76.

255. Most European Union countries started a more systematic monitoring of antibiotic resistance among animal and human *C. jejuni/C. coli* in the middle of the 1990s as required by the European Union. Hanninen WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI can neither admit nor deny this PFOF as it does not give a reference for what the EU countries are being compared to.

256. The US started a national monitoring program in 1996, called the National Antimicrobial Resistance Monitoring System (NARMS). Hanninen WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

257. In Finland, enrofloxacin has never been used in poultry. Hanninen WDT: page 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF. Enrofloxacin was never sold commercially for poultry in Finland. Fluoroquinolone-resistant *Campylobacter* from humans in Finland has been higher than in the U.S., (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881.

258. In Spain, Thailand and Portugal, enrofloxacin has been used in poultry. Hanninen WDT: page 2, ¶ 3

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

259. Spain, Thailand and Portugal are common destinations for Finnish tourists. Hanninen WDT: page 2, ¶ 3

Bayer/AHI Response: Bayer/AHI neither admit nor deny this PFOF. This PFOF is unsupported by the witness.

260. The fluoroquinolone resistance among Finnish poultry *Campylobacter* isolates is low and among Spanish and Thai poultry isolates it is high. Hanninen WDT: page 2, ¶ 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Whether fluoroquinolone resistance among poultry *Campylobacter* isolates is "low" or "high" is subjective, especially since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

261. In 1999, ciprofloxacin resistance was very low among the *C. jejuni* isolates from patients who had not traveled abroad before their illness. In contrast, most of the strains from the patients who had been in Spain or Thailand before their illness were ciprofloxacin-resistant.

These Finnish results indicate a very low resistance among human domestic *C. jejuni* strains in spite of the fact that these antimicrobial agents have been used for treatment of diarrhea in humans since 1987. The finding that a high percentage of ciprofloxacin-resistant strains from patients who traveled to Spain before their illness in concordant with the Spanish results on high ciprofloxacin resistance among Spanish *C. jejuni* isolates. Hanninen WDT: p. 3, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this compound PFOF. First, whether fluoroquinolone resistance among the *C. jejuni* isolates from patients who had not traveled abroad before their illness is "very low" or "high" is subjective, especially since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Evidence in the record demonstrates that fluoroquinolone-resistant *Campylobacter* from humans in Finland has been high (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881. Moreover, the conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, Bayer's Submission of Facts, Information and Analyses in Response to the Notice of Opportunity for Hearing (B-1(A)) P.10).

262. Our results from Finland show that where fluoroquinolones are not used in poultry, there is a high level of susceptibility to fluoroquinolones among chicken and human *C. jejuni* strains even after more than ten years of fluoroquinolone use to treat human diarrhea. Hanninen WDT: p. 4, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by evidence in the record showing fluoroquinolone-resistant *Campylobacter* from humans in Finland has been higher than in the U.S., (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

263. In Sweden fluoroquinolones resistance among domestic poultry *Campylobacter* isolates is low because Baytril has not been approved for treatment of poultry. Similarly, fluoroquinolone resistance among human *Campylobacter* isolates of domestic origin seems to be low, and an increasing resistance has been recognized among isolates from patients who have acquired the infection while traveling in Spain or Thailand. These results are concordant with the Finnish experience. Hanninen WDT: p. 4, ¶ 5

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI dispute this PFOF. First, whether fluoroquinolone resistance among poultry *Campylobacter* isolates is "low" or "high" is subjective. A study in Sweden published in 1981, long before fluoroquinolones had been introduced for either human or veterinary medicine, showed that 39% of *C. jejuni* isolates from chickens were then already resistant to nalidixic acid, as were 11% of human isolates. A-201 P.14 L.9-11; citing B-1851. Additional evidence in the record shows that poultry *Campylobacter* isolates from Sweden were 4.5% without use of fluoroquinolones in poultry. B-1(A)) P.9 (citing B-12). Human resistance has been as high as 30% in Sweden. B-1(A)) P.9 (citing B-58). Evidence in the record demonstrates that fluoroquinolone-resistant *Campylobacter* from humans in Finland has been high (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881. Moreover, the conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, B-1(A) P.10).

264. In 1995 Denmark started an integrated program to monitor antibiotic resistance (Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP)) in animals, food and humans. Hanninen WDT: p. 4, ¶ 6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

265. The data suggest that fluoroquinolone resistance in *Campylobacter* has appeared after the use of Baytril in Denmark's chicken industry started after 1993. Hanninen WDT: p. 5, ¶ 6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

266. The number of human patients infected with ciprofloxacin- or nalidixic acid-resistant *Campylobacter* strain acquired in Denmark has increased very much from 1997 to 2000: from 6-7% to 22-25%, respectively. In 2000, 22% of domestic infections were ciprofloxacin resistant when 43% of patients with travel history had ciprofloxacin-resistant strain. In studies at the county level no correlation was found on the quantity of fluoroquinolones used for treatment of human domestic infections and the percentage of NAL resistant human isolates. These results suggest that human clinical use does not produce increased resistance to fluoroquinolones. Hanninen WDT: p. 5, ¶ 6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

267. The Netherlands is one of the first countries where an increased resistance to fluoroquinolones was observed among human *Campylobacter* isolated in the early 1990s (Endtz et al 1991). Baytril was approved for use in the Netherlands, in 1987, and used there extensively in poultry since 1987. Hanninen WDT: p. 5, ¶ 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

268. In the Netherlands, no fluoroquinolone-resistant human strains of *Campylobacter* were identified in the first half of the 1980s and resistance soon appeared after the use of Baytril started in poultry. During the 1990s, an increasing resistance to fluoroquinolones in *Campylobacter* has been reported in both poultry and human isolates. Hanninen WDT: page 5, ¶ 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

269. In Spain, fluoroquinolone resistance among chicken strains was nonexistent among strains isolated before 1987. In 1997 – 1998, ten years after the fluoroquinolone use started

in poultry in Spain, a high percentage (99%) of *C. jejuni* strains isolated from poultry (fecal and meat samples) were fluoroquinolone-resistant, strongly suggesting association between veterinary medical use of fluoroquinolones and high level of resistance among *C. jejuni* from poultry. Hanninen WDT: p. 6, ¶ 9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Moreover, the conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, B-1(A) P.10).

270. Fluoroquinolone resistance of human *Campylobacter* strains in Spain was nonexistent before 1987. In 1997 – 1998, 72% of human strains were fluoroquinolone-resistant. Hanninen WDT: p. 6, ¶ 9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Moreover, the conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, B-1(A) P.10).

271. Studies indicate a strong temporal and spatial association between fluoroquinolone-resistant human *Campylobacter* strains and a high level of resistance among chicken *Campylobacter* strains after use of FQs in poultry. Hanninen WDT: p. 6, ¶ 9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Whether the level of fluoroquinolone resistance is "low" or "high" is subjective, especially since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and

B-1901 P.78 (citing B-50). Moreover, data from other countries is of limited value because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

272. *Campylobacter jejuni* and *coli* are zoonotic bacteria. Zoonotic bacteria are those bacteria that can be acquired from animals. Consumption of chicken or handling chicken has been shown in most of the epidemiologic studies from USA and Europe to be a recognized risk factor for acquisition of the infection. Hanninen WDT: p. 7, ¶ 10

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI agree with the first 2 sentences of this PFOF. Bayer/AHI dispute the last sentence of this PFOF because evidence in the record disputes the contention that poultry is an important source of *Campylobacters* causing infections in humans, particularly in the U.S. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19;. B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is an important source of *Campylobacters* causing infections in humans.

273. Serotyping and molecular typing are important tools in tracing the sources and routes of transmission of human *Campylobacter* infections. Hanninen WDT: p. 7, ¶ 11

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but note that these tools cannot be used and interpreted independently of an epidemiologic analysis. G-589.

274. Hanninen compared Finnish chicken and human strains of *Campylobacter* using several genotyping techniques (PFGE, AFLP ribotyping) in combination with serotyping and found several human isolates were identical to those found in chicken. Hanninen WDT: page 7, ¶ 11

Bayer/AHI Response: Bayer/AHI do not dispute that Hanninen made such a comparison.

275. An additional evidence for transmission of fluoroquinolone-resistant strains from chickens to humans comes from the studies of Smith et al. (1999) where the authors found that the PCR-RFLP genotypes were partially overlapping among fluoroquinolone-resistant strains from chickens and fluoroquinolone-resistant strains from humans. Hanninen WDT: p. 7, ¶ 11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458 P.7 ¶ 11).

276. Jacobs-Reitsma's study indicates a rapid induction of Baytril resistance in chickens colonized with *Campylobacter* and then treated with fluoroquinolones. Hanninen WDT: p. 7, ¶ 11

Bayer/AHI Response: Bayer/AHI agree with this PFOF except for CVM's characterization that broilers that were colonized with fluoroquinolone-sensitive *Campylobacter*, then treated with Baytril, showed a "rapid induction" of fluoroquinolone-resistant *Campylobacter*. Rather, the study presents that the broilers in this group were not tested until three days after the first treatment (i.e., day 29), at which point they were found to be cross-resistant to quinolones. G-315.

277. McDermott's study showed that Baytril exposure at doses used in practical conditions induce high level ciprofloxacin MICs, and that these resistant strains persist weeks after stopping treatment. Hanninen WDT: p. 7, ¶ 12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "high level" is subjective. While experimental studies have shown that birds inoculated with *Campylobacter* and then treated with Baytril have shown fluoroquinolone resistance within 24 hours of treatment, the resistance does not always persist, and susceptible *Campylobacter* can recolonize the chicken intestine. B-868; A-190. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. In another study, Zhang's experiment showed that in

chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone resistant. A-190. Thus, not all resistant *C. jejuni* isolates persist in the birds.

278. Rapid and persistent induction of resistance to fluoroquinolones after the use of Baytril in chickens with approved doses has been shown to take place in two separate studies which both have concordant results. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. While experimental studies have shown that birds inoculated with *Campylobacter* and then treated with Baytril have shown fluoroquinolone resistance within 24 hours of treatment, the resistance does not always persist, and susceptible *Campylobacter* can recolonize the chicken intestine. B-868; A-190. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. In another study, Zhang's experiment showed that in chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone resistant. A-190. Thus, not all resistant *C. jejuni* isolates persist in the birds. In addition, this PFOF does not identify the "two separate studies" and further fails for lack of adequate support.

279. Human-to-human transmission of *C. jejuni/C. coli* has not been reported as a significant factor. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214.

280. Poultry meat is frequently contaminated by *Campylobacter*. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI do not dispute that poultry meat may have *Campylobacter* on it. Bayer/AHI do not admit that this rises to the level of "frequently" as used here.

281. Many epidemiological studies show an association between poultry and an increased risk for human *Campylobacter* disease. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The most recent and robust U.S. data dispute the contention that there is an association between poultry and an increased risk for human *Campylobacter* disease. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-

185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest there is an association between poultry and an increased risk for human *Campylobacter* disease.

282. Enrofloxacin has been used for treatment of poultry in a large number of countries all over the world starting from the middle of the 1980s. In all countries which have reported antimicrobial sensitivity data on poultry *Campylobacter* isolates, increasing resistance to enrofloxacin has been reported soon after use has started. In follow-up studies for a longer period of time, such as in Spain or The Netherlands, (where poultry use began in 1987), an increased resistance has been identified in both chicken and human strains. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Moreover, the conditions of fluoroquinolone use in Spain are different than in the U.S. The indiscriminate use of quinolones in humans and animals in Spain is described in G-557 (*See also*, B-1(A) P.10).

283. In countries such as the UK, USA, and Denmark where the use in poultry started in the middle of 1990s, the early stages of emerging resistance among chicken and human *Campylobacter* strains have been observed. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

284. In countries where fluoroquinolones have never been used for treatment of poultry, enrofloxacin resistance among chicken strains is very low or nonexistent (Finland, Sweden). Similarly fluoroquinolone resistance among human *Campylobacter* strains of domestic origin has been low before the fluoroquinolone era and has remained low even where ciprofloxacin has been in use in human medicine (Finland, Sweden). Hanninen WDT: p. 9, ¶ 13

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI dispute this PFOF. First, whether fluoroquinolone resistance among chicken *Campylobacter* strains is "very low" or "high" is subjective. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Nevertheless, this PFOF is refuted by a study in Sweden published in 1981, long before fluoroquinolones had been introduced for either human or veterinary medicine, showing that 39% of *C. jejuni* isolates from chickens were then already resistant to nalidixic acid, as were 11% of human isolates. A-201 P.14 L.9-11; citing B-1851. Additional evidence in the record shows that poultry *Campylobacter* isolates from Sweden were 4.5% without use of fluoroquinolones in poultry. B-1(A)) P.9 (citing B-12). Human resistance has been as high as 30% in Sweden. B-1(A)) P.9 (citing B-58). Evidence in the record demonstrates that fluoroquinolone-resistant *Campylobacter* from humans in Finland has been high (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881.

285. In countries (Finland, Sweden) where fluoroquinolone resistance among human domestically acquired *C. jejuni* strains is low, high and increasing frequency of resistant strains have been isolated from patients who have acquired the infection in traveling to countries where fluoroquinolone has been in extensive use in poultry (Spain, Portugal, Thailand). Similarly in countries where fluoroquinolone resistance has been increasing among domestic *Campylobacter* isolates (e.g. UK), a more intensive increase in resistant strains has been found among travelers to Spain and Thailand. Hanninen WDT: p. 8, ¶ 13

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI dispute this PFOF. First, whether fluoroquinolone resistance among chicken *Campylobacter* strains is "very low" or "high" is subjective. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Nevertheless, this PFOF is refuted by a study in Sweden published in 1981, long before fluoroquinolones had been introduced for either human or veterinary medicine, showing that 39% of *C. jejuni* isolates from chickens were then already resistant to nalidixic acid, as were 11% of human isolates. A-201 P.14 L.9-11; citing B-1851. Additional evidence in the record shows that poultry *Campylobacter* isolates from Sweden were 4.5% without use of fluoroquinolones in poultry. B-1(A)) P.9 (citing B-12). Human resistance has been as high as 30% in Sweden. B-1(A)) P.9 (citing B-58). Evidence in the record demonstrates that fluoroquinolone-resistant *Campylobacter* from humans in Finland has been high (9% in 1990, 17% in 1993, 20% in 1995, 32% in 1996 to 35-37% in 1997), despite the fact that enrofloxacin has never been used in poultry in Finland. B-44, B-625, B-881.

286. Human-human transmission in *Campylobacter* infections is extremely uncommon. Hanninen WDT: p. 9, ¶ 17

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214.

287. Ciprofloxacin is frequently used for treatment of human diarrhea including diarrhea caused by *Campylobacter*. Hanninen WDT: p. 9, ¶ 18

Bayer/AHI Response: Bayer/AHI do not dispute that ciprofloxacin is used for the treatment of human diarrhea but do not believe it rises to the level of "frequently." Evidence in the record demonstrates that quinolones are prescribed in only 0.32% of all foodborne illness cases, including viral causes, that only about 14,442 *Campylobacter* patients in the US would receive empiric fluoroquinolone treatment. B-1906 P.11 L.20-22 – P.12 L.1-11.

Wilma Jacobs-Reitsma (G-1459)

288. Dr. Jacobs-Reitsma is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

289. The most important species of *Campylobacter* in relation to human medicine is *Campylobacter jejuni* and to a lesser extent *Campylobacter coli*. Jacobs-Reitsma WDT: p. 2, lines 4-5

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF since it is not clear what is meant by "important". They would agree that *C. jejuni* is the most frequently cultured *Campylobacter* species, however, far more serious infections are caused by *C. fetus*.

290. The optimum temperature for *C. jejuni* and *C. coli* to grow is 37°C-42°C. Jacobs-Reitsma WDT: p. 2, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

291. The normal body temperature of poultry is 42°C. Jacobs-Reitsma WDT: p. 2, lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

292. The normal body temperature of humans is 37°C. Jacobs-Reitsma WDT: p. 2, lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

293. Transmission of *Campylobacter* organisms from animals to humans is via food products produced from those colonized animals. Jacobs-Reitsma WDT: p. 2 , lines 17-18

Bayer/AHI Response: Bayer/AHI object to this PFOF on the grounds that transmission of *Campylobacter* organisms from animals to humans may result from, or may be influenced by, factors other than food products produced from colonized animals. These factors include, but are not limited to, contact with animals (farm animals as well as cats or dogs); drinking milk contaminated by birds; drinking unpasteurized milk; contact with feces from cats and dogs;

drinking untreated water (non-chlorinated); having contact with contaminated recreational water, wastewater, or raw sewage; taking medication; having an underlying disease; foreign travel; faecal-oral transmission from person to person; transmission from ill food handlers; biofilms in drinking water pipe distribution networks; and eating in restaurants. G-1483 P.9 L.1-4; G-1483 P.10 L.30-31; G-1483 P.13 L.12; G-1483 P.15 L.13-18; G-1483 P.20 L.11-12; G-1475 P.5 L.43 – P.6 L.1; G-1743; B-1908 P.21 L.16-19; B-1900 P.9 L.28-30; G-1470 P.4 L.22-29; G-1475 P.6 L.27-29; G-1470 P.4 L.23-26; G-1460 P.9 L.10-11; G-1452 Attachment 1 P.46; G-1470 P.4 L.25-26; G-1452 Attachment 3 P.82; G-1452 Attachment 3 P.82; G-1452 P.9 L.28-29; B-1908 P.23 L.3-4; B-1910 P.4 L.20-22; B-1910 P.5 L.15-19; G-1452 Attachment 3 P.82; B-1910 P.3 L.12-14; B-1908 P.7 L.24 – P.8 L.3; B-1910 P.14 L.15-16; G-1475 P.6 L.38-42; B-1910 P.6 L.20-22; B-1910 P.7 L.20-22; B-1910 P.9 L.18-19; B-1910 P.10 L.3-4; B-1908 P.22 L.13-17; B-1910 P.10 L.12-14, citing to, *inter alia*, B-50, B-1774, B-1800 and Sorum and L'Abee-Lund, 2002; B-1910 P.19 L.13-14; B-1910 P.19 L.9-13; B-1908 P.7 L.8-11; B-1910 P.27 L.8-11; B-1910 P.28 L.1-2; B-1910) P.6 L.8-9; B-1910 P.6 L.9-11; G-1452 Attachment 1 P.46; G-1452 Attachment 1 P.46; B-1900 P.9, L.39-41; G-1452 P.10 L.46 – P.11 L.2; G-1452 Attachment 3 P.88; G-1460 P.7 L.5-7; G-1460 P.7 L.9-11.

Moreover, the sources and routes of transmission of campylobacteriosis, and the relative contribution of all these potential sources, remain unclear. B-1908 P.21 L.19-20.

294. Colonized refers to the growth of bacteria in or on an animal. Jacobs-Reitsma WDT: p. 2, lines 18-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

295. During slaughter, intestinal contents of poultry may spread on the carcasses causing contamination of end-products. Jacobs-Reitsma WDT: p. 2, lines 19-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

296. *Campylobacter* is not considered normal intestinal flora of humans. Jacobs-Reitsma WDT: p. 2, line 28

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that many persons with *Campylobacter* infections - perhaps as many as 25% of all persons infected - do not exhibit clinical symptoms and are therefore "asymptomatic". B-1909 P.3 L.23, P.4 L.1-3, G-70 P.3. In those persons, *Campylobacter* could be considered normal intestinal flora.

297. *Campylobacter* is considered normal intestinal flora in broilers, laying hens, breeders and turkeys. Jacobs-Reitsma WDT: p. 2, lines 28-29

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

298. Normal flora refers to the types of bacteria that are present in or on a healthy animal without causing disease. Jacobs-Reitsma WDT: p. 2, lines 29-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

299. Broiler chicks typically become colonized after two weeks of age. Jacobs-Reitsma WDT: p. 2, lines 32-33; p. 7, lines 27-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

300. No clinical symptoms are seen in broiler chicks even when the broiler chicks carry large numbers of *Campylobacter* in their intestines. Jacobs-Reitsma WDT: p. 2, lines 33-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

301. In humans, the replication of *Campylobacter* in the intestines results in acute inflammatory enteritis. Jacobs-Reitsma WDT: p. 2, lines 41-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that many persons with *Campylobacter* infections - perhaps as many as 25% of all persons infected - do not exhibit clinical symptoms and are therefore "asymptomatic". B-1909 P.3 L.23, P.4 L.1-3, G-70 P.3. In those persons, replication of *Campylobacter* in the intestines does not result in acute inflammatory enteritis.

302. Humans continue to excrete *Campylobacter* in their feces for several weeks after they have clinically recovered. Jacobs-Reitsma WDT: p. 2, lines 44-45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

303. Long term carriage of *Campylobacter* has been observed in patients with immune deficiency. Jacobs-Reitsma WDT: p. 2, lines 45-46

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

304. *Campylobacter* colonization of broilers is mainly found in the caecum, as well as other parts of the intestinal tract. Jacobs-Reitsma WDT: p. 2, lines 48-49

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

305. There are approximately 10^7 – 10^9 (10 million – 1 billion) *Campylobacter* colony forming units (CFUs) per gram of caecal content in a colonized broiler. Jacobs-Reitsma WDT: p. 2, line 49 – p 3, line 2; p. 7, lines 28-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

306. The average concentration of *Campylobacters* in turkeys is between 1.2×10^4 to 1.5×10^7 CFUs of *C. jejuni* per gram of caecal content. Jacobs-Reitsma WDT: p. 3, lines 5-9; p. 7, lines 30-32

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

307. Colonized broilers excrete the *Campylobacter* bacteria in their droppings and continue to do so during several weeks (at least up to slaughter at 6-7 weeks of age). Jacobs-Reitsma WDT: p. 3, lines 9-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

308. Once colonized, turkeys continue to excrete *Campylobacter* in their fecal droppings until slaughter. Jacobs-Reitsma WDT: p. 3, line 12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

309. The number of *Campylobacter* organisms per gram of feces is lower for other food animals such as cattle, pigs and sheep, than in poultry. Jacobs-Reitsma WDT: p. 3, lines 13-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is inapplicable to the hearing in that any comparison between cattle, pigs and sheep to poultry is not an issue at this hearing.

310. Vertical transmission from breeder flocks to their progeny is not regarded to be of major importance. Jacobs-Reitsma WDT: p. 3, lines 26-27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

311. The majority of broilers are colonized with *Campylobacter*. Jacobs-Reitsma WDT: p. 3, lines 37-38, and lines 44-45, and lines 48-49

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that it is both inaccurate and an oversimplification. Evidence shows that prevalence of flock infection can vary from 10% to over 90%. B-1908 P.3 L.19-21. Moreover, the percentage of broiler flocks that are colonized with *Campylobacter* varies by country and by season. G-1459 P.4 L.38-39, P.4 L.41-43; B-1908 P.3 L.22-23. Finally, broiler chickens are predominantly colonized by *C. jejuni*, and not other types of *Campylobacter*. G-1459 P.7 L.27-28; G-1475 P.10 L.26-30; G-1484 P.2 L.42-45.

312. *Campylobacter* is generally isolated for the first time in broilers between 3 and 4 weeks of age. Jacobs-Reitsma WDT: p. 3, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

313. Colonization in turkeys starts at between 7-15 days of age. Jacobs-Reitsma WDT: p. 4, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

314. In turkeys, flocks remain 100% colonized once *Campylobacter* has become established. Jacobs-Reitsma WDT: p. 4, lines 9-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. The limited studies cited by Jacobs-Reitsma do not adequately support the proposition. G-1459 P.4. L.9-11. There exists no nationwide sampling program that would provide accurate data on the percentage of turkeys that remain colonized by *Campylobacter* once *Campylobacter* has become established. In addition, turkeys are preferentially colonized by *Campylobacter coli* compared to *Campylobacter jejuni* for chickens. A-201 P.12 L.17-23 and P.13 L.3-9; G-727; B-1908 P.4 L.7-8; A-210 P.12 L.16 – P.13 L.3; B-1917 P.20 L.1-5.

315. Soon after the first bird(s) becomes colonized by *Campylobacter*, the other broilers or turkeys in the same poultry house become infected very quickly, most likely through ingestion of contaminated fecal droppings (coprophagia) and later also through contaminated water and feed in open systems. Jacobs-Reitsma WDT: p. 4, lines 13-16; G-1415, p. 19-27

Bayer/AHI Response: Bayer/AHI do not dispute that cross contamination of *Campylobacter* within a poultry house may occur after initial colonization, through ingestion of contaminated fecal droppings (coprophagia) and later also through contaminated water and feed in open systems. However, Bayer/AHI disagree with the inference of this PFOF that all broiler or turkey houses become infected on the grounds that, as noted in Bayer's response to PROF 311, prevalence of flock infection varies from 10% to over 90%, by country, and by season. B-1908 P.3 L.19-21 and L.22-23; G-1459 P.4 L.38-39.

In addition, *Campylobacter* colonization in broilers and turkeys may have significant host specific differences. B-1908 P.4 L.11-12. Differences between turkeys and chickens including differences in *Campylobacter* prevalence between the species *jejuni* and *coli* have been known for years. A-201 P.16 L.15-17; B-1917 P.20 L.6-7. Therefore, colonization between turkeys and broilers may also vary in ways inconsistent with this PFOF.

316. In an experiment of a small (400 animal) turkey flock, when three experimentally infected seeder birds colonized with *Campylobacter* were introduced into the flock, the remaining turkeys became infected within 9-12 days. Jacobs-Reitsma WDT: p. 4, lines 18-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that it omits critical information relating to sampling size of the study (*i.e.*, 50 animals). G-1459 P.4 L.20. Bayer/AHI does not object to a PFOF that properly reflects the limited nature and sample size of this study.

317. Coprophagia means ingestion of feces. Jacobs-Reitsma WDT: p. 4, line 15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

318. Colonization in commercial poultry flocks can be with more than one *C. jejuni* and/or *C. coli* subtype at the same time, with a succession of strains appearing. Jacobs-Reitsma WDT: p. 4, lines 27-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

319. Transport-induced stress increases the exterior concentration of *Campylobacter* on birds and shedding of *Campylobacter* that may subsequently result in carcass contamination. Jacobs-Reitsma WDT: p. 5, lines 6-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

320. The transport vehicles and crates used in shipping may be an additional source of contamination between batches of birds and farms. Jacobs-Reitsma WDT: p. 5, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

321. Contaminated crates may be a serious risk for *Campylobacter* transmission during partial depopulation of broiler houses. Jacobs-Reitsma WDT: p. 5, lines 13-15; G-1663

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

322. Contamination of retail poultry with *Campylobacter* is higher than contamination of pork or beef. Jacobs-Reitsma WDT: p. 5, lines 18-20; G-444, p. 467-481

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that this PFOF is inapplicable to the hearing. Any comparison between poultry and pork or beef is not at issue in this hearing.

323. Zhang found that when fluoroquinolone-resistant and susceptible strains of *Campylobacter* are given together in equal numbers to chickens, the fluoroquinolone-resistant strains take over, displacing the susceptible ones. Jacobs-Reitsma WDT: p. 6, lines 17-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is inaccurate. As noted in Bayer's response to 481, McDermott's testimony indicates that this information is based solely on "preliminary results" and is based on a personal communication with Qijing Zhang. G-1465 P.6 L.18-21. Preliminary results of a unpublished study are insufficient support for the proposed finding of fact. Furthermore, CVM's own witness Jacobs-Reitsma acknowledges that this "phenomenon was not observed" in *in vitro* studies. G-1459 P.6 L.20-21. In addition, published studies by both McDermott and Zhang indicate that fluoroquinolone-susceptible strains can recolonize and thus can "out-compete" the fluoroquinolone-resistant strains. B-868; A-190.

324. During 1992 and 1993, Jacobs-Reitsma tested 187 broiler flocks from 160 farms for the presence of *Campylobacter*. 617 isolates from 150 different flocks were tested for

susceptibility to nalidixic acid, flumequine, enrofloxacin, and ciprofloxacin by disc diffusion method. In all, 29.3% were found to be cross-resistant to the quinolones tested. These isolates originated from 38% of the flocks tested, indicating even more widespread existence of quinolone resistant *Campylobacter*. Jacobs-Reitsma WDT: p. 6, lines 43-49

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that this PFOF is misleading in that the data present in the article do not support the statement that there was an "even more widespread existence" of quinolone resistance. The PFOF also does not reflect that it was unknown whether the birds tested in the study had been treated with a fluoroquinolone or not. G-1459 P.6 L.50 – P.7 L.1; G-319.

325. In 1994, Jacobs-Reitsma led a study to assess the impact of Baytril therapy on the development of quinolone resistance in *Campylobacter*. Jacobs-Reitsma WDT: p. 7, lines 7-9; G-315

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds it is misleading in that Jacobs-Reitsma's 1994 study involved more than one fluoroquinolone. In addition, the study only focused on chickens. G-1459 P.7 L.7-22.

326. In her 1994 study, Jacobs-Reitsma inoculated six groups of broilers with a fluoroquinolone-sensitive *Campylobacter jejuni* strain at 19 days of age. At 26 days of age, five groups of broilers were given Flumesol or Baytril in the drinking water for four days. Those inoculated with fluoroquinolone-sensitive *Campylobacter,* then treated with Baytril, rapidly colonized with fluoroquinolone-resistant *Campylobacter*. One group of broilers was given enrofloxacin on days 1-4 of age, well before they were inoculated with *Campylobacter* on day 19. Jacobs-Reitsma found that treatment of broilers with Baytril before the broilers are colonized with *Campylobacter* does not lead to fluoroquinolone-resistant *Campylobacter*. Jacobs-Reitsma WDT: p. 7, lines 9-16; p. 12, Table 1; G-315

Bayer/AHI Response: Bayer/AHI agree to this PFOF except for CVM's characterization that broilers that were inoculated with fluoroquinolone-sensitive *Campylobacter*, then treated with Baytril, became "rapidly" colonized with fluoroquinolone-resistant *Campylobacter*. Rather, the study presents that the broilers in this group were not tested until three days after the first treatment (i.e., day 29), at which point they were found to be cross-resistant to quinolones. G-315.

327. *Campylobacter* isolates treated with enrofloxacin by Jacobs-Reitsma in her 1994 study were all found to be cross resistant to nalidixic acid, flumequine and enrofloxacin using a disc diffusion method. Jacobs-Reitsma WDT: p. 7, lines 18-21; G-315

Bayer/AHI Response: Bayer/AHI dispute this PFOF. In Jacob-Reitsma's 1994 study, broilers that were given enrofloxacin on days 1-4 of age did not produce "quinolone resistance"; that is, the findings were that the broilers "did not notably change in their susceptibility to nalidixic acid, flumequine or enrofloxacin." G-1459 P.7 L.16-18.

328. Once the first chicken or turkey in a flock becomes infected with *Campylobacter* the rest of the flock quickly becomes colonized with *Campylobacter*. Jacobs-Reitsma WDT: p. 7, lines 32-33

Bayer/AHI Response: As noted in their response to PFOF 315, Bayer/AHI do not in general dispute that cross contamination of *Campylobacter* within an entire poultry house may occur after the initial colonization. However, Bayer/AHI disagree with the inference of this PFOF that all chicken or turkey houses are infected with *Campylobacter* on the grounds that, as noted in Bayer's response to PROF 311, prevalence of flock infection varies from 10% to over 90%, by country, and by season. B-1908 P.3 L.19-21 and L.22-23; G-1459 P.4 L.38-39.

329. Once colonized, both chickens and turkeys tend to stay colonized until slaughter. Jacobs-Reitsma WDT: p. 7, line 34

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "tend" is not adequately defined, and therefore Bayer cannot adequately interpret this sentence. The source of infection also has not been adequately identified, thereby leaving the meaning of the statement in question. Finally, Bayer/AHI disagree with the inference of this PFOF that all chicken or turkey houses are infected with *Campylobacter* on the grounds that, as noted in Bayer's response to PFOF 311, prevalence of flock infection varies from 10% to over 90%, by country, and by season. B-1908 P.3 L.19-21 and L.22-23; G-1459 P.4 L.38-39.

330. The use of fluoroquinolones in poultry that are colonized with *Campylobacter* selects for fluoroquinolone-resistant *Campylobacter* in those poultry. Jacobs-Reitsma WDT: p. 7, lines 35-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

331. Cross contamination of chickens and turkeys occur during the transport and slaughter of commercially raised chickens and turkeys. Jacobs-Reitsma WDT: p. 7, lines 36-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

332. *Campylobacter* are typically present normally and in high numbers in poultry. Jacobs-Reitsma WDT: p. 7, lines 38-39

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that the meaning of the terms "typically", "normally" and "high numbers" are not adequately defined, and therefore Bayer cannot adequately interpret this sentence. In addition, Bayer has previously agreed to a more specific PFOF on this subject, see PFOF # 220, so this PFOF is also repetitive and unnecessary.

333. Treatment of *Campylobacter* colonized broilers with Baytril quickly results in the broilers becoming colonized with fluoroquinolone-resistant *Campylobacter*. Jacobs-Reitsma WDT: p. 12, Table 1; G-315

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "quickly" is not adequately defined, and therefore Bayer cannot adequately interpret this sentence. The statement also mischaracterizes fluoroquinolone-resistant *Campylobacter*. Fluoroquinolone resistance develops in *Campylobacter* as a spontaneous genetic mutation within a *Campylobacter* population and is not as a result of exposure to fluoroquinolones. Fluoroquinolone exposure then can select for resistant *Campylobacter*. Joint Stipulation 1; G-219 at P.68-69; G-1465 P.2 L.18-19, P.4. L.8-9. Also, 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; G-1458 P.4, ¶ 3; G-1459 P.6 L.36-37; B-1908 P.17 L.1-6. Finally, fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4.

Heidi Kassenborg (G-1460)

334. Dr. Kassenborg is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination, except where Dr. Kassenborg testifies to matters related to causality and to causal analysis and interpretation of data.

335. *Campylobacter* causes a significant amount of diarrheal illness in the United States. Kassenborg WDT: p. 2, lines 10-11

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as vague. "Significant" is not defined.

336. *Campylobacter* is the most commonly reported cause of bacterial gastroenteritis in the United States. Kassenborg WDT: p. 2, lines 11-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is inaccurate and misleading. In 2002, CDC reported that for 2001, *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States. This is the most recent information available on this subject. G-1391.

337. *Campylobacter* causes an estimated 2.4 million human infections in the United States annually. Kassenborg WDT: p. 2, line 12; G-410.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is inaccurate and misleading. CDC estimates the US incidence of *Campylobacter* infections in 1999 was 1.4 million and since then has declined. CVM proposed finding of fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. Angulo (G-1452) P.7 L.13-14, L.16-18, P.17 L.10.

338. When antibiotics are indicated for the treatment of *Campylobacter* gastroenteritis, the drug of choice is either a fluoroquinolone (e.g., ciprofloxacin) or erythromycin. Kassenborg WDT: p. 2, lines 12-14.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is inaccurate and misleading. In situations where antibiotic therapy is indicated, macrolides such as erythromycin or azithromycin are the preferred treatment for campylobacteriosis. B-1905 P.4. L.9-12.

339. There is an increasing proportion of human *Campylobacter* isolates resistant to fluoroquinolones in most regions of the world. Kassenborg WDT: p. 2, lines 16-18

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being an unsubstantiated opinion. It does not correct for changes in isolation criteria and procedures over time that are expected to have caused *reported* resistance rates to increase even where *true* rates have not. B1901 P.71-72.

340. Poultry is the most frequently identified source of *Campylobacter* infections. Kassenborg WDT: p. 2, lines 20-21

Bayer/AHI Response: Bayer/AHI dispute this PFOF because recent evidence in the record disputes the contention that chicken or turkey is a major source of *Campylobacter* infections. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis.

341. In 1998-1999, Kassenborg led a 12 month study in FoodNet sites to look at risk factors associated with non-outbreak related fluoroquinolone-resistant *Campylobacter* infections. Kassenborg WDT: p. 3, lines 1-3; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

342. FoodNet is an acronym for the Foodborne Diseases Active Surveillance Network. Kassenborg WDT: p. 3, lines 3-4.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. An acronym is a word formed from the initial letters of a name or parts of a series of words. Bayer/AHI do not dispute that FoodNet is shorthand for the Foodborne Diseases Active Surveillance Network.

343. FoodNet was initiated in 1995 as a collaborative effort among the Centers for Disease Control and Prevention (CDC), the U.S. Department of Agriculture, the U.S. Food and Drug Administration, and selected state health departments. Kassenborg WDT: p. 3, lines 4-7.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

344. Kassenborg's study enrolled patients from a population of 20,723, 982 people in FoodNet sites (or 7.7% of the U.S. population). Kassenborg WDT: p. 3, lines 11-12; G-337.

Bayer/AHI Response: Bayer/AHI can neither admit nor deny this PFOF. G-337 P.5 states that during the study period the population in the FoodNet catchment area was 25,859,311.

345. The purpose of FoodNet is to better determine the burden of foodborne illnesses including *Campylobacter* infections in the United States. Kassenborg WDT: p. 3, lines 7-8.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

346. NARMS is a collaborative effort among the FDA, USDA, and CDC to monitor changes in susceptibility of enteric bacteria to antimicrobial drugs used in animals and humans. Kassenborg WDT: p. 3, lines 21-23.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

347. There is no official breakpoint for establishing resistance to ciprofloxacin among *Campylobacter* isolates. Kassenborg WDT: p. 4, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

348. The National Committee for Clinical Laboratory Standards (NCCLS) uses an MIC of $\geq$4 μg/ml for ciprofloxacin resistance to *Enterobacteriaceae*. Kassenborg WDT: p. 4, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

349. The Kassenborg study is a case-control study. Kassenborg WDT: p. 4, lines 9-10; G-337

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

350. In the Kassenborg study, of the 858 *Campylobacter* isolates from humans tested for susceptibility to fluoroquinolones, 94 (11%) were fluoroquinolone-resistant. Kassenborg WDT: p. 6, line 3; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and potentially misleading. There are no official interpretive criteria for what constitutes "fluoroquinolone-resistant" for *Campylobacter* (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). Thus, asserting that 11% were "fluoroquinolone-resistant" uses a term that lacks any accepted definition to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that 11% of the isolates in question were resistant to clinically relevant doses of fluoroquinolones. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: P.2 L.40-43; Smith, G-1473 P.10 ¶ 22) Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in PFOF #350 that "94 (11%) were fluoroquinolone-resistant. Kassenborg WDT: P.6 L.3; G-337" is vague and misleading. It is also incorrect if "fluoroquinolone-resistant" is taken to mean, imply, or suggest "resistant to fluoroquinolone administered *in vivo*".

351. In the Kassenborg study, taking a fluoroquinolone antibiotic prior to coming down with illness due to *Campylobacter* infection did not account for the fluoroquinolone-resistant strain of *Campylobacter.* Kassenborg WDT: p. 6, line 19- p. 7, line 4; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Kassenborg's data from the survey questionnaire are missing a substantial amount of information on prior antibiotic use. Kassenborg's study includes people who took an antibiotic but did not identify it by class or type. Those responses should be eliminated from consideration. Kassenborg left them in her analysis. B-1900 P.32 L.19-24. Prior human use is clearly a risk factor for developing fluoroquinolone-resistant *Campylobacter.* Fluoroquinolone use in humans can act as a selection pressure for fluoroquinolone-resistant bacteria in the human digestive tract. Joint Stipulation 6. Human use of fluoroquinolones, including use for treatment of campylobacteriosis, can lead to the emergence of fluoroquinolone-resistant *Campylobacter* in the treated individual. Joint Stipulation 8. It is logical to exclude not only patients reporting fluoroquinolone use prior to culture but to also exclude those who reportedly took an unknown antimicrobial. B-1900 P.32 L.19-24. The use of a quinolone beginning one or more days before collection of stool specimen was independently associated with resistant *C. jejuni* infections. G-589 P.4. This PFOF is also refuted by B-1901 P.49, 59, and 79.

352. In the Kassenborg study, patients with fluoroquinolone-resistant *Campylobacter* infections were not more likely to have taken fluoroquinolones in the month before stool specimen collections than were those with susceptible infections. Kassenborg WDT: p. 6 lines 22-23; p 7, lines 1-4; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Kassenborg's data from the survey questionnaire are missing a substantial amount of information on prior antibiotic use. Kassenborg's study includes people who took an antibiotic but did not identify it by class or type. Those responses should be eliminated from consideration. Kassenborg left them in her analysis. B-1900 P.32 L.19-24. Prior human use is clearly a risk factor for developing fluoroquinolone-resistant *Campylobacter.* Fluoroquinolone use in humans can act as a selection pressure for fluoroquinolone-resistant bacteria in the human digestive tract. Joint Stipulation 6. Human use of fluoroquinolones, including use for treatment of campylobacteriosis, can lead to

the emergence of fluoroquinolone-resistant *Campylobacter* in the treated individual. Joint Stipulation 8. It is logical to exclude not only patients reporting fluoroquinolone use prior to culture but to also exclude those who reportedly took an unknown antimicrobial. B-1900 P.32 L.19-24. The use of a quinolone beginning one or more days before collection of stool specimen was independently associated with resistant *C. jejuni* infections. G-589 P.4. This PFOF is also refuted by B-1901 P.49, 59, and 79.

353. Of the 27 foreign travel-associated fluoroquinolone-resistant *Campylobacter* cases found in the Kassenborg study, 9 (33%) traveled to Western Europe, seven (26%) traveled to Mexico, five (19%) each traveled to Asia and South America and one (4%) traveled to Central America. Kassenborg WDT: p. 7 lines 14-17; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. A number of patients in the Kassenborg study did not report whether or not they traveled out of the country. Such patient information should have been eliminated from the analysis. B-1900 P.26 L.22-23.

354. 58% of patients with fluoroquinolone-resistant *Campylobacter* infections in Kassenborg's study had domestically acquired fluoroquinolone-resistant *Campylobacter* infections. Kassenborg WDT: p. 7, lines 19-22; and p. 9, lines 5-6; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. A number of patients in the Kassenborg study did not report whether or not they traveled out of the country. Such patient information should have been eliminated from the analysis. B-1900 P.26 L.22-23.

355. In the univariate analysis comparing cases with their age matched well controls in the Kassenborg study, domestically acquired fluoroquinolone-resistant *Campylobacter* infections were associated with eating chicken or turkey cooked at a commercial establishment during the 7 days before illness onset. Kassenborg WDT: p. 8, lines 3-5; G-337

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

356. A multivariate model is used to see if identified risk factors are independently statistically significant. Kassenborg WDT: p. 8, lines 9-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

357. Using a stepwise conditional logistic regression in Kassenborg's study, eating chicken or turkey at a commercial establishment was the only risk factor that remained independently associated with illness. Kassenborg WDT: p. 8, lines 11-18; G-337

Bayer/AHI Response: Bayer/AHI dispute the PFOF. Stepwise conditional logistic regression is an inappropriate statistical method for this data set. The stated conclusion (that "eating chicken or turkey at a commercial establishment was the only risk factor that remained independently associated with illness") is not a fact, but rather a result of improper statistical analysis. Cox B-1901 P.33. The method used (e.g., forward or backward stepwise variable selection) has not been specified in enough detail to allow independent replication of the alleged

findings. The conclusion of this PFOF that "eating chicken or turkey at a commercial establishment was the only risk factor that remained independently associated with illness" is refuted in B-1901 P.33, "For example, an initial classification tree analysis shows that *ground beef outside the home and raw milk both appear to be significant risk factors for FQ-r CP,* in contrast to Dr. Kassenborg's claim that "eating chicken or turkey in a commercial establishment was the only risk factor that remained independently associated with [FQ-r CP] illness."

358. In Kassenborg's study, patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infections were 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). Kassenborg WDT: p. 8, lines 18-20; G-337

Bayer/AHI Response: Bayer/AHI Response: Bayer/AHI dispute the PFOF as containing unstated and incorrect assumptions. The MOR of 10 is based on a model that is not appropriate for these data and for which no validation has been done (or at least has been reported). B-1901 P.33. Thus, the PFOF states as a fact an inference from a hypothetical and unvalidated model that is not in agreement with the data. B-1901 P.33.

An extract from rxcamp4, the data set provided to us by CDC that contains CIPRES, gives the following table for cases without foreign travel (CACO=1 and TRAVEL=0):

	CIPRES=0,CACO=0	CIPRES=1,CACO=1
CORT=0	393	40
CORT=1	122	20

CORT = chicken or turkey cooked at a commercial establishment

In Kassenborg's terms, "Patients with domestically-acquired fluoroquinolone-resistant *Campylobacter* infections" (CIPRES = 1, CACO = 1) have a probability 20/(20 + 40) = 0.33 of reporting having eaten chicken or turkey at a commercial establishment. "Well controls" (CIPRES = 0, CACO = 0) have a probability 122/(122 + 393) = 0.24 of reporting having eaten chicken or turkey at a commercial establishment. Thus, while the PFOF claims that "Patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infections were 10 times more likely to report having eaten chicken or turkey at a commercial establishment than were well control subjects", the unvarnished data in the above table show that the ratio is only 0.33/0.24 = 1.4.

The discrepancy between a 1.4-fold increase and a 10-fold increase (approximately a 7-fold discrepancy) illustrates how CVM experts can and do use unvalidated statistical models to exaggerate and/or create risks. The data in the above table give a ratio that falls below the claimed "lower 95% confidence interval" of 1.3 reported by Kassenborg. This is presumably not because anything unlikely or surprising has happened, but because the so-called "95% confidence interval" presented by Dr. Kassenborg ignores all model uncertainty while using a model that is inappropriate for the data.

These comparisons illustrate that the PFOF is not a "fact" at all, but purely a result of (unstated) modeling assumptions. Until Dr. Kassenborg (and CVM and its witnesses) start using well-validated models, as good modeling practice requires and as they have without exception failed to do, their model-based claims and PFOFs about quantitative risks must be rejected as unvalidated speculations, rather than as facts.

359. Fluoroquinolone-resistant *Campylobacter* is present on chicken products at U.S. grocery stores. Kassenborg WDT: p. 9, lines 19-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

360. A population attributable fraction is the reduction in incidence that would be achieved if the population had been entirely unexposed compared with its current (actual) exposure pattern. Kassenborg WDT: p. 9, lines 1-3

Bayer/AHI Response: Bayer/AHI dispute the PFOF. This is an incorrect understanding of what a population attributable fraction is. The population attributable fractions calculated by Kassenborg do not correct for confounding and cannot be assigned a causal interpretation. Her method of calculation can produce significantly positive population attributable fractions even for purely protective factors. It is inappropriate for use in this setting and her interpretations of population attributable fractions are mistaken. Cox B-1901 P.38-39, P.57.

361. Eating chicken or turkey at a commercial establishment account for 38% of the population-attributable fraction for domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the Kassenborg study. Kassenborg WDT: p. 9, lines 3-5; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by G-1452 P.10 L.41-44. Moreover, the population-attributable fraction for domestically acquired fluoroquinolone-resistant *Campylobacter* infections cited by Kassenborg have not been calculated correctly. In fact, calculations in evidence show that approximately 0% of all fluoroquinolone-resistant infections can be attributed to eating chicken in a commercial establishment. Cox B-1901 P.38-39, P.57-62.

362. In the Kassenborg study, 22% of all fluoroquinolone-resistant infections could be attributed to eating chicken or turkey in a commercial establishment. Kassenborg WDT: p. 9, lines 7-8; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by G-1452 P.10 L. 41-44. Moreover, the attributable risks cited by Kassenborg have not been calculated correctly. In fact, calculations in evidence show that approximately 0% of all fluoroquinolone-resistant infections can be attributed to eating chicken in a commercial establishment. Cox B-1901 P.38-39, P.57-62.

363. Poultry is the dominant source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the United States. Kassenborg WDT: p. 9, lines 21-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is the dominant source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the United States.

364. Many studies suggest that fluoroquinolone use in poultry is a major contributor to the increase in human fluoroquinolone-resistant *Campylobacter* infections. Kassenborg WDT: p. 10, lines 2-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. Evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis, specifically including fluoroquinolone-resistant campylobacteriosis. B-1901, P. 40. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, Bayer/AHI dispute the premise of this PFOF, that there has been an "increase in human fluoroquinolone-resistant *Campylobacter* infections". The national surveillance network designed to monitor human fluoroquinolone-resistant *Campylobacter* infections in the U.S., NARMS, has not produced reliable national prevalence results capable of demonstrating any increasing trend. A-200 P.17 L.23-24 – P.18 L.1-2, P.19 L.16-17, P.19 L.23 – P.20 L.1-2, P.20 L.14-15, P.21 L.10-13, P.25 L.18-22, P.27 L.5-24, P.55 L.6-7, P.30 L.1 – P.33 L.17. Human NARMS does not show a national prevalence. A-199 P.11-13. Moreover, in the U.S. there is no reliable baseline to compare pre-approval and post-approval levels of human fluoroquinolone-resistant *Campylobacter*. B-1900 P.3 L. 35-37.

365. Many travel-associated *Campylobacter* cases may also be a consequence of fluoroquinolone use in food-producing animals. Kassenborg WDT: p. 10, lines 4-5

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The PFOF is speculative on its face and is not supported by any evidence.

366. The average person's risk for fluoroquinolone-resistant *Campylobacter* infection could potentially be reduced 22% if the risk associated with commercially prepared chicken and turkey were eliminated. Kassenborg WDT: p. 10, lines 17-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This is not a fact, but an unjustified speculation based on a misinterpretation of PARs as having a direct causal interpretation. Cox B-1901 P.38-39, P.57. This PFOF is refuted by G-1452 P.10 L. 41-44. Moreover, the attributable risks cited by Kassenborg have not been calculated correctly. In fact, calculations in evidence show that approximately 0% of all fluoroquinolone-resistant infections can be attributed to eating chicken in a commercial establishment. Cox B-1901 P.38-39, P.57-62.

367. Fluoroquinolone use in humans did not contribute directly to the observed resistance in Kassenborg's study. Kassenborg WDT: p. 10, line 22; G-337

Bayer/AHI Response: Bayer/AHI dispute the PFOF. This PFOF ignores the likely possibility that foodborne pathogens such as *Campylobacter* can become resistant from fluoroquinolone use in humans, become present in the environment and be transferred to humans (and poultry) from the environment. This PFOF is therefore refuted by the fact that human use of a fluoroquinolone, including use for treatment of campylobacteriosis, can lead to the emergence of fluoroquinolone-resistant *Campylobacter* in the treated individual. Joint Stipulation 8; B-127 P.1; G-589 P.4, 6; G-707 P.11. Sewage treatment plants discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of resistant bacteria, including fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9. *Campylobacter* can be isolated from many species of wild animals including, field mice, foxes, rabbits, badgers, and wild birds including passiformes and columiformes. B-1908 P.9 L.18-29; G-1459 P.3 L.21-23; B-263. *Campylobacter* is found in the environment, including in water and at beaches. G-1459 P.3 L.21-23; B-1910 P.4 L.4-6; G-75. *Campylobacter*, including fluoroquinolone-resistant *Campylobacter* are frequently isolated in surface and ground waters, including drinking water supplies. B-1910 P.4 L.9-10. Thus, fluoroquinolone use in humans can contribute directly to the observed resistance in Kassenborg's study, even if study subjects were not aware of having been exposed (e.g., to ciprofloxacin-contaminated drinking water) and even if such exposure was not recorded.

368. In Kassenborg's study, patients with fluoroquinolone-resistant *Campylobacter* infections were no more likely to have taken a fluoroquinolone before the specimen was collected than were patients with fluoroquinolone sensitive infections. Kassenborg WDT: p. 10, line 22 – p. 11, line 2; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Kassenborg's data are missing a substantial amount of information from the survey questionnaire on prior antibiotic use, and it is generally accepted that prior use is clearly a risk factor for developing fluoroquinolone-resistant *Campylobacter*. It is logical to exclude not only patients reporting fluoroquinolone use prior to culture but to also exclude those who reportedly took an unknown antimicrobial. B-1900 P.32 L.19-24. If more cases than controls had taken a fluoroquinolone as the unknown antimicrobial, then the results would have been confounded. To eliminate this potential, all patients with a

known history of fluoroquinolone use prior to culture and those who took an unknown antibiotic must be eliminated from the analysis. Smith states in his paper that the use of a quinolone beginning one or more days before collection of stool specimen was independently associated with resistant *C. jejuni* infections. G-589 P.4.

369. Approximately 320,000 fluoroquinolone-resistant *Campylobacter* infections occurred in 1998 in the United States. Kassenborg WDT: p. 11, lines 8-9; G-337

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This is an inaccurate and misleading estimation. Kassenborg based her calculation on the assumption there are 2.4 million annual cases of *Campylobacter* infection. CDC has confirmed that this number is now less than 1.4 million, therefore the 320,000 infections is an overestimation. CVM proposed finding of fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10

370. The Kassenborg study defined fluoroquinolone resistance as a MIC greater than or equal to 4 micrograms per milliliter for ciprofloxacin. Kassenborg WDT: p. 4, lines 2-3.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, provided that "define" means only "define for purposes of statistical analysis" (rather than referring to any legal or scientific or clinically relevant definition) and provided that "resistance" means only "resistance *in vitro*.". The *in vitro* resistant definitions have not been validated to affirm that clinical resistance correlates with these levels. Burkhart (B-1900) P.4 L.22-24. No data link in vitro MICs conducted on *Campylobacter* spp. to clinical resistance in humans. Burkhart (B-1900) P.10 L.1-2. 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.

371. The Kassenborg study used the following methods: (a) a case was defined as diarrheal illness in a person living in a FoodNet site whose stool sample yielded a *Campylobacter* isolate and who was not part of a recognized outbreak; (b) diarrhea was defined as three or more loose stools in a 24-hour period; (c) one control subject was obtained for each infected person; and (d) controls were persons without infection who were matched by age group to the case. Kassenborg WDT: p. 4, lines 7-20; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

372. The Kassenborg study defined "foreign travel-associated" cases as *Campylobacter* infection in persons who had traveled outside the United States during the week before their illness onset and "domestically acquired" cases as infection in those who did not travel outside the United States during the week before their illness onset. Kassenborg WDT: p. 5, lines 17-20; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

373. The Kassenborg study excluded potential case and control subjects if they could not speak English, if they did not have a home telephone, if they or a household member had a

confirmed case of *Campylobacter* infection in the 28 days before the potential case subject's stool collection date, or if they were otherwise unable to complete the interview. Kassenborg WDT: p. 5, lines 4-8; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

374. The Kassenborg study also excluded potential case subjects if their diarrhea started more than 10 days before their stool sample was collected, if they were unreachable by telephone within 21 days after their stool collection date, or if they could not recall their illness onset date and also excluded potential control subjects if they had diarrhea in the 28 days before their matching case subject's onset date. Kassenborg WDT: p. 4, line 23 through p. 5, line 4; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

375. Of the 858 persons whose fluoroquinolone resistance status was known, 646 (75%) were interviewed and enrolled in the Kassenborg study. Kassenborg WDT: p. 6, lines 5-7; G-337.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

376. Of the 646 persons with a *Campylobacter* infection, 64 persons had a fluoroquinolone-resistant *Campylobacter* infection and 582 persons had a fluoroquinolone-sensitive *Campylobacter* infection in the Kassenborg study. Kassenborg WDT: p. 6, lines 7-8; G-337.

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and misleading. There are no official interpretive criteria for what constitutes "fluoroquinolone-resistant" *Campylobacter* (CVM PFOF #347 and #747, citing K. Smith WDT: p. 4, lines 4-5) and the specific term "fluoroquinolone-resistant *Campylobacter* infection" is undefined. Infection is an in vivo process, and the term "fluoroquinolone-resistant *Campylobacter*" has not been defined for *in vivo* applications. Thus, asserting that "64 persons had a fluoroquinolone-resistant *Campylobacter* infection" uses a term that lacks any accepted definition and that suggests the false conclusion that 64 persons had infections that were resistant to fluoroquinolones. This is not what was shown.

Stuart Levy (G-1463)

377. Dr. Levy is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

378. APUA is a non-profit organization, founded in 1981, dedicated to research and education on antibiotic use and antibiotic resistance. Levy WDT: p. 1, lines 42-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

379. Overuse of antimicrobials can render them ineffective. Levy WDT: p. 2, line 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and inaccurate in general. This finding of fact is so general and non-specific that it is not applicable to the specific issues in this proceeding. The finding of fact specifies neither particular antimicrobials nor particular bacteria, so that as a general statement it has no applicability to this proceeding. Moreover, while overuse of antimicrobials can render them **less** effective, Bayer is unaware of any antibiotic that has become ineffective due to overuse. Many antibiotics have been used (arguably, "overused") for decades, yet remain effective. The witness provides no support for this statement and no definition of "overuse".

380. Infections caused by multi-resistant bacteria can be difficult or impossible to treat. Levy WDT: p. 2, lines 12-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is overly broad and non-specific to the issues in this case. This PFOF is not supported by any documentation. Multi-resistant infections require selection of the appropriate antimicrobial to which the pathogen is susceptible. If the appropriate antimicrobial is selected, it will not result in an infection that is "difficult or impossible to treat". As relates to the issues in this case (fluoroquinolone resistance in *Campylobacter*), the clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation #14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "difficult or impossible to treat." Evidence in the record demonstrates that so called fluoroquinolone-resistant *Campylobacter* infections are fully treatable with Ciprofloxacin. B-1913 P.19 L.10-19, P.20 L.3-11, P.17 L.8 – P.18 L.15.

381. One way that bacterial antibiotic resistance genes appears is through mutation in the target chromosomal gene. Levy WDT: p. 2, lines 39-40

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

382. The emergence of fluoroquinolone resistance among *Campylobacter* (following fluoroquinolone use in poultry) involves spontaneous mutation in the target gene for the fluoroquinolones (the gyrase or topoisomerase, enzymes essential for bacterial replication) which prevents the drug's inhibition of the enzyme activity. Levy WDT: p. 3, lines 20-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is misleading as it implies that the mechanism by which fluoroquinolone resistance emerges only applies "following fluoroquinolone use in poultry". Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and

continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. This PFOF also fails to acknowledge that the identical spontaneous mutation mechanism is involved regardless of source of selective pressure. Joint Stipulation 1. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. (B-1908 P.15 L.12-13.

383. *Campylobacter* is unique in that the single target gene mutation is enough to produce a sufficiently high level of fluoroquinolone resistance to thwart treatment of the bacteria in a clinical disease. Levy WDT: p. 3, lines 26-28

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate, vague, and misleading. The meaning of the term "sufficiently high level of fluoroquinolone resistance to thwart treatment" is not defined clinically. No clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "thwart treatment." Further, there is evidence refuting the implied statement, "high level of fluoroquinolone resistance [thwarts] treatment of the bacteria in a clinical disease" (e.g., Piddock, 1999, cited in B-1901. 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. show that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

384. The single target gene mutation seen in *Campylobacter* can explain why fluoroquinolone resistance emerges more rapidly in *Campylobacter* following fluoroquinolone use than in other enteric pathogens as *E. coli* and *Salmonella*. Levy WDT: p. 3, lines 32-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF as speculative and inaccurate. The implied assertion that "fluoroquinolone resistance emerges more rapidly in *Campylobacter* following fluoroquinolone use than in other enteric pathogens as *E. coli* and *Salmonella*" is unsubstantiated in this PFOF. The PFOF makes a comparison between *Campylobacter* and *E. coli* and *Salmonella* without explaining the types of mutations that occur in each bacteria. It also is misleading insofar as it implies or suggests that "resistant" *Campylobacter* have clinical significance. As previously stated, the clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating

loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

385. The endogenous multidrug efflux system identified in *Campylobacter* (CmeABC) has only been shown to contribute to intrinsic low-level resistance to a fluoroquinolone and not to clinical resistance levels. Levy WDT: p. 3, lines 37-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being misleading and inaccurate. It uses the undefined term "clinical resistance levels" in a context suggests that *Campylobacter* exhibits "clinical resistance levels" as well as "intrinsic low-level resistance". But, as previously stated, no "clinical resistance levels" have been defined or reported for *Campylobacter*. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance levels. 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

386. In *Campylobacter*, the endogenously expressed efflux pump amplifies the effect of a single mutation in the target gene, making these single gene mutants more easily selected and the resistance they specify more clinically relevant than are single target mutations in other bacteria. Levy WDT: p. 3, lines 42-46

Bayer/AHI Response: Bayer/AHI dispute this PFOF as speculative and inaccurate. It refers to "making these single gene mutants more easily selected and the resistance they specify more clinically relevant" when no clinical relevance has been established for the resistance in question. As previously stated, the "clinical relevance" of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss

of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce "clinically relevant" resistance. 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

387. Fluoroquinolone resistance in *Campylobacter* is attributable to a chromosomal mutation. Levy WDT: p. 4, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

388. Fluoroquinolone resistance in *Campylobacter* is not transferable because this organism is not able to transfer DNA from one strain to another by the mechanism of transformation. Levy WDT: p. 4, lines 1-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

389. The increase in the frequency of fluoroquinolone resistance among the *Campylobacter* associated with poultry is the result of multiplication and spread of the original mutant and not the transfer of the resistance gene itself. Levy WDT: p. 4, lines 4-7

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI dispute that there is an increase in the frequency of fluoroquinolone resistance among *Campylobacter* associated with poultry. G-119; G-205; G-206; G-207; G-760; G-1363. Bayer/AHI agree that the evidence demonstrates that fluoroquinolone resistance does not spread via gene transfer.

390. The emergence, selection, and mechanism of fluoroquinolone resistance in bacteria is characteristic of the bacterium and not the host animal in which resistance is selected. Levy WDT: p. 4, lines 9-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

391. What we observe in the selection of fluoroquinolone resistance in *Campylobacter* from chickens is what we would expect to see emerge in *Campylobacter* associated with people, turkeys, cattle, pigs, and other animals when given fluoroquinolones. Levy WDT: p. 4, lines 13-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

392. Multiple studies demonstrate the ease with which bacteria, including *Campylobacter,* harbored in animals on farms can be passed via food products from animals to people leading to disease. Levy WDT: p. 4, lines 30-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. This witness provides no documentation for this statement, nor do we believe it is correct. In fact, the available evidence suggests that most people eat chicken and do *not* develop campylobacteriosis from doing so (B-1901), arguing against the hypothesized "ease with which bacteria, including *Campylobacter,* harbored in animals on farms can be passed via food products from animals to people leading to disease". B-1901 P.67.

393. APUA initiated a two-year project called Facts about Antimicrobials in Animals and the Impact on Resistance (FAAIR) and convened a Scientific Advisory Panel, whose charge was to gather evidence and draw conclusions about human health impacts of antimicrobial use in agriculture. Levy WDT: p. 4, lines 41-46

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

394. Scientific and medical evidence indicates that resistant pathogens may be transferred directly from food animals to humans through the food supply. Levy WDT: p. 6, lines 11-12; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as speculative and inaccurate. This proposed finding of fact is taken out of context and misrepresents the witness testimony. This statement was one of several bullet points preceded by the statement, "The FAAIR report addressed the following points:" The proposed finding of fact misrepresents this statement as a definitive conclusion when in actuality it was a point to be addressed, not a conclusion. Levy WDT: P.6 L.11-12; G-1350.

395. Antimicrobial resistance may limit treatment options, and increase the number, severity and duration of infections in humans and animals. Levy WDT: p. 6, lines 16-18; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF because, as related to fluoroquinolones and *Campylobacter*, it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "limit treatment options." Furthermore, the record contradicts that for *Campylobacter* there would be any increase in the number, severity and duration of infections in humans. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment #4, P.116-118; G-1489 P.10-11. Epidemiological data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness in patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. B-1901 P.78.

396. Precise figures describing the extent and quantity of antimicrobial use in food animal production and plant agriculture are not publicly available. Levy WDT: p. 6, lines 44-45; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This witness provides no documentation for this statement and the proposed finding of fact is not relevant to this proceeding.

397. Resistant infections may be more severe than susceptible infections. Levy WDT: p. 7, lines 20; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as speculative and because, as related to fluoroquinolones and *Campylobacter*, it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. Furthermore, the record contradicts that for *Campylobacter* resistant infections are "more severe" than susceptible infections. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment #4, P.116-118; G-1489 P.10-11. Epidemiological

data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness in patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. B-1901 P.78.

398. Infections caused by resistant pathogens may be more difficult to treat because doctors have to try several different drugs before they find one that is effective. Levy WDT: p. 7, lines 21-23; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF because, as related to fluoroquinolones and *Campylobacter*, it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. Furthermore, the record contradicts that for *Campylobacter* resistant infections "may be more difficult to treat" than susceptible infections. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment 4, P.116-118; G-1489 P.10-11. Epidemiological data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness in patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. B-1901 P.78.

399. Resistance accounts for an additional 17,668 *Campylobacter jejuni* infections, resulting in 95 hospitalizations per year in the United States. Levy WDT: p. 7, lines 37-39; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate, containing hidden and incorrect assumptions, and unsubstantiated. First, the "additional 17,668 *Campylobacter jejuni* infections, resulting in 95 hospitalizations per year in the United States" reflects hypothetical assumption-driven estimates, not data points or facts. Second, the PFOF makes a causal attribution of hospitalizations to resistance when in fact, no causal analysis supporting this conclusion has been done. The source on which this claim is based uses assumption-driven analyses that do not correct for confounding and that do not correctly distinguish between association and causation. Finally, evidence in the record refutes this PFOF by showing that a correct causal analysis indicates that resistance is associated with approximately zero additional *Campylobacter jejuni* infections per year in the United States, rather than 17,668. B-1901 P.40.

400. Resistance to fluoroquinolones, the drug of choice for severe food poisoning in humans, results in an estimated 400,000 more days of diarrhea per year in the U.S. Levy WDT: p. 7, lines 44-46; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate, containing hidden and incorrect assumptions, and unsubstantiated. First, the "estimated 400,000 more days of diarrhea per year in the U.S." is a hypothetical assumption-driven estimate, based on incorrect assumptions; it is not a data point or a fact. Second, the source on which this claim is based uses assumption-driven analyses that do not correct for confounding and that do not correctly distinguish between association and causation. Thus, the term "results in" in the PFOF is unjustified. Finally, evidence in the record refutes this PFOF by showing that a correct causal analysis indicates that resistance is associated with approximately zero additional days of diarrhea per year in the United States. B-1901 P.40. The "estimated 400,000 more days of diarrhea per year in the U.S." referred to in this PFOF is refuted by analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. showing that there is no significant difference in the mean duration of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

401. In the United States, the total amount of antimicrobials administered to animals is comparable to that used in human medicine. Levy WDT: p. 8, lines 17-18; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague, misleading and unsubstantiated. The meaning of "comparable" in this context is not defined in this PFOF. If it means "comparable in magnitude of resulting contribution to resistance in bacterial pathogens leading to treatment failures in humans", then we believe it is false and misleading.

402. Transfer of bacteria from food animals to humans is a common occurrence. Levy WDT: p. 8, line 22; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate as it applies specifically to poultry and *Campylobacter*. This witness provides no documentation for this statement in this context, nor do we believe it is correct. In fact, the available evidence suggests that most people eat chicken and do *not* develop campylobacteriosis from doing so (B-1901), arguing against the hypothesized "ease with which bacteria, including *Campylobacter*, harbored in animals on farms can be passed via food products from animals to people leading to disease". B-1901 P.67.

403. Antimicrobial resistance limits treatment options and increases the number, severity and duration of infection in humans. Levy WDT: p. 8, lines 24-25; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF because, as related to fluoroquinolones and *Campylobacter*, it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of

resistance is necessary to produce clinical resistance and "limit treatment options." Furthermore, the record contradicts that for *Campylobacter* there would be any increase in the number, severity and duration of infections in humans. There are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. 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. *Campylobacter* enteritis resolves itself without treatment in the vast majority of cases (e.g., is "self-limiting") whether fluoroquinolone-susceptible or fluoroquinolone-resistant. B-1909 P.3 L.16-17; G-240 P.1; G-530 P.1; G-622 P.1. There is no statistical difference between the mean durations of diarrhea for fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* cases. B-1901 P.39; B-1900 P.35 L.4-6; P.36 L.4-5; Angulo (G-1452), Attachment 4, P.116-118; G-1489 P.10-11. Epidemiological data support the conclusion that treatment of fluoroquinolone-resistant *Campylobacter* illness in patients with ciprofloxacin is usually effective, and as effective as treatment of patients with fluoroquinolone-susceptible *Campylobacter* illness. B-1901 P.78.

The PFOF is inaccurate specifically for domestically acquired fluoroquinolone-resistant *Campylobacter* infections, the subject of this proceeding. 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.

404. The loss of antibiotics because of resistance severely limits the clinician's choice for treatment and can lead to death of the patient. Levy WDT: p. 9, lines 26-28; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as irrelevant and inaccurate in the context of fluoroquinolones and *Campylobacter*, for which it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated; see our response to PFOF 403.

405. Some antibiotics, including the fluoroquinolones, are among the most important antibiotics in the clinician's armamentarium because they are last-resort drugs for multidrug resistant bacterial infections. Levy WDT: p. 9, lines 30-33; G-1350

Bayer/AHI Response: Bayer/AHI dispute this PFOF as irrelevant, inaccurate, and misleading in the specific context of fluoroquinolones and *Campylobacter*, for which it is refuted by evidence in the record. The clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated; see our response to PFOF 403. In situations where antibiotic therapy is indicated, macrolides such as erythromycin or azithromycin are the

preferred treatment for campylobacteriosis. Iannini WDT: P.4. L.9-12. Fluoroquinolones are *not* "last-resort drugs for multidrug resistant [*Campylobacter*] infections.

406. Fluoroquinolone use in poultry contributes to the selection of fluoroquinolone-resistant *Campylobacter* which may be transferred through the food chain to humans. Levy WDT: p. 9, lines 34-36

Bayer/AHI Response: Bayer/AHI dispute this PFOF as compound, speculative, unsubstantiated, and inaccurate. The meaning of "contributes" is not defined and thus Bayer is unable to adequately interpret this sentence. While we agree that use of fluoroquinolones acts as a selective pressure for resistant strains in chickens, we disagree that fluoroquinolone-resistant *Campylobacter* is necessarily or usually "transferred though the food chain to humans". Nor is the meaning of "transferred... to human" specified in the PFOF: in general, consuming chicken with one or more resistant CFUs does not equate to infection and disease in the human. The risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *Campylobacter* ingested. [JS 27] 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. Thus, many persons with campylobacteriosis - perhaps as many as 25% of all persons infected - do not exhibit clinical symptoms and are therefore "asymptomatic". Pasternack (B-1909) P.3 L.23, P.4 L.3; (G-70) P.3.

407. Because antimicrobial treatment is usually initiated before the antimicrobial susceptibilities of *Campylobacter* are known, the initial choice of antimicrobial must be made empirically. Levy WDT: p. 9, lines 36-38

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This witness provides no documentation for this statement. In addition it is misleading concerning the subject of this proceeding since 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.

408. The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections. Levy WDT: p. 10, lines 1-4

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. This witness provides no documentation or basis for this statement. This PFOF is contrary to available data. It also is misleading as it implies that "resistant" *Campylobacter* have clinical significance. As previously stated, the clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14

L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "compromise human chemotherapy." 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13. Moreover, there are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4.

Catherine Logue (G-1464)

409. Dr. Logue is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

410. Stresses associated with transporting poultry from farms to commercial slaughter facilities prior to slaughter, such as the actual transport, pre-slaughter holding and feed withdrawal, can increase pathogen populations such as *Salmonella* and *Campylobacter* in the intestinal tract, fecal material and on carcass exteriors. Logue WDT: p. 2, lines 4-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

411. Poultry presented for processing can have greater bacterial carcass contamination levels than compared to what was on the birds originally at the farm. Logue WDT: p. 2, lines 8-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

412. Poultry carcasses provide a significant source of bacterial cross contamination (including *Campylobacter spp.)* of other carcasses during commercial processing. Logue WDT: p. 2, lines 11-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

413. At the processing level, the gut of live birds is the principal source of *Campylobacter spp.* and can be transferred between the birds' skin during slaughter and processing. Logue WDT: p. 2, lines 16-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

414. Chill water and the chilling process can be a significant source of pathogen contamination contributing to cross contamination between carcasses during chilling. Logue WDT: p. 2, lines 18-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

415. A small number of contaminated carcasses may have an impact in spreading contamination. Logue WDT: p. 2, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

416. Handling (during carcass orientation and hanging), defeathering, and evisceration contribute to cross contamination between carcasses. Logue WDT: p. 2, lines 23-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

417. Logue studied the prevalence of *Campylobacter*, including fluoroquinolone-resistant *Campylobacter,* from turkey carcasses at slaughter. Logue WDT: p. 2, line 27 – p. 3, line 2;. G-1677

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

418. Logue's study involved two processing plants; one had a processing rate of 800 carcasses per hour, the other 8000 carcasses per hour. Logue WDT: p. 3, lines 27-31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

419. Turkeys stay in the chill tank for approximately 4 hours. Logue WDT: p. 3, line 27 – p. 4, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

420. Over 1/3 of 2412 turkey carcasses sampled by Logue were positive for *Campylobacter spp*. Logue WDT: p 5, L 22-23; p. 6, lines 27-29; p. 7, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

421. 841 of 2412 (34.9%) turkey carcass sampled by Logue were positive for *Campylobacter spp.*

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

422. Logue WDT: p. 5, L 22-23; p. 6, lines 27-29; p. 7, lines 9-10

Bayer/AHI Response: Bayer/AHI presume that this is the citation for PFOF 421 to which no response is required.

423. *Campylobacter* isolates recovered and tested from one turkey slaughter plant (processing 800 turkeys/hour) had 20% resistance to erythromycin, 8.8% resistance to ciprofloxacin and 6.6% resistance to nalidixic acid. Logue WDT: p. 6, lines 14-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

424. *Campylobacter* isolates recovered from one turkey slaughter plant (processing 8000 turkeys/hour) exhibited resistance to nalidixic acid 77.6%, ciprofloxacin 65.3%, and erythromycin 20.4%. Logue WDT: p. 6, lines 17-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

425. Organic material in chill tanks reduces the effectiveness of chlorine compounds in the chill tanks. Logue WDT: p. 7, lines 20-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

426. The rate of production influences *Campylobacter* contamination rates of turkey carcasses. Logue WDT: p. 7, lines 23-24

Bayer/AHI Response: Bayer/AHI dispute that *Campylobacter* constitutes "contamination."

427. Size and processing line speed are factors influencing overall carcass contamination rates. Logue WDT: p. 7, line 31 – p. 8, line 1

Bayer/AHI Response: Bayer/AHI dispute that *Campylobacter* constitutes "contamination" in the sense used here. Bayer/AHI agree that bird size influences the load of *Campylobacter* and other enteric pathogens. 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. B-1912 P.38 L.7-15.

428. *C. jejuni* and *C. coli* are the most common species of *Campylobacter* recovered from turkey carcasses. Logue WDT: p. 8, lines 4-5

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence shows that turkeys are preferentially colonized by *Campylobacter coli* compared to *Campylobacter jejuni*. A-201 P.12 L.17-23; G-727; B-1908 P.4 L.7-8.

429. Logue's study observed multiple-drug resistant *Campylobacter* strains. Logue WDT: p. 8, lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

430. The high isolation rate of fluoroquinolone-resistant *Campylobacter* from turkey carcasses indicates that fluoroquinolone use in turkey production is selecting for drug resistant variants that could result in fluoroquinolone-resistant *Campylobacter* infections in humans associated with contaminated turkey. Logue WDT: p. 8, line 31- p. 9, line 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the phrase "high isolate rate" is not defined. Any interpretation of the word "high" is disputed by CVM's own witness Dr. White, who's testimony cites a recent study showing a prevalence rate of 14% for turkeys in that limited retail study. G-1484 P.3 L.7-24; G-727. Moreover, Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that turkey is a major source of campylobacteriosis. A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail poultry handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis or fluoroquinolone-resistant campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis or fluoroquinolone-resistant campylobacteriosis.

431. Fluoroquinolone-resistant *Campylobacter* infections may not respond to human fluoroquinolone antimicrobials. Logue WDT: p. 9, line 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance and "may not respond to human fluoroquinolone antimicrobials." 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. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L.4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P.2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

432. The use of antimicrobials (i.e., fluoroquinolones) at the farm level is an influencing factor in promoting the selection of antimicrobial resistant *Campylobacter.* Logue WDT: p. 9, lines 4-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

Patrick McDermott (G-1465)

433. Dr. McDermott is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

434. Fluoroquinolones are a class of highly potent antibacterial agents. McDermott WDT: p. 1, lines 45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

435. Fluoroquinolone compounds include human agents such as ciprofloxacin and levofloxacin, and the animal drugs, enrofloxacin and sarafloxacin. McDermott WDT: p. 2, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

436. Fluoroquinolones are easy to use, have good distribution in the body and are effective against a broad range of bacteria. McDermott WDT: p. 2, lines 2-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

437. Given their ease of use, good distribution in the body, and effectiveness against a broad range of bacteria, fluoroquinolones are a valuable group of compounds for treating bacterial infections. McDermott WDT: p. 2, lines 2-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

438. Currently, the only fluoroquinolone approved for use in poultry in the United States is Baytril™ (enrofloxacin). McDermott WDT: p. 2, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

439. Saraflox™ (sarafloxacin) was approved for poultry use in 1995 in the United States, but has since been voluntarily withdrawn from the market by the manufacturer. McDermott WDT: p. 2, lines 6-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

440. As labeled, Baytril antimicrobial solution (3.23%) is approved for treatment of *E. coli* infections in chickens and for *E. coli* and *Pasteurella* infections in turkeys. McDermott WDT: p. 2, lines 11-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

441. Baytril is a water soluble product administered at a final concentration of 25-50 ppm in drinking water, as the sole source of drinking water, for 3 to 7 days. McDermott WDT: p. 2, lines 13-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

442. Like other fluoroquinolones, Baytril acts by binding to DNA gyrase, a gene involved in DNA metabolism. McDermott WDT: p. 2, lines 17-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

443. Mutations in this gene (gyrA) has been linked to fluoroquinolone resistance in *Campylobacter* and many other bacteria. McDermott WDT: p. 2, lines 18-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the understanding that "resistance" is not understood to reflect clinical resistance because the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

444. McDermott conducted an experiment to measure the impact of Baytril when used according to label indications on the development of fluoroquinolone resistance in *Campylobacter jejuni* present in the gut of broiler chickens. McDermott WDT: p. 2, lines 21-24; B-868

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

445. McDermott's experiment used the following methods: (a) chicks were purchased from a commercial supplier; (b) intestinal colonization was established by inoculating the birds orally at 24 days of age with *C. jejuni*, which had a ciprofloxacin MIC of 0.250 μg/mL; (c) two groups of *Campylobacter*-infected chickens were examined: one control group of infected, non-treated chickens and one group of chickens that were treated with Baytril at the

highest dose stipulated on the product label (50 ppm) for 5 consecutive days; (d) fecal samples were collected just prior to treatment and 1, 3, 5, 12 and 21 days after starting fluoroquinolone treatment; and (e) *C. jejuni* isolates were tested for susceptibility to ciprofloxacin and to enrofloxacin to assess development of resistance in the antibiotic-treated groups. McDermott WDT: p. 2, lines 21-40; B-868.

Bayer/AHI Response: Bayer/AHI agree to this PFOF except that (d) does not reflect that the fecal samples were pooled together. B-868.

446. In McDermott's experiment, within 24 hours of Baytril treatment, the *C. jejuni* present in the chicken gut were seven-fold more resistant to ciprofloxacin than before treatment. McDermott WDT: p. 3, lines 1-3; B-868

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

447. In McDermott's experiment, within 24 hours of Baytril treatment, ciprofloxacin minimum inhibitory concentrations (MICs) increased from a base of 0.250 μg/mL to 32 μg/mL; enrofloxacin MICs increased from 0.06 μg/mL to 8 μg/mL. McDermott WDT: p. 3, lines 3-5; B-868

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

448. In McDermott's experiment, resistant bacteria remained in the birds throughout the life span of production birds (up to 7 weeks of age). McDermott WDT: p. 3, lines 6-7; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF inaccurately describes the results of McDermott's experiment. To begin, the experiment did not test for "resistant bacteria", but only for *C. jejuni*. B-868. In McDermott's experiment, they inoculated chickens with *C. jejuni*, administered either sarafloxacin or enrofloxacin at 40 ppm, and then took fecal samples of the birds which were cultured for *C. jejuni*. B-868. These samples were then pooled together and subjected to agar-dilution susceptibility testing. B-868. The chickens had remained free of *Campylobacter,* both resistant and susceptible until they were inoculated orally at either 16 days of age (sarafloxacin treated) or 24 days of age (enrofloxacin treated). B-868. Finally, not all resistant *C. jejuni* remained in the birds, since in *C. jejuni* from chickens treated with sarafloxacin, at day 26 (3 weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. Thus not all resistant *C. jejuni* isolates remained in the birds throughout the life span of the birds.

449. In McDermott's experiment, fluoroquinolone-resistant organisms appeared rapidly and did not go away. McDermott WDT: p. 3, lines 8-9; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "rapidly" is not defined, and therefore Bayer cannot adequately interpret this sentence. However, as noted in the response to 448, this proposed finding of fact inaccurately describes the results of McDermott's experiment. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40 ppm,

at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. Thus not all resistant isolates remained in the birds, and it is thus incorrect to state the resistant isolates "did not go away".

450. In McDermott's experiment, no resistant *Campylobacter* isolates were detected in the non-Baytril treated control group. McDermott WDT: p. 3, lines 9-10; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact mischaracterizes McDermott's experiment. Bayer would admit to a finding of fact stating, "In McDermott's experiment, in the non-fluoroquinolone treated control group, the *Campylobacter* fluoroquinolone MICs remained within a 2-fold dilution of the pre-exposure values." B-868.

451. In McDermott's experiment, the action of Baytril itself was responsible for causing the observed resistance. McDermott WDT: p. 3, lines 10-11; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. In the first instance, this sentence is grammatically indecipherable. The phrase, "The action of Baytril itself" does not make sense, but if CVM means to propose that the use of Baytril in chickens was responsible for causing the observed resistance, this is also incorrect. Resistance is not "caused" by the use of fluoroquinolones. Resistance occurs as the result of a natural mutation of the gyrA gene. G-1465. P.4 L.8-9; B-1908 P.12 L.2-3, L.21-22; G-1451 P.8 L.9-11; Joint Stipulation 1. CVM's attempt to assign "responsibility for causing" the resistance to Baytril is incorrect.

452. In McDermott's experiment, in the Baytril-treated group, 100% of isolates displayed high-level resistance to ciprofloxacin (≥32 μg/mL). McDermott WDT: p. 3, lines 11-12; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is misleading and inaccurate because it fails to identify that the individual samples were combined into composite samples before they were subjected to agar-dilution susceptibility testing. B-868. Since only composite samples were tested, it is impossible to conclude that 100% of isolates displayed resistance >32 μg/mL, since it is possible that susceptible isolates were pooled with resistant isolates and therefore contaminated. B-868.

453. McDermott's study was published in the Journal of Infectious Diseases. McDermott WDT: p. 3, lines 12-13; B-868

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

454. McDermott found that isolates with high level MICS (≥32 μg/ml) contain a single gyrA mutation resulting in an amino acid substitution at position 86 from threonine to isoleucine. McDermott WDT: p. 4, lines 5-7; B-868

Bayer/AHI Response: Bayer/AHI can neither admit nor deny this PFOF because although McDermott's testimony describes the examination of mutations in the DNA gyrase gene (G-

1465 P.4 L.2-7), the citation to McDermott's article that CVM provides for support does not contain any evidence that would support this citation. As such, Bayer/AHI cannot adequately analysis this PFOF, and it must be denied for lack of support.

455. Only a single *gyrA* mutation is necessary to confer fluoroquinolone resistance in *Campylobacter*. McDermott WDT: p. 4, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the caveat that "resistance" is not understood to reflect clinical resistance since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

456. Jacobs-Reitsma found fluoroquinolone-resistant *Campylobacter* emerging during enrofloxacin treatment of broilers. McDermott WDT: p. 4, lines 13-14; G-315

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

457. Jacobs-Reitsma observed fluoroquinolone-resistant *Campylobacter* organisms persisted for two weeks following enrofloxacin treatment. McDermott WDT: p. 4, line 15; G-315

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

458. Fluoroquinolone treatment does not eliminate *Campylobacter* from the intestinal tract of chickens, but rather, rapidly selects for fluoroquinolone-resistant isolates. McDermott WDT: p. 4, lines 21-23; G-315; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. CVM does not define the term "rapidly." Bayer acknowledges that fluoroquinolone treatment may not entirely eliminate *Campylobacter* from the intestinal tract of chickens, and may select for fluoroquinolone-resistant isolates.

459. Fluoroquinolone-resistant isolates remain weeks after stopping exposure to the drug. McDermott WDT: p. 4, lines 21-23; G-315; B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This finding of fact does not provide enough information to properly evaluate it. If CVM means to propose that fluoroquinolone-resistant C. *jejuni* isolates in chickens remain weeks after stopping exposure to a fluoroquinolone drug, then Bayer responds as noted in the response to 493, this proposed finding of fact does not accurately describe the results of experiments including McDermott's and Zhang's. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. In another study, Zhang's experiment showed that in chickens treated with a 25ppm dose of

enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone-resistant. A-190. Thus, not all resistant *C. jejuni* isolates remain in the birds.

460. Zhang found fluoroquinolone-resistant *Campylobacter* in chickens emerging within 24-48 hours after Baytril treatment. McDermott WDT: p. 4, lines 27-30; A-190

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

461. Zhang found fluoroquinolone-resistant *Campylobacter* in chickens persisted after ending Baytril treatment. McDermott WDT: p. 4, lines 27-31; A-190

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF inaccurately describes the results of Zhang's experiment. Zhang's experiment showed that in chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone-resistant. A-190. Thus, many fluoroquinolone-resistant *Campylobacter* do not persist.

462. A single genetic change in the gyrase gene (*gyrA*) confers high-level fluoroquinolone resistance. McDermott WDT: p. 4, lines 32-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "high-level fluoroquinolone resistance" is not defined, and as previously stated, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Bayer/AHI do agree to the PFOF 455.

463. There is emergence of high-level MICs in *C. jejuni* following Baytril treatment. McDermott WDT: p. 4, lines 36-37

Bayer/AHI Response: Bayer/AHI dispute this PFOF. CVM's unequivocal finding of fact is inaccurate. While CVM does not define "high level resistance", assuming they mean MICs greater than 32, a limited number of studies have shown that high-level MICs may result in *C. jejuni* following treatment with fluoroquinolones. B-868; A-190; G-315.

464. Newell observed resistance to enrofloxacin and ciprofloxacin measured by a 7-8 fold increase in MICs in all *C. jejuni* recovered 48 hours after starting Baytril treatment of the chickens. McDermott WDT: p. 4, lines 38-39; G-1465 Attachment, p. 25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

465. Newell found a single mutation in the gyrase gene (gyrA) conferred fluoroquinolone-resistance in *Campylobacter*. McDermott WDT: p. 4, lines 39-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

466. There is a bimodal MIC distribution of fluoroquinolone-resistant *Campylobacter* isolates in both chickens and humans. McDermott WDT: p. 4, line 44-p. 5, line 5; G-1517; G-99; B-868

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

467. McDermott found that *Campylobacter* isolates from chickens are either susceptible to fluoroquinolones or highly resistant to fluoroquinolones. McDermott WDT: p. 5, line 6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. CVM does not define "highly resistant" and therefore Bayer/AHI is unable to adequately interpret this PFOF. McDermott's study did report that MICs above 32 were found in *C. jejuni* following treatment with fluoroquinolones. B-868.

468. A single point mutation in the gyrase gene (gyrA) occurs in approximately 1 to 5 in 100 million cells (i.e., 1-5 in 10^8 cells). McDermott WDT: p. 5, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

469. The single point mutation in the gyrase gene (gyrA) in *Campylobacter* leads to high level fluoroquinolone resistance. McDermott WDT: p. 5, lines 9-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. CVM does not define "high level fluoroquinolone resistance" and therefore Bayer/AHI is unable to adequately interpret this PFOF. As noted previously, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

470. The cells involved in the point mutation in the gyrase gene in *Campylobacter* are also cross resistant to other fluoroquinolones. McDermott WDT: p. 5, lines 10-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that this sentence is grammatically indecipherable. As noted above, Bayer/AHI agree to the statement that a *gyrA* mutation in *Campylobacter* can confer fluoroquinolone resistance, see PFOF 455.

471. In *E. coli*, two genetic mutations are necessary for high level resistance in *Campylobacter*. McDermott WDT: p. 5, lines 13-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is not applicable to the issues in this proceeding.

472. The probability of high level resistance appearing in a fully susceptible *E. coli* cell is much lower than in a *Campylobacter* cell. McDermott WDT: p. 5, lines 15-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is not applicable to the issues in this proceeding.

473. *Campylobacter* are present in the chicken gut at approximately 10^5 – 10^9 organisms per gram of fecal material. McDermott WDT: p. 5, lines 19-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

474. Whenever chickens are exposed to a fluoroquinolone in the manner indicated on the Baytril product label, the susceptible cells rapidly die off allowing the naturally resistant variants to quickly take over and multiply, colonizing the chicken with fluoroquinolone-resistant *Campylobacter*. McDermott WDT: p. 5, lines 21-24

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the terms "rapidly" and "quickly" are not defined, therefore Bayer/AHI cannot adequately interpret this PFOF. Moreover, the PFOF is inaccurate in that studies show that resistance does not always remain. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. In another study, Zhang's experiment showed that in chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone-resistant. A-190. Thus, not all resistant *C. jejuni* isolates remain in the birds.

475. The prevalence of fluoroquinolone-resistance among *Campylobacter jejuni* is high compared to other intestinal organisms such as *E. coli*. McDermott WDT: p. 5, lines 28-29

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF does not define "high prevalence."

476. *Campylobacter* are intrinsically less susceptible to fluoroquinolones than are other enteric organisms. McDermott WDT: p. 6, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

477. In *Campylobacter*, a continuously-active efflux pump encoded by the *cmeB* gene has been shown to contribute much of the baseline fluoroquinolone resistance in this organism. McDermott WDT: p. 6, lines 4-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The efflux pump may contribute low level resistance but it has not "been shown to contribute much of the baseline fluoroquinolone resistance" in *Campylobacter*.

478. Mutations in the gyrA genes are essential to impart clinically significant resistance. McDermott WDT: p. 6, lines 6-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is inaccurate because it does not identify the specific organism to which the PFOF corresponds. Assuming however, CVM means mutations in the *Campylobacter* gyrA gene, as noted in Bayer's response to 451, resistance occurs as the result of a spontaneous natural mutation of the gyrA gene. Joint Stipulation 1; G-1465 P. 4 L. 8-9; B-1908 P. 12 L. 2-3, L. 21-22; G-1451 P. 8 L. 9-11. However, CVM uses the term "clinically significant resistance," when the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Thus, there are no recommended antibiotic breakpoint concentrations (or an agreed susceptibility testing method) for *Campylobacter* spp. B-1913; citing Piddock et. al., 2000, Attachment 1 P.46 ¶ 2. Without a clinical breakpoint for *Campylobacter*, what is essential or not essential for resistance cannot be determined. Finally, this PFOF is not true for *Campylobacter lari* which is naturally resistant to fluoroquinolones. G-1453 P.2 L.37-44.

479. The widespread dissemination of fluoroquinolone resistance does not emerge in the absence of direct selection pressure brought about by fluoroquinolone exposure. McDermott WDT: p. 6, lines 9-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The presence of fluoroquinolone resistance in untreated flocks refutes the contention that fluoroquinolone resistance does not emerge in the absence of direct selection pressure by fluoroquinolone use. B-36 P.2-3; G-62 1-2; G-1458 P.4, ¶ 3; G-1459 P.6 L.36-37; B-1908 P.17 L.1-6. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. B-1908 P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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.

480. In the poultry production environment, the multiplication of resistant *Campylobacter* under fluoroquinolone selection pressure is the major means of the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in chickens and turkeys. McDermott WDT: p. 6, lines 13-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of "major means" is not defined and thus Bayer/AHI is unable to adequately interpret this sentence. However, as noted in Bayer's response to 479, the presence of fluoroquinolone resistance in untreated flocks refutes the contention that fluoroquinolone resistance does not emerge in the absence of direct

selection pressure by fluoroquinolone use. B-36 P. 2-3; G-62 1-2; G-1458 P.4, ¶ 3; G-1459 P. 6 L.36-37; B-1908 P. 17 L. 1-6.

481. In one study, *Campylobacter* was found in both organic and conventionally raised chickens, but fluoroquinolone-resistant *Campylobacter* was found in very low levels (i.e. 1%) in organic flocks compared to very high levels (up to 90%) in conventionally raised flocks. McDermott WDT: p. 6, lines 18-21

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is inaccurate. McDermott's testimony indicates that this information is based solely on "preliminary results" and is based on a personal communication with Qijing Zhang. G-1465 P. 6 L. 18-21. Preliminary results of a unpublished study are insufficient support for the proposed finding of fact.

482. Zhang observed that when a mixture containing equal numbers of fluoroquinolone-resistant and fluoroquinolone-susceptible stains are introduced into a chicken, the fluoroquinolone-resistant strains consistently out-compete the susceptible strains. McDermott WDT: p 6, lines 23-26; G-1746; G-1465 Attachment, p. 26-39

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is inaccurate. As noted in Bayer/AHI's response to 481, McDermott's testimony indicates that this information is. based solely on "preliminary results" and is based on a personal communication with Qijing Zhang. G-1465 P. 6 L. 18-21. Preliminary results of a unpublished study are insufficient support for the proposed finding of fact. Furthermore, CVM's own witness Jacobs-Reitsma acknowledges that this "phenomenon was not observed" in *in vitro* studies. G-1459 P. 6 L. 20-21. In addition, published studies by both McDermott and Zhang indicate that fluoroquinolone-susceptible strains can recolonize and thus can "out-compete" the fluoroquinolone-resistant strains. B-868; A-190.

483. Zhang's results suggest that once a fluoroquinolone drug is introduced into a poultry house, a resistant strain has an advantage over susceptible strains in colonizing other birds, even in the absence of concurrent drug exposure. McDermott WDT: p. 6, lines 27-29

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is inaccurate. As noted in Bayer's response to 482, McDermott's testimony indicates that this information is based solely on "preliminary results" and is based on a personal communication with Qijing Zhang. G-1465 P. 6 L. 18-21. Preliminary results of a unpublished study are insufficient support for the proposed finding of fact. Furthermore, CVM's own witness Jacobs-Reitsma acknowledges that this "phenomenon was not observed" in *in vitro* studies. G-1459 P. 6 L. 20-21. In addition, published studies by both McDermott and Zhang indicate that fluoroquinolone-susceptible strains can recolonize and thus can "out-compete" the fluoroquinolone-resistant strains. B-868; A-190.

484. Fluoroquinolone antibacterial activity is based on dose-dependent pharmacokinetics. McDermott WDT: p 6, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

485. Dose-dependent pharmacokinetics means the peak concentration of the drug at the infected site, rather than the time of the drug at the infected site, is the parameter that predicts efficacy. McDermott WDT: p. 6, lines 39-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

486. Ideally, a peak concentration 8 - 10 times the MIC is needed to kill *Campylobacter.* McDermott WDT: p. 6, lines 41-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF. McDermott's testimony does not support this proposed finding of fact. McDermott's testimony states that "Ideally, a peak concentration 8 - 10 times the MIC is needed to kill the pathogen. Since McDermott is discussing chickens, *Campylobacter* is not a pathogen. G-1484 P. 2 L. 42-43; G-1475 P.10 L.26-30. Thus, CVM provides no support for its proposed finding of fact.

487. Fluoroquinolone concentrations near or below the MIC are more apt to select for fluoroquinolone-resistant bacteria. McDermott WDT: p. 6, lines 42-43

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The PFOF does not define if it is, referring to gut, serum or tissue concentrations.

488. The current method of medicating chickens is by treating the entire house via water, even though relatively few birds may be ill at the time. McDermott WDT: p. 6, line 46- p 7, lines 2

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. Water medication is an approved method of delivery for fluoroquinolone use in poultry, see Joint Stipulation 18, however it is incorrect to state that when treating, "relatively few birds may be ill at the time." In fact, by the time a grower notices sickness, dying, or dead birds in a particular house, all the birds have been exposed and are likely incubating the illness and exposing more birds. A-202 P.13 L.15-22; B-1915 P.4 L.15 – P.5 L.2. CVM's own witness Carey acknowledges that due to their common housing, feeding, drinking and litter exposure, an entire flock has exposure to the challenge. G-1456 P.4 L.34-37.

489. The practice of treating the entire poultry house via water exposes more organisms to the antimicrobial and is therefore more likely to result in the emergence of resistance. McDermott WDT: p. 7, lines 2-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF. CVM's PFOF makes a comparison without explaining what it is comparing. 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 does not explain what it is comparing water delivery to when it claims water delivery exposes "more organisms to the antimicrobial" or that it is "more likely" to result in the emergence of resistance. CVM acknowledges that 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. 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. B-1914 P.22 L.19-21. Therefore, CVM's proposed finding of fact is misleading and inaccurate, since water delivery is the only approved and feasible method of delivery.

490. Medication of poultry via the drinking water does not always ensure an adequate dose of active enrofloxacin is taken up by the treated birds. McDermott WDT: p. 7, lines 6-8; G-52

Bayer/AHI Response: Bayer/AHI dispute this PFOF. 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. Dr. McDermott's statement, that birds do not or may not 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. B-1915 P. 6 L. 15 - P. 7 L. 15; B-1903 P. 5 L. 21 - P. 6 L. 6. That data demonstrates that enrofloxacin almost uniformly produces a dramatic, measurable clinical response, and controls morbidity, mortality, and condemnation in the manner expected of an effective antimicrobial. B-1915 P. 6 L. 15 - P. 7 L. 15; B-1903 P. 5 L. 21 - P. 6 L. 6; B-1914 P.28 L.2-5, L.15-17. The safety and efficacy data for enrofloxacin demonstrate that diseased birds drank the medicated water in sufficient quantities to treat disease. In one study, turkeys were challenged with *Pasteurella multocida* (Fowl Cholera) and 98% of the nonmedicated control birds died compared to 8%, 0% and 0% of the enrofloxacin treated birds, treated at 12.5, 25 and 50 ppm respectively. B-1117; B-1915 P.5 L. 14-16. 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. B-1915 P.6 L. 19 - P.7 L. 1. The flexible labeling of enrofloxacin enables the veterinarian to prescribe a therapeutic regimen that is safe and efficacious, unlike any other available antimicrobials for poultry. The labeling also provides pharmacokinetic and pharmacodynamic information designed to aid veterinarians in selecting a dosing regimen that maximizes efficacy while minimizing selection for resistance. B-1915 P.6 L. 10-14.

491. Lack of control over the amount of water consumed by the chickens, especially older birds, may result in sub-optimal dosing (*i.e.*, doses <8 - 10 times the MIC). McDermott WDT: p. 7, lines 8-10

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As indicated in Bayer/AHI response 490, water delivery is a safe and effective means to administer therapeutic animal drugs, including antibiotics, to commercially grown broiler chickens and turkeys. Joint Stipulation 18. Water medication in poultry is effective since sick birds typically maintain water intake. B-1571 P.4 L.8, B-1117 P.177. Efficacy data submitted to CVM in support of the NADA and published data clearly demonstrate that adequate quantities of enrofloxacin are consumed. B-1915 P. 6 L. 15 - P. 7 L. 15; B-1903 P. 5 L. 21 - P. 6 L. 6. That data demonstrates that enrofloxacin almost uniformly produces a dramatic, measurable clinical response, and controls morbidity, mortality, and condemnation in the manner expected of an effective antimicrobial. B-1915 P. 6 L. 15 - P. 7

L. 15; B-1903 P. 5 L. 21 - P. 6 L. 6; B-1914 P.28 L.2-5, L.15-17. The safety and efficacy data for enrofloxacin demonstrate that diseased birds drank the medicated water in sufficient quantities to treat disease. In one study, turkeys were challenged with *Pasteurella multocida* (Fowl Cholera) and 98% of the nonmedicated control birds died compared to 8%, 0% and 0% of the enrofloxacin treated birds, treated at 12.5, 25 and 50 ppm respectively. B-1117; B-1915 P.5 L. 14-16. 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. B-1915 P.6 L. 19 - P.7 L. 1. The flexible labeling of enrofloxacin enables the veterinarian to prescribe a therapeutic regimen that is safe and efficacious, unlike any other available antimicrobials for poultry. The labeling also provides pharmacokinetic and pharmacodynamic information designed to aid veterinarians in selecting a dosing regimen that maximizes efficacy while minimizing selection for resistance. B-1915 P.6 L. 10-14.

492. Suboptimal dosing increases the probability of selecting for resistant *Campylobacter* in both healthy and diseased birds. McDermott WDT: p. lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As indicated in Bayer response 490, water delivery is a safe and effective means to administer therapeutic animal drugs, including antibiotics, to commercially grown broiler chickens and turkeys, Joint Stipulation 18, and data submitted in support of Baytril's NADA demonstrated that birds drank enfloxacin-medicated water in sufficient quantities to effectively treat disease. B-1915 P. 7 L 11-12; B-1117. Moreover, the statement is misleading since *Campylobacter* is not a pathogen organism for chickens or turkeys and therefore the dosing (i.e., use) of enrofloxacin is not meant to treat *Campylobacter*. G-1484 P. 2 L 42-43; G-1475 P.10 L.26-28.

493. Resistant *Campylobacter* persist long after stopping fluoroquinolone treatment. McDermott WDT: p. 7, lines 13-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As noted in Bayer's response to PFOF 448, this proposed finding of fact inaccurately describes the results of McDermott's experiment. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 28% of the isolates tested were susceptible to fluoroquinolones. B-868. This contrasts with 100% resistance at day 5 (the first day these isolates were tested). B-868. In another study, Zhang's experiment showed that in chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone-resistant. A-190. Thus, not all resistant *C. jejuni* isolates persist in the birds.

494. Animals previously medicated with fluoroquinolones will carry fluoroquinolone-resistant *Campylobacter* in their intestines at slaughter. McDermott WDT: p. 7, lines 14-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact is irrelevant to the hearing. Fluoroquinolone use in "animals" is not at issue in this hearing. However, even assuming CVM means either poultry or chickens and/or turkeys when they say "animals", as noted in the response to 448, this proposed finding of fact is not consistent with studies that show that fluoroquinolone resistance does not entirely persist. Notably, in *C. jejuni* from chickens treated with sarafloxacin 40ppm, at day 26 (weeks after ending treatment), 72% of

the isolates displayed MICs >32. B-868. This is in contrast to 100% resistance at day 5 (the first day isolates were tested). B-868. In another study, Zhang's experiment showed that in chickens treated with a 25ppm dose of enrofloxacin, at 12 and 15 days after treatment, only 33% of the population were fluoroquinolone-resistant. A-190. Thus not all resistant isolates persist in treated birds. In addition, because the prevalence of flock infection varies from 10% to over 90%, not all chickens medicated with fluoroquinolone will be carrying *Campylobacter*. B-1908 P.3 L.19-20. Therefore the unequivocal statement that CVM has proposed is not accurate.

495. Retail meat surveillance studies regularly find that 70 - 80% of retail chicken is contaminated with *Campylobacter*. McDermott WDT: p. 7, lines 18-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "regularly" is not defined and thus Bayer/AHI are unable to adequately interpret this sentence. Bayer/AHI would agree that a limited retail meat surveillance study found that approximately 70% of the retail chicken tested had contained *Campylobacter*. G-727; G-1466 P.2 L.26-35. Other retail studies show much smaller levels of contamination. G-1484 P.4 L. 24-26; G-1452 P. 12 L. 10; G-1528.

496. Approximately one quarter to one third of *Campylobacter*-contaminated retail chicken meat products carry a fluoroquinolone-resistant strain. McDermott WDT: p. 7, lines 20-21

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The single citation that CVM provides for this proposed finding of fact is not representative of the entire United States, therefore CVM's proposed finding of fact that "approximately one quarter to one third of *Campylobacter*-contaminated retail chicken meat products carry a fluoroquinolone-resistant strain" is inaccurate. There is no nationwide sampling program that would provide accurate data on the prevalence of *Campylobacter*-contaminated retail chicken meat products which carry a fluoroquinolone-resistant strain.

497. The use of nalidixic acid in *Campylobacter* speciation has likely resulted in a substantial under-estimation of fluoroquinolone resistance among *C. jejuni/coli* reported to local and national surveillance systems. McDermott WDT: p. 7, lines 32-34

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF. Notably, evidence in the record demonstrates that *any Campylobacter* isolation, speciation and susceptibility testing protocol relying on nalidixic acid susceptibility as a criterion to identify *C. jejuni* or *C. coli*, such as would have been used in the 1980s and early 1990s (G-1453 P.3 L.1-12) would have excluded all quinolone-resistant isolates from surveillance and therefore underreport resistance in *C. jejuni* and *C. coli*. G-1453 P.3 L.31-36.

498. The use of Baytril in chickens rapidly produces high-level fluoroquinolone resistance in *Campylobacters* residing in the chicken intestine. McDermott WDT: p. 7, lines 38-40

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the terms "rapidly" and "high level fluoroquinolone resistance" are not defined and thus Bayer/AHI are unable to adequately interpret this sentence. While experimental studies have shown that birds inoculated

with *Campylobacter* and then treated with Baytril have shown fluoroquinolone resistance within 24 hours of treatment, the resistance does not always persist, and susceptible *Campylobacter* can recolonize the chicken intestine. B-868; A-190.

499. The use of fluoroquinolones in poultry is the leading cause of the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in poultry. McDermott WDT: p. 7, lines 41-43

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The presence of fluoroquinolone resistance in untreated flocks shows that fluoroquinolone resistance may emerge in the absence of direct selection pressure by fluoroquinolone use. B-36 P.2-3; G-62 1-2; G-1458 P.4, ¶ 3; G-1459 P.6 L.36-37; B-1908 P.17 L.1-6. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. B-1908 P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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.

500. The use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant foodborne *Campylobacter* infections in humans. McDermott WDT: p. 7, lines 44-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The presence of fluoroquinolone resistance in untreated flocks shows that fluoroquinolone resistance may emerge in the absence of direct selection pressure by fluoroquinolone use. B-36 P.2-3; G-62 1-2; G-1458 P.4, ¶ 3; G-1459 P.6 L.36-37; B-1908 P.17 L.1-6. Resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. B-1908 P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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. Bayer/AHI also dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent evidence in the record does not show or even merely suggest that the use of

fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant foodborne *Campylobacter* infections in humans.

Jianghong Meng (G-1466)

501. Dr. Meng is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination. Additionally, Dr. Meng is not qualified to testify about treatments for human diseases as noted in reply to PFOF 515.

502. Leakage of intestinal contents during the slaughtering process almost inevitably contaminates poultry carcasses with *Campylobacter*. Meng WDT: p. 1, lines 38-40

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

503. Most retail fresh chicken carcasses and some turkey carcasses are contaminated with *Campylobacter*. Meng WDT: p. 1, lines 41-42

Bayer/AHI Response: Bayer/AHI do not dispute that *Campylobacter* can be found on retail fresh chicken and turkey carcasses. Bayer/AHI dispute that it is on "most" and that it constitutes "contamination."

504. In Zhao's survey of 184 chicken carcasses and 172 turkey breasts bought from retail stores in the Washington, D.C. area between June 1999 and July 2000, the prevalence of *Campylobacter* was 70.7% in chickens and 14.5% in turkeys. Meng WDT: p. 2, lines 26-34; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

505. In Zhao's study, approximately half (53.6%) of the isolates were identified as *C. jejuni,* 41.3% as *C. coli,* and 5.1% as other species. Meng WDT: p. 3, lines 14-16; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

506. In Zhao's study, both *C. jejuni* and *C. coli* were isolated more frequently from retail chicken than from turkey, pork, or beef. Meng WDT: p. 3, lines 16-17; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

507. In Zhao's study, *C. coli* was more often recovered from retail turkey samples than *C. jejuni*. Meng WDT: p. 3, lines 17-18; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

508. In vitro antimicrobial susceptibilities of 378 *Campylobacter jejuni* and *coli* isolates from 159 contaminated retail raw meats (130 chicken, 25 turkey, 3 pork, and 1 beef) analyzed by Ge showed resistance among the *Campylobacter* poultry isolates to erythromycin (54%), nalidixic acid (41%), and ciprofloxacin (35%). Meng WDT: p. 3, lines 24-29; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

509. *C. coli* isolates displayed significantly higher resistance rates ($p<0.05$) to ciprofloxacin and erythromycin than *C. jejuni* in Ge's study. Meng WDT: p. 3, lines 31-32; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

510. Turkey isolates, from either *Campylobacter* species, showed significantly higher resistance rates ($p<0.05$) to ciprofloxacin and erythromycin than *Campylobacter* isolates from retail chickens in Ge's study. Meng WDT: p. 3, lines 32-35; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

511. Ge found that multi-drug resistant *Campylobacter* were commonly present in poultry products. Meng WDT: p. 3, lines 35-36; G-1778

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Ge says "*Campylobacter* resistant to antimicrobial agents used for treating human campylobacteriosis are common in retail meats". (G-1778)

512. All the ciprofloxacin-resistant *Campylobacter* analyzed by Ge were also resistant to nalidixic acid. Meng WDT: p. 3, lines 39-40; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

513. Ge found co-resistance to ciprofloxacin and erythromycin in *Campylobacter* from 41 (26%) of 159 contaminated meat samples. Meng WDT: p. 3, lines 43-44; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

514. Multi-drug resistance, including co-resistance to fluoroquinolones and erythromycin (a macrolide antimicrobial), has been identified in *Campylobacter* isolated from retail meat products and from humans. Meng WDT: p. 3, lines 44-47G-549; G-191; G-1778

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

515. Co-resistance to fluoroquinolones and erythromycin in *Campylobacter* is highly undesirable because those two antimicrobials are generally advocated as first-line drugs for treatment of human campylobacteriosis. Meng WDT: p. 4, lines 1-4

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that it is not adequately supported by the citation. Dr. Meng is a veterinarian and microbiologist and is therefore not qualified to make expert opinion statements about treatments for human diseases. G-1466 P.1 L.25-36.

516. In *Campylobacter,* acquired resistance to fluoroquinolones appears to be due mostly to mutations in genes *(gyrA)* encoding DNA gyrase. Meng WDT: p. 4, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the caveat that "resistance" is not understood to reflect clinical resistance since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

517. Cloning and sequencing of the *gyrA* gene show that mutations in *gyrA* at positions Thr-86, Asp-90, and Ala-70 can be detected in fluoroquinolone-resistant isolates. Meng WDT: p. 4, lines 12-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the caveat that "fluoroquinolone-resistant isolates" is not understood to reflect clinical resistance since the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

518. Point mutations in *gyrA* occur frequently. Meng WDT: p. 4, line 32

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

519. Contamination with *C. jejuni* and *C. coli* is widespread in poultry. Meng WDT: p. 4, lines 42-43

Bayer/AHI Response: Bayer/AHI dispute that *Campylobacter jejuni* or *coli* is a "contaminant" in the sense used here.

520. Poultry products often become contaminated during processing. Meng WDT: p. 4, lines 43-44

Bayer/AHI Response: Bayer/AHI do not dispute that enteric pathogens are spread from product to product during poultry processing.

521. *Campylobacter* often survives food processing and storage. Meng WDT: p. 4, lines 44-45

Bayer/AHI Response: Bayer/AHI disputes this PFOF. Often times poultry "food processing" includes steps such as cooking, freezing or other processes that will kill *Campylobacter*. Like nearly all other bacteria *Campylobacter* is sensitive to cooking, and it is assumed that an adequately cooked chicken will harbor no viable *Campylobacter*. G-1483 P.9 L.21-23; G-1459 P.5 L.26-28. 181. Freezing and thawing of meat kills a proportion of the viable *Campylobacter* in the meat. G-1483 P.5 L.26-27; Joint Stipulation 24. A chicken-product that has been frozen and thawed harbors less viable *Campylobacter* than the equivalent fresh product. G-1483 P.5 L.29-30. Freezing of poultry reduces the number of live *Campylobacter* in the products. G-1483 P.5 L.31. Under the normal conditions of food storage, freezing chicken products may reduce the population of *Campylobacter*. Joint Stipulation 31. Freezing chicken (and turkey) products may reduce the population of *Campylobacter*. Joint Stipulation 24. Poultry meat undergoing any heat treatment or freezing during processing will harbor less *Campylobacter* than meat produced without such treatment. G-1483 P.8 L.2-3. Meat which is dried, cured, salted, smoked, irradiated or exposed to other preservation methods, will harbor less *Campylobacter* compared to the unpreserved product. G-1483 P.5 L.4-6.

522. *Campylobacter* are present in most retail chicken meats and some retail turkey meats. Meng WDT: p. 4, lines 44-46

Bayer/AHI Response: Bayer/AHI do not dispute that *Campylobacter* can be present on. retail poultry meats, but dispute that it is on "most."

523. Many *Campylobacter* isolates recovered from retail poultry carcasses are resistant to antimicrobials. Meng WDT: p. 5, lines 1-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the grounds that the precise meaning of the word "many" is unknown here. Bayer/AHI do not dispute that the evidence in the record shows that some number of *Campylobacter* isolates recovered from retail poultry carcasses are resistant to antimicrobials.

524. Fluoroquinolone use in poultry has contributed to an increase of fluoroquinolone-resistant *Campylobacter* on poultry carcasses. Meng WDT: p. 5, lines 4-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the assertion that there has been an increase of fluoroquinolone-resistant *Campylobacter* on poultry carcasses. Bayer/AHI dispute that the levels of resistance to fluoroquinolones in the chicken carcass isolates of *Campylobacter jejuni* reported by the animal arm of NARMS are an accurate representation of national poultry resistance levels. This is the result of problems or changes in sampling sources and schemes, problems or changes in isolation methods, and problems or changes in resistance testing methods. G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8. In addition, the PFOF does not identify the time frame in which it asserts the increase to have occurred.

525. Retail poultry meat is a source of fluoroquinolone-resistant *Campylobacter* and subsequent human campylobacteriosis infections. Meng WDT: p. 5, lines 6-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry meat is a major source of fluoroquinolone-resistant *Campylobacter* and subsequent human campylobacteriosis infections.

Carolyn Minnich (G-1467)

526. Dr. Minnich is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

527. The average chicken plant slaughters over 60,000 birds per shift. Minnich WDT: p. 2, lines 27-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

528. Chicken plants usually operate 1 - 2 shifts per day, 5 days per week. Minnich WDT: p. 2, line 28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

529. Live chickens arrive at slaughter plants in crates which are stacked on top of each other on the back of tractor trailers. Minnich WDT: p. 2, line 32-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

530. A tractor trailer contains between 20-1000 chicken crates, depending on the size of the crates. Minnich WDT: p. 2, lines 34-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

531. A plant may slaughter up to 14 or more trucks of chickens per shift. Minnich WDT: p. 2, lines 35-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

532. Chickens remain on the trucks after arrival at the plant for 1-8 hours. Minnich WDT: p. 2, lines 37-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

533. Chickens are unloaded from the crates onto conveyor belts that transport them inside of the plant. Minnich WDT: p. 2, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

534. Chickens are slaughtered by cutting their necks (by hand or through the use of a mechanical blade). Minnich WDT: p. 2, lines 41-42

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

535. The chicken scalder tank is between 60-120 feet long and contains over 2000 gallons of water. Minnich WDT: p. 2, lines 42-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

536. The water in the chicken scalder tank is 130°F or greater. Minnich WDT: p. 2, lines 43-44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

537. The purpose of the scalder is to allow the chicken's feathers to be more easily removed. Minnich WDT: p. 2, lines 44-45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

538. Fresh water is added to the scalder constantly and it takes approximately 1 - 3 hours for the water in the chicken scalder to completely exchange. Minnich WDT: p. 3, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

539. There are 300 or more chickens in the scalder at any given time and they remain there for 1-3 minutes. Minnich WDT: p. 3, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

540. Mechanical picking machines remove feathers from chicken carcasses. Minnich WDT: p. 3, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

541. Picking machines are metal cabinets with rubber projections that vibrate. Minnich WDT: p. 3, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

542. During evisceration, chickens' body cavities are opened mechanically. Minnich WDT: p. 3, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

543. Neither water nor antimicrobial washes eliminate all bacteria from chicken carcasses. Minnich WDT: p. 4, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

544. Chicken chilling tanks are metal structures that are 125-140 feet or more in length. Minnich WDT: p. 5, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

545. Chicken chilling tanks hold over 20,000 gallons of water when full. Minnich WDT: p. 5, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

546. Chickens remain in the chill tank for approximately 1 to 2 hours. Minnich WDT: p. 5, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

547. Water in the chicken chill tank is exchanged every 3-5 hours. Minnich WDT: p. 5, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

548. Live turkeys are transported to the slaughter plant in crates approximately 18 cubic feet in size, containing 8 - 24 turkeys each. Minnich WDT: p. 6, lines 22-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

549. An average turkey transport truck will hold 32 or more crates. Minnich WDT: p. 6, lines 23-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

550. A turkey slaughter plant may slaughter up to 20 - 30 trucks of turkeys per shift. Minnich WDT: p. 6, line 24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

551. The average turkey slaughter plant operates 1 - 2 shifts per day, 5 days per week. Minnich WDT: p. 6, lines 24-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

552. About 23,000 – 60,000 turkeys or more are slaughtered per day at the average turkey slaughtering plant. Minnich WDT: p. 6, lines 25-26

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

553. The turkey scalder used is about 40-65 feet long and contains over 7000 gallons of water. Minnich WDT: p. 6, lines 28-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

554. It takes approximately 3 hours for the water in the turkey scalder plant to completely exchange. Minnich WDT: p. 6, lines 30-31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

555. There are over 100 turkeys in the scalder at any given time and they remain in the scalder for 1-3 minutes. Minnich WDT: p. 6, lines 31-32

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

556. Turkey slaughter plants have less mechanical equipment than seen in chicken slaughter plants. Minnich WDT: p. 6, line 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

557. Variation in turkey process size makes it more practical to manually process turkeys rather than try to fit and adjust equipment to a variety of bird sizes. Minnich WDT: p.6, lines 18-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

558. Evisceration of turkey carcasses is accomplished manually rather than mechanically. Minnich WDT: p. 6, line 37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

559. Chill tanks in turkey slaughter plants are over 160 feet in total length. Minnich WDT: p. 7, line 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

560. Chill tanks in turkey slaughter plants hold over 120,000 gallons of water when full. Minnich WDT: p. 7, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

561. Turkey carcasses remain in the chiller for approximately 3 - 6 hours. Minnich WDT: p. 7, line 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

562. The water in the turkey chill tank is exchanged approximately once per shift. Minnich. WDT: p. 7, lines 7-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

563. Line speeds at chicken slaughter plants range from 70 - 175 chickens per minute. Minnich WDT: p. 5, line 43- p. 6, line 8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

564. Line speeds at turkey slaughter plants range from 30 - 51 turkeys per minute. Minnich WDT: p. 7, lines 16-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

565. It is possible for chickens and turkeys that were free from *Campylobacter* at the farm to become contaminated with *Campylobacter* during the transportation and slaughter process. Minnich WDT: p. 7, lines 23-25

Bayer/AHI Response: Bayer/AHI agree that chickens and turkeys can be colonized in this way, but dispute that this constitutes "contamination."

566. There are numerous places where cross-contamination may occur between chickens/turkeys or chicken/turkey carcasses with *Campylobacter* and, if present, fluoroquinolone-resistant *Campylobacter*, and those carcasses without *Campylobacter* in the slaughter plant. Minnich WDT: p. 7, lines 25-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

567. Even when equipment is washed in water containing an antimicrobial agent such as chlorine, when equipment is not completely rinsed clean of debris between carcasses or when heavily contaminated carcasses are processed, it is possible that cross-contamination between carcasses with bacteria may occur. Minnich WDT: p. 7, lines 28-31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

568. Washing equipment with chlorine rinse does not necessarily eliminate bacteria on the equipment. Minnich WDT: p. 7, lines 28-31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

569. Product-contact parts of machines are only exposed to antimicrobials for less than 10 seconds before the next carcass comes into contact with the equipment, making it still possible to spread bacteria, such as *Campylobacter,* between carcasses. Minnich WDT: p. 7, lines 33-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

570. Plants operate using equipment for up to 20 hours per day depending on the size of the establishment and number of shifts without cleaning the equipment with soap and water. Minnich WDT: p. 7, lines 36-37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

571. Equipment is generally cleaned with chemicals (e.g., soap) once every 24 hours. Minnich WDT: p.7, line 38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

572. Tap water rinse is available to plant employees and inspection personnel at evisceration line positions. Minnich WDT: p. 7, lines 38-40

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

573. Soap is generally not available to plant employees or inspection personnel at evisceration line positions. Minnich WDT: p. 7, line 41

Bayer/AHI Response: Bayer/AHI object to this PFOF as being too general. Neither the witness nor CVM can state this as a categorical fact.

574. Personnel rarely rinse their hands in tap water between each carcass. Minnich WDT: p. 7, lines 41-42

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

575. Line personnel cannot reach hand sinks equipped with soap without leaving their posted positions. Minnich WDT: p. 7, lines 44-46

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

576. In order to leave the line, an employee (either USDA or plant) would either have to be replaced on the line or the line would have to be stopped until they returned. Minnich WDT: p. 7, line 46 – p. 8, line 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

577. If a utensil is contaminated (either with gastrointestinal contents or by being dropped on the floor), it is usually rinsed in the tap water (without antimicrobials) at the line position before being reused. Minnich WDT: p. 8, lines 4-6

Bayer/AHI Response: Bayer/AHI object to this PFOF as being too general. Neither the witness nor CVM can state this as a categorical fact.

578. When chickens and turkeys are transported to the slaughter plant, and while the animals remain on the trucks awaiting slaughter, the animals are kept in crates stacked on top of each other. Minnich WDT: p. 8, lines 12-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

579. Poultry transport crates have openings on the top, bottom and sides. Minnich WDT: p. 8, line 15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

580. It is very easy for feces that may contain bacteria such as *Campylobacter* to spread or drop from one animal to another during the transportation of chickens and turkeys to the slaughter house. Minnich WDT: p. 8, line 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

581. The transportation of chickens and turkeys represent a source of contamination and cross-contamination with bacteria, including *Campylobacter* and/or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 8, lines 8-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

582. Conveyer belts used to transport chicken and turkey from the transportation crates into the plant can become contaminated with chicken or turkey feces and contaminate the exterior of the animals with bacteria. Minnich WDT: p. 8, lines 18-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

583. The conveyor belts used to transport chickens and turkeys from transport crates into the plant represents a source of cross-contamination with *Campylobacter* and/or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 8, lines 8-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

584. Mechanical blades or hand held knives represent a source of contamination and cross-contamination with *Campylobacter* and/or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 8, lines 22-27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

585. External contamination on the chicken or turkey carcass frequently comes off in the scalding tank. Minnich WDT: p. 8, lines 29-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

586. Scalder water at chicken plants stays murky brown throughout each day from the dirt and feces in it. Minnich WDT: p. 8, lines 32-33

Bayer/AHI Response: Bayer/AHI object to this PFOF as being too general. CVM cannot state this as a categorical fact.

587. Scalder water represents a potential for bacterial cross-contamination between chickens. Minnich WDT: p. 8, lines 33-34

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

588. The picking machine equipment is not washed between carcasses and represents a source of contamination and cross-contamination with *Campylobacter* and/or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 8, lines 36-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

589. The head puller bars (used to remove chickens' heads) are not washed in between each carcass and represent a source of contamination and cross-contamination with *Campylobacter* and/or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 8, lines 40-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

590. The machinery used to detach the feet from the chickens and turkeys present a vehicle for cross-contamination. Minnich WDT: p. 9, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

591. Mechanical equipment used to transfer chickens from the kill line to the evisceration line may present a point of cross-contamination. Minnich WDT: p. 9, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

592. At both the opening/venting and the evisceration steps in chicken and turkey processing, there is a risk of cross-contamination due to the breakage of intestinal contents by plant employees or their equipment. Minnich WDT: p. 9, lines 8-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

593. Most chicken plants have a visible contamination rate following venting, opening, and evisceration of 5% or more. Minnich WDT: p. 8, lines 12-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Most plants have 5% or less visible contamination rate.

594. During the viscera removal and separation process in both chicken and turkey processing, scissors or mechanical equipment may transfer bacteria from one carcass to another. Minnich WDT: p. 9, lines 15-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

595. The chilling tanks for chilling chicken and turkey giblets may be a point of cross-contamination of giblets with bacteria. Minnich WDT: p. 9, lines 19-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

596. Bacteria from the knife and from employee's hands during final trimming in chicken and turkey processing represents a point of cross-contamination. Minnich WDT: p. 9, lines 26-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

597. Mechanical or hand held blades during oil gland removal represents a source of contamination or cross-contamination with *Campylobacter* or fluoroquinolone-resistant *Campylobacter*. Minnich WDT: p. 9, lines 30-32

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

598. Water in the chill tank represents a point for cross-contamination for chickens and turkeys due to the number of carcasses within it at any given time. Minnich WDT: p. 9, lines 34-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

599. Chill tank water facilitates the spread of bacteria. Minnich WDT: p. 9, lines 34-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

600. Packing and further processing (cut-up and deboning) areas represent a point of cross-contamination. Minnich WDT: p. 9, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Kare Molbak (G-1468)

601. Dr. Molbak is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to. cross-examination, except where Dr. Molbak testifies on matters related to causality, causal interpretations of data, or statistical data analysis.

602. *Campylobacter spp.* is one of the most common causes of gastrointestinal infections in humans. Molbak WDT: page 2, line 21

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to the current status in the United States, which is the relevant time and location for the issues in this hearing. Most gastrointestinal infections in the U. S. are viral. As relates to bacterial infections in the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject.

603. Gastrointestinal infections are frequently acquired during foreign travel, i.e., traveler's diarrhea. The risk of a gastrointestinal infection is highest for persons traveling from an industrialized country to a less developed region of the world. Traveler's diarrhea is, however, not any different from other gastrointestinal infection; it is usually a food- or waterborne infection acquired away from home. A higher prevalence of fluoroquinolone-resistant *Campylobacter* in isolates from individuals with travel acquired infection than in domestically acquired infections reflects that there is a higher prevalence of resistance in the foreign sources than the indigenous. Molbak WDT: p. 2, line 31 – p. 3, line 6

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being compound and in part inaccurate. We specifically disagree with Dr. Molbak's assertion that "Traveler's diarrhea is,

however, not any different from other gastrointestinal infection". For example, statistical analysis of CDC case-control data shows conclusively that traveler's diarrhea from foreign travel-associated campylobacteriosis is associated with significantly longer duration of illness than domestically acquired campylobacteriosis [Burkhart (B-1900) P. 35 L. 4-6; P. 36 L. 4-5; Cox (B-1901) P.22]

604. In patients who have moderate-to-severe dysentery (diarrhea with blood), who are elderly, who are presumed to be bacteremic with chills and systemic symptoms, or who are at increased risk of complications such as immunocompromised patients, patients with underlying disease, or pregnant women, antimicrobial treatment may be of significant benefit. Molbak WDT: p. 3, lines 21- 26

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being overly broad, vague and a speculation, rather than a finding of fact. It says that "antimicrobial treatment may be of significant benefit", but without saying what specific treatments are included in the scope of the assertion. Does this PFOF apply to ciprofloxacin? Secondly, the claim is that some unspecified antimicrobial treatment "may be" of significant benefit. This is a vague speculation, not a fact.

605. It is essential to be able to treat *Campylobacter* with antibiotics, and critical to preserve the efficacy of fluoroquinolones. Molbak WDT: p. 3, lines 28-29

Bayer/AHI Response: Bayer/AHI disagree with both parts of this compound PFOF as being overly broad, vague, and inaccurate. The statement is vague in that it does not specify for what purpose is it "essential to be able to treat *Campylobacter* with antibiotics". Since most strains of *Campylobacter jejuni* and *Campylobacter coli* are susceptible to the bactericidal (killing) activity of blood-serum, bacteremia is usually self-limiting and often remains untreated. [Kist (B-1906) P.5 L.7-9]. Routine empiric antimicrobial treatment is generally not recommended for diarrheal illness [Iannini (B-1905) P.3 L.15-18; Ohl (G-1485) P.9 L.36-46, P.10 L.1-7], and macrolides rather than fluoroquinolones are recommended for treatment of known cases of campylobacteriosis, [Molbak (G-1468) P.19 L.1-6, 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 ¶ 4; Morris (G-1469) P.5 L.3-5; (G-557) P.3; (B-816) P.2], so the adjectives "essential" and "critical" in this PFOF are inappropriate and misleading. The PFOF is also overly broad in that it does not specify which specific *Campylobacter* (*coli*? *jejuni*? other?) are being referred to or how/whether this relates to preservation of the efficacy of fluoroquinolones in the treatment of human campylobacteriosis caused by *C. jejuni* and *C. coli*. It is inaccurate in that fluoroquinolones are generally *not* recommended for treating campylobacteriosis and may not have efficacy in this use. Hence, it is not "critical to preserve the efficacy of fluoroquinolones" for this use. The PFOF appears to be an unsubstantiated and vague statement of opinion, not a finding of fact.

606. Campylobacteriosis in the industrialized countries is primarily a foodborne disease, with poultry as a principle source. Molbak WDT: p. 3, lines 32-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. It is an incorrect and unsubstantiated claim. Evidence in the record disputes the contention that chicken or turkey is a principle source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21

P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data, particularly in the U.S., demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or suggest that poultry is a principle source of campylobacteriosis, but refutes this supposition.

607. Human-to-human transmission of campylobacteriosis is uncommon, and it is therefore the contribution from the poultry reservoir that pays the lead role in the emergence of fluoroquinolone resistance in *Campylobacter*. Molbak WDT: p. 3, lines 34-36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and illogical. From the premise "Human-to-human transmission of campylobacteriosis is uncommon", it does *not* follow that "therefore the contribution from the poultry reservoir plays the lead role in the emergence of fluoroquinolone resistance in *Campylobacter*." In fact, human use of ciprofloxacin and contamination of drinking water by runoff from human ciprofloxacin use are much more likely to "play the lead role in the emergence of fluoroquinolone resistance in *Campylobacter*." [Patterson (B-1910) P.13 L.15-19; Patterson (B-1910) P.13 L.12-14; Burkhart (B-1900) P.4 L.4-9]. Moreover, we disagree with the premise that "Human-to-human transmission of campylobacteriosis is uncommon". The rates of transmission from restaurant workers to customers (and possibly among children in day care centers) in the US is unknown, but is not necessarily as uncommon as has been supposed (Angulo (G-1452) P.9 L.28-29). Finally, we disagree with the conclusion that "it is the contribution from the poultry reservoir that plays the lead role in the emergence of fluoroquinolone resistance in *Campylobacter*". This is an unsubstantiated speculation, not a fact. In reality it appears that the emergence of fluoroquinolone resistance in *Campylobacter* is explained wholly or primarily by use of fluoroquinolones in human medicine, with the contribution from chicken being very minor or undetectably small (Cox and Popken, 2003).

608. The Emerging Infections Program (EIP) Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative project with the CDC, nine EIP state health departments, the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA), and the United States Food and Drug Administration (FDA). FoodNet currently collects data on ten foodborne diseases in the nine sites to quantify and monitor foodborne illnesses in the United States. Molbak WDT: p. 3, lines 42-47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

609. Between 1997 and 2001, the prevalence of fluoroquinolone resistance in the United States increased significantly. Molbak WDT: p. 8, line 25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being unsubstantiated speculation rather than fact. See our responses to CVM PFOFs # 41, 78, 87, 88. No representative surveillance plan for the US exists that shows what happened to the prevalence of fluoroquinolone resistance in the general United States population over this period. While there were upward trends and increases in some states (e.g., MN and CT, which dominate the NARMS and FoodNet human statistics), there were downward trends in other states (e.g., NY). There is so much variability among locations that it is invalid to extrapolate from the sampled locations to any general conclusions about what happened to the prevalence of fluoroquinolone resistance in the United States between 1997 and 2001. (The sample locations do not even predict changes for each other, let alone for the rest of the US.) However, resistance rates given in various peer-reviewed publications prior to 1995 are in many cases higher than resistance rates measured after 1995, contradicting the opinion given here that "Between 1997 and 2001, the prevalence of fluoroquinolone resistance in the United States increased significantly." [Cox (B-1901) P.42, referring to G-589 (Smith 1999) and G-1517 (Nachamkin 2002); DeGroot (A-200) P.17 L.23-24 – P.18 L.1-2]

610. 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 fluoroquinolone-resistant infection had increased. Thus, the 27% decrease in the incidence is more than outweighed by the 61% to 98% increase in proportion of isolates that are resistant. Molbak WDT: p. 8, lines 39-42

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. The arithmetic cited here is incorrect, in that the 27% decrease in the incidence prevents far more cases than the alleged 61% to 98% increase in resistance proportion affects. (Cox WDT, B 1901, Attachment 1, p. 85, comment on Molbak testimony).

611. In Iceland, the incidence of *Campylobacter* infection increased from 15 in 1995 to 157 per 100,000 in 1999. The incidence in 2000 was 87 and in 2001, 78 per 100,000 population. This marked decrease was due to an intervention program that was based on a screening procedure. which ensured that *Campylobacter* positive flocks were diverted to frozen poultry products and *Campylobacter* negative flocks primarily were used for chilled products. Molbak WDT: p. 12, lines 9-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being speculation, not fact. The causes of the decrease have not been established. This PFOF is refuted by B-1902 P.39 L.12 – P.40 L.2 and B-1901 P.52.

612. In Belgium, June 1999, the dioxin crisis, caused by dioxin-contaminated feed components resulted in withdrawal of chicken and eggs from the market. Through the sentinel surveillance system, a decrease in *Campylobacter* infections during June 1999 was noticed. A statistical analysis showed a significant decline (40%) in the number of infections, mainly because of the withdrawal of poultry. Molbak WDT: p. 12, lines 15-19, G-672

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. This causal attribution ("mainly because of the withdrawal of poultry") is speculation, not fact. As shown in Cox WDT, B 1901, Attachment 1, cf p. 94], the decline in infection during 1999 was similar to that in other years and has no apparent connection with chicken consumption.

613. In a Danish study to compare the mortality of patients with a group of individuals without known bacterial gastrointestinal infections (the reference group), 10 persons matched by age, gender and county of residence were randomly selected for every patient with culture-confirmed *Campylobacter*. These persons were all alive on the date of receipt of sample. The researchers obtained information on vital status, date of change of vital status (i.e., date of death or emigration) and county of residence for patients and individuals included in the reference group. Finally, from the National Registry of Patients and the Cancer Registry, the researchers obtained data on all hospital discharges, outpatient attendances (since January 1995) and cancer diagnoses up to 5 years prior to entry in the study, allowing the researchers to control for pre-existing illness (comorbidity). Molbak WDT: p. 12, line 44 – p. 13, line 4. G –1799.

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1900 P.49 L.23-31 and B-1901 P.26.

614. The Danish study's analysis included 16,180 *Campylobacter* patients, of which 190 (1.2%) died within one year after the diagnosis of *Campylobacter*. This mortality rate was 2.33 times higher than the background population (95% CI 1.98 to 2.73). In other words, 57% of these deaths were in excess of the background mortality. Among the patients, 695 were identified with one or more diseases included in the comorbidity index. Molbak WDT: p. 13, lines 26-29

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1900 P.49 L.23-31 and B-1901 P.26.

615. After the adjustment for underlying conditions, the relative rate decreased from 2.33 to 1.86 (95% CI 1.56 to 2.20). In other words, of 100 deaths occurring after a *Campylobacter* infection, 46 are caused by the bacterial infection, 11 by underlying illness, and 43 are coincidental and may be explained by the general mortality. We estimate, at the current level of incidence, may be some 25 annual *Campylobacter* deaths in Denmark. Molbak WDT: p. 13, lines 40-44

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and unsubstantiated speculation rather than factual. The offered causal interpretation ("46 are caused by the bacterial infection") is unjustified. It is a speculative interpretation, not a finding of fact, as no causal analysis was done. The "adjustment for underlying conditions" referred to was inadequate. It relied on a comorbidity index, not validated for *Campylobacter*, well known to be imperfect, that accounted for only a small percent of relevant differences in mortality rates. As a result, the fact that AIDS patients and other very sick people are more likely both to acquire bacterial infections and also to die sooner explains the association between infection and

mortality rates, without the former causing the latter. (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

616. The relative mortality was highest in the acute phase of *Campylobacter* infection, defined 30 days after episode date. The Danish study found an excess mortality up to one year after *Campylobacter* infection. Molbak WDT: p. 13, lines 47 – 48, and p. 14, Tables 7 and 8

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. This is not a correct statement of what was found if "excess" means "in excess of what would have occurred in the absence of campylobacteriosis infection." Rather, the Danish study found that AIDS patients, leukemia patients, etc. have elevated mortality rates and also elevated rates of bacterial infections. There is no demonstration of any facts proving or suggesting that bacterial infections (rather than AIDS, leukemia, etc.) cause any excess mortality rates. (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

617. To determine the relative rate of intestinal, extra-intestinal and late-onset complications of *Campylobacter* infections Dr. Molbak and others determined the rate of these diagnoses in the National Registry of Patients, and compared these rates with the rate in the reference population. Of the 16,180 patients with *Campylobacter* infection, one or more diagnoses were found in 269 (1.7%), compared with 1363 (0.8%) of 161,967 persons from the Danish background population. Molbak WDT: p. 15, lines 3-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1900 P.49 L.23-31 and B-1901 P.26. Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

618. In the determination of the relative rates in the Danish study, these diagnoses groups were combined into groups as shown in table 10 of Dr. Molbak's testimony. The scientists found, in particular, elevated risks of Guillain-Barré syndrome, inflammatory bowel disease, acute abdominal conditions, pancreatitis, unexpected death, and reactive or rheumatoid arthritis (Table 10). The elevated risk of acute abdominal conditions, invasive illness, inflammatory

bowel disease and arthritis were statistically significant even in the period 91 to 360 days after the *Campylobacter* infection. Molbak WDT: p. 15, lines 10-15 and p.16, Table 10

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. This is not a correct statement of what was found if "elevated" means "above what would have occurred in the absence of campylobacteriosis infection." Rather, the Danish study found that AIDS patients, leukemia patients, etc. have elevated mortality rates and also elevated rates of bacterial infections. There is no demonstration of any facts proving or suggesting that bacterial infections (rather than AIDS, leukemia, etc.) cause any excess mortality rates. (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

619. The findings of the Danish study underscore that *Campylobacter* infection is associated with an excess risk of complications. While the absolute risk for the individual patient may be small, the public health burden is considerable due to the high incidence of *Campylobacter* infections. Molbak WDT: p. 16, lines 25-27

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It is not a correct statement of what was found if "excess" means "above what would have occurred in the absence of campylobacteriosis infection" and if "public health burden" means "public health burden caused by excess risk of complications caused by *Campylobacter* infection." Rather, the Danish study found that AIDS patients, leukemia patients, etc. have elevated complication rates and also elevated rates of bacterial infections. There is no finding proving or suggesting that bacterial infections (rather than AIDS, leukemia, etc.) cause any excess complication rates or excess public health burden. (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Thus, the interpretation given here is not a finding of fact, but a speculation. Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

620. There are data that suggest that infections with fluoroquinolone-resistant *Campylobacter* are associated with an increased morbidity compared with sensitive strains. The a priori expectation is that a detrimental effect of resistance can be demonstrated in patients treated with fluoroquinolones. Among those, the drug may be harmful because it suppresses the normal gut flora (and possibly other side effects), while the patients do not benefit from the

drug because the *Campylobacter* is resistant. This scenario will result in longer disease duration among treated patients. Molbak WDT: p. 19, lines 15-21

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being compound, inaccurate, and speculative. We disagree that "There are data that suggest that infections with fluoroquinolone-resistant *Campylobacter* are associated with an increased morbidity compared with sensitive strains." (See our responses to CVM PFOFs # 89 and 90). As discussed there and elsewhere, the data do not in reality "suggest that infections with fluoroquinolone-resistant *Campylobacter* are associated with an increased morbidity compared with sensitive strains", but rather show that cases acquired via foreign travel are associated with both increased probability of fluoroquinolone-resistance and increased illness-days (Cox, 2002 and direct testimony)

We further disagree that "The a priori expectation is that a detrimental effect of resistance can be demonstrated in patients treated with fluoroquinolones. Among those, the drug may be harmful because it suppresses the normal gut flora (and possibly other side effects), while the patients do not benefit from the drug because the *Campylobacter* is resistant. This scenario will result in longer disease duration among treated patients." We consider this to be a hypothetical scenario coupled with a statement about Dr, Molbak's "a priori expectation", not a finding of fact. The data relied on by Molbak herein are preliminary results which were deemed unreliable and not in evidence.

621. Smith, Marano, Neimann, and McClellan all showed an increased duration of diarrhea in fluoroquinolone treated patients infected with fluoroquinolone-resistant *Campylobacter* strains compared to patients with fluoroquinolone-susceptible *Campylobacter* strains. Molbak WDT: p. 19, Table 12

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We disagree that the above analysis for Smith, Marano and McClellan "showed an increased duration of diarrhea in fluoroquinolone treated patients infected with fluoroquinolone-resistant *Campylobacter* strains compared to patients with fluoroquinolone-susceptible *Campylobacter* strains." Rather, they showed an increased duration of diarrhea among foreign-travel-associated cases compared to domestically acquired cases. The analyses were not adjusted for foreign travel and are therefore not valid (Burkhart (B-1900) P. 35 L. 4-6; P. 36 L. 4-5; Burkhart (B-1900) P. 36 Table 8]). After correcting for confounding by foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P. 30. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P. 5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P. 59, P. 57. When adjusting the Smith and CDC *Campylobacter* case-control study data for foreign travel, neither Feldman nor Burkhart found a statistical difference in duration of diarrhea between patients with a ciprofloxacin-resistant *Campylobacter* infection and patients with a ciprofloxacin-susceptible *Campylobacter* infection. B-1900, B-1902.

Additionally, the differences presented for Neimann and McClellan are not statistically significant and therefore could have occurred by chance alone. Not acknowledging the lack of statistical significance misrepresents the findings.

622. Molbak's Table 12 reflects four different studies showing an increased duration of diarrhea in fluoroquinolone-treated patients infected with fluoroquinolone-resistant *Campylobacter* strains. The increased duration of diarrhea of the four studies ranged from 2 additional days of diarrhea to 5 additional days of diarrhea. Molbak WDT: p. 19, Table 12

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and vague. It refers to "an increased duration of diarrhea in fluoroquinolone-treated patients infected with fluoroquinolone-resistant *Campylobacter* strains" without saying increased compared to what. If it means "increased compared to what would have occurred had the *Campylobacter* strains been susceptible", then it is incorrect (it is not what the studies show). The above analysis for Smith, Marano, and McClellan were not adjusted for foreign travel and are therefore not valid. After correcting for confounding of foreign travel, there is no significant association between FQ-r CP and duration of diarrhea. B-1901 P. 30. McClellan found no statistically significant relation between ciprofloxacin resistance and duration of diarrhea, even without adjusting directly for international travel. G-1679 P. 5, 6, 54, 56, 57. Only by improperly ignoring confounders can an apparent positive association between them be created. McClellen even states that foreign travel could be an unmeasured confounder to explain the difference in duration of diarrhea between people with fluoroquinolone-resistant *Campylobacter* infections and people with fluoroquinolone-susceptible infections. G-1679 P. 59, P. 57. When adjusting the Smith and CDC *Campylobacter* case-control study data for foreign travel, neither Feldman nor Burkhart found a statistical difference in duration of diarrhea between patients with a ciprofloxacin-resistant *Campylobacter* infection and patients with a ciprofloxacin-susceptible *Campylobacter* infection. B-1900, B-1902.

Additionally, the differences presented for Neimann and McClellan are not statistically significant and therefore could have occurred by chance alone. Not acknowledging the lack of statistical significance missrepresents the findings.

623. In the Danish study, the risk of a complication was 3.7 times higher in patients with a resistant *Campylobacter* isolate compared to patients with a sensitive *Campylobacter* (95% CI 1.5 to 8.9, p=0.004). Molbak WDT: p. 21, lines 6-7

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate and as being based on preliminary data that was deemed unreliable and not in evidence. See our response to CVM PFOF #620.

624. In the period up to one year after *Campylobacter* infection a total of 48 (0.9%) deaths were registered among 5,393 *Campylobacter* patients and 212 (0.4%) deaths among 53,874 referents. Median age among the 48 deaths was 73.4 years (range 10.4-92.3). Overall, patients with *Campylobacter* were 2.42 times (95% CI 1.77 to 3.32) more likely to die than referents in the one year following infection. After adjusting for co-morbidity, the relative rate was 2.41 (95% CI 1.73 to 3.34). Molbak WDT: p. 21, lines 19-24

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Specifically, we disagree that "After adjusting for co-morbidity, the relative rate was 2.41", since co-morbidity was only *partially* adjusted for in the cited work. (The percentage adjusted for may have been about 2%, not the 100% implied by this proposed FOF.) (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Additionally, this fact is not relevant to whether fluoroquinolone-resistant *Campylobacter* have additional adverse human health effects in Denmark, much less the U.S.

625. The one-year mortality rate for patients infected with fluoroquinolone-resistant *Campylobacter* strains was 3.73 (95% CI 2.10-6.64) times higher than the general population, compared with a relative rate of 2.01 (95% CI 1.34-3.00) among those with resistant strains (all estimates adjusted for comorbidity). The p-value for homogeneity of the relative rates was 0.08. Molbak WDT: p. 21, lines 26-29

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Specifically, we disagree with the crucial phrase "all estimates adjusted for comorbidity", since co-morbidity was only partially (very slightly) adjusted for – the vast majority of it was not adjusted for. Moreover, the proposed adjustment has not been validated for this application, so the adjustment may not be correct (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, with response by Dr. Molbak acknowledging that "It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals."). The data relied on by Molbak herein are preliminary results which were deemed unreliable and not in evidence.

626. Data from Denmark suggest that the detrimental effects of fluoroquinolone resistance in *Campylobacter* is not limited to an increased duration of disease, but that there is an increased risk of intestinal and extraintestinal complications. Molbak WDT: p. 21, line 40 -p. 22, line 1

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. First, it has not been demonstrated (or even made plausible by data) that there are any "detrimental effects of [i.e., caused by] fluoroquinolone resistance in *Campylobacter* " In fact, no causal analysis has been undertaken. Thus the implication in this PFOF that *Campylobacter* causes these "detrimental effects" is an unsubstantiated speculation, not a finding of fact. Instead, *imperfectly controlled confounding* can explain the patterns in the data in the absence of the causal relations that Dr. Molbak postulates here (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, with response by Dr. Molbak acknowledging that "It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") Thus, the interpretation given here is not a finding of fact, but a speculation. The data relied on

by Molbak herein are preliminary results which were deemed unreliable and not in evidence; see our response to CVM PFOF #620.

627. The data from the Danish study corroborates the hypothesis that fluoroquinolone resistance in *Campylobacter,* at the current level of resistance, has a negative impact on public health. Molbak WDT: p. 21, line 40 – p. 22, line 6.

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate, for the reasons given in the responses to CVM's PFOFs #626 and in Cox's 2003 letter to BMJ (http://bmj.com/cgi/eletters/326/7385/357#29767, with response by Dr. Molbak acknowledging that "It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.") The data relied on by Molbak herein are preliminary results which were deemed unreliable and not in evidence; see our response to CVM PFOF #620.

628. It is essential to preserve fluoroquinolone sensitivity in *Campylobacter,* in particular in a global scenario where larger segments of the population have chronic diseases, are elderly, or otherwise vulnerable to severe outcomes after *Campylobacter* infection. Molbak WDT: p. 22, lines 10-12

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and vague, for the reasons given in our response to CVM's PFOFs #605. The statement is also inaccurate and vague as it does not explain the connection between fluoroquinolone sensitivity and the "larger" segments vulnerable to severe outcomes and how this relates to fluoroquinolone resistance in *C. jejuni* and *C. coli.* The assertion that "It is essential to preserve fluoroquinolone sensitivity in *Campylobacter*" is an unsubstantiated opinion, not a finding of fact.

629. The marked decline in the incidence of *Campylobacter* in the US has in part been set back by an increase in fluoroquinolone resistance in *Campylobacter.* Molbak WDT: p. 22, lines 14-15

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate, speculative, vague and misleading. First, it makes an unsubstantiated assumption that fluoroquinolone resistance in *Campylobacter* has increased in the US, but this is not known (see responses to CVM PFOFs # 41, 78, 87, 88, and 609). Second, the marked decline in the incidence of *Campylobacter* in the US prevents illness-days (1-10 days per incident), while the increase in fluoroquinolone resistance in *Campylobacter* appears to have no clinical relevance (see our responses to CVM PFOFs # 19, 20, 620); hence, the opinion that the former is "in part set back" by the latter is an unjustified interpretation.

Finally, suppose for purposes of conceptual discussion that (a) an increase in fluoroquinolone-resistance in *Campylobacter* has occurred and (b) that it is due solely to the effects of enrofloxacin in reducing airsacculitis and resulting risk of chicken-associated campylobacteriosis (which is relatively unlikely to be resistant) in humans (Cox and Popken, 2003); and (c) enrofloxacin use has no other effects. Chicken-associated campylobacteriosis is less likely to be fluoroquinolone-resistant than campylobacteriosis from non-poultry sources (e.g., ciprofloxacin-

contaminated water) [Burkhart (B-1900) P.22 L. 40-43 referring to G-589 (Smith 1999)]). Hence, the reductions in risk of chicken-associated campylobacteriosis due to successful enrofloxacin use (part (b) in the above scenario) would tend to cause a higher proportion of non-chicken-associated (and hence more resistant) campylobacteriosis cases. But this "increase in fluoroquinolone resistance in *Campylobacter*" would *not* in any sense "partly set back" the "marked decline in the incidence of *Campylobacter* in the US as Molbak suggests here. Rather, the success of enrofloxacin use in reducing chicken-associated campylobacteriosis would both reduce the number of cases and eliminate the cases (those associated with chicken) that are least likely to be resistant. CVM's PFOF #629 assumes a particular interpretation (that enrofloxacin creates new resistant cases that would not have happened anyway) that is not implied by the data, as this counter-example shows. Hence, PFOF #629 is not a finding of fact, but is based on an unjustified and speculative interpretation of data.

630. In Denmark where only very small amounts of fluoroquinolones are used in food production, the prevalence of fluoroquinolone resistance is relatively lower in indigenous infections compared with infections acquired abroad. Molbak WDT: p. 22, lines 17-19

Bayer/AHI Response: Denied: The statement is not accurate as DANMAP 2001 (G 1606) reports that in Denmark in 2001 452 kg active compound of quinolones and fluoroquinolones (179 and 273 kg respectively) were sold from pharmacies for use in animals, excluding pets, which cannot be considered as very small amounts.

631. Data from Denmark suggest that the mortality of *Campylobacter* infections is underestimated, and confirms that *Campylobacter* infection may be associated with serious late onset complications. The detrimental effects of fluoroquinolone resistance in *Campylobacter* is not limited to an increased duration of disease, but is also associated with an increased risk of intestinal and extraintestinal complications, and possibly also an increased mortality. Molbak WDT: p. 22, lines 21-25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. See our responses to CVM PFOFs # 619-621. The PFOF incorporates false assumptions, such as that "fluoroquinolone resistance in *Campylobacter* [causes] an increased duration of disease". This conclusion is not valid (Burkhart (B-1900) P.35 L.4-6; P.36 L.4-5; Burkhart (B-1900) P.36 Table 8]). After correcting for confounding by foreign travel, there is no significant association between fluoroquinolone-resistant *Campylobacter* and duration of diarrhea. B-1901 P.30.

J. Glenn Morris (G-1469)

632. Dr. Morris is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

633. There has been a rapid increase in antimicrobial resistance among the bacteria that cause illness in humans. Morris WDT: p. 3, lines 11-12

Bayer/AHI Response: NARMS data is not reliable, and even assuming it were, the data do not show an increase, let alone a "rapid increase". Also refer to Bayer/AHI responses to proposed findings of fact 1320 and 1342.

634. Rates of quinolone resistance among clinical *Campylobacter* isolates are rising. Morris WDT: p. 3, lines 13-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF because clinical resistance has not been established through the accepted protocols and the incidence of "treatment failures" for quinolone-resistant and quinolone-susceptible *Campylobacter* infections is similar. See Bayer/AHI responses to findings of fact 1342 [Pasternack] B-1909 P.14 L.19-22, P.15 L.1-16, P.17 L. 4-6; [Silley] B-1914 P.17 L.15-23, P.18 L.1-15, Att.1 P.46 ¶ 2; [Kassenborg] G-1460 P.4 L.3-4; B-44 P.6; G-1789 P.11; G-191 P.4; G-624 P.1

635. *Campylobacter* species cause approximately 2 million foodborne cases, 10,539 hospitalizations, and 99 deaths each year. Morris WDT: p. 3, lines 17-18

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is inaccurate and misleading. CDC estimates the US incidence of *Campylobacter* infections in 1999 was 1.4 million and since then has declined. CVM proposed finding of fact #36, G-1452 Attachment 3. P.82; CVM Response to Bayer's Interrogatory 28. Angulo (G-1452) P.7 L.13-14, L.16-18, P.17 L.10. Bayer/AHI also disagree with the proposed finding of fact for the reasons stated in their responses to proposed findings of fact 1286, 1291, 1299, 1305 and 1348.

636. *Campylobacter* is the most common bacterial cause of foodborne illness in the United States. Morris WDT: p. 3, lines 18-19

Bayer/AHI Response: Bayer/AHI object to this PFOF because it does not accurately reflect the current public health impact of *Campylobacter* disease in the United States. This PFOF cites to G-410 (Mead, et. al 1999) which on its face used data from 1996 and 1997 to estimate the incidence of foodborne illness. (G-410 P.3). It is undisputed that from 1996 to 2001 foodborne disease rates in the United States have fallen significantly. Specifically, in the United States, the incidence of *Campylobacter* infections as measured through the Foodborne Disease Active Surveillance Network (FoodNet) decreased by 27% between 1996 and 2001. G-1452 P.5 L.21-23, Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. In 2002, CDC reported that for 2001, *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States. G-1391. Therefore it is not true that *Campylobacter* is the most common bacterial cause of foodborne illness in the United States.

637. *Campylobacter* is the most common bacterial cause of severe diarrheal illness in adults. Morris WDT: p. 3, lines 19-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no basis for the statement is provided by the witness and for the reasons stated in their response to proposed finding of fact 1291.

638. Diminution of the ability to effectively treat infections due to *Campylobacter* is a major public health concern. Morris WDT: p. 4, lines 1-2

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is not relevant to this proceeding since the issue of concern is domestically acquired fluoroquinolone-resistant *Campylobacter*. 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] Bayer/AHI also disagree with the proposed finding of fact for the reasons stated in their responses to proposed findings of fact 1305, 1307 and 1342.

639. *Campylobacter jejuni* causes a gastroenteritis syndrome that may include diarrhea, vomiting, abdominal pain, and fever. Morris WDT: p. 4, lines 3-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

640. Up to 20% of persons with *Campylobacter* infections have grossly bloody diarrhea,. making it the most common cause of bloody diarrhea among adults. Morris WDT: p. 4, lines 5-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons state in their response to proposed finding of fact 1291.

641. Severe *Campylobacter* infections can include fever, diarrhea filled with blood and mucus, abdominal pain, muscle aches, and headache. Morris WDT: p. 4, lines 7-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness's testimony states that such symptoms are "at the more severe end of the disease spectrum" (Morris WDT: P.4 L.7), while the vast majority of *Campylobacter* infections are mild and resolve in 5 days or less without treatment (see Bayer/AHI responses to proposed findings of fact 1304 and 1305).

642. Otherwise healthy adults with *Campylobacter* infections can be totally incapacitated for well over a week. Morris WDT: p. 4, lines 10-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 641. Bayer/AHI also disagree with this proposed finding of fact because it is misleading. While some patients with *Campylobacter* enteritis may be ill enough to be incapacitated for some period of time, the vast majority of patients (as many as 17 out of 18) do not even seek treatment, and as this observation suggests, the vast majority of *Campylobacter* infections are mild and resolve in 5 days or less without treatment. G-615 P.3; B-1909 P.4 L.4-6; B-1485 P.5 L.30-31; G-1477 P.2 ¶ 3.

643. *Campylobacter* has been linked with occurrence of Guillian-Barre syndrome. Morris WDT: p. 4, lines 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, it is misleading and not relevant to this proceeding since there are no data associating complications such as reactive arthritis and Guillain-Barre with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. B-1906 P.16 L.6-7, P.18 L.6-7 L.12-13; B-1908 P.47 L.23-24, P.48 L.1-2.

644. A clear clinical response has been observed in persons infected with *Campylobacter* who are treated with appropriate antibiotics. Morris WDT: p. 4, lines 18-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons state in their response to proposed finding of fact 1322.

645. Antibiotic therapy early in the course of illness is efficacious. Morris WDT: p. 4, lines 21-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1330.

646. Quinolones have been shown to have clinical efficacy in *Campylobacter* infections. Morris WDT: p. 4, line 23 – p. 5, line 1

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the term "clinical efficacy" is too vague. Bayer/AHI also note that actual studies are in conflict with one another on the effectiveness of antibiotic therapy (Pasternack WDT: P.11 L.19-22, P.12 L.1-22, P.13 L.1-8; B-44 P.7; G-705 P.1; B-816 P.2-3; G-188 P.1, 3, 4, 5; G-172 P.3. In addition, the IDSA guidelines classify the evidence underlying even their recommendation for selective antibiotic treatment for *Campylobacter* as being "moderately" supportive and not based on a properly randomized, controlled clinical trial. G-261 P.2-3. Also refer to the response for proposed finding of fact 1330.

647. Fluoroquinolone therapy must be started as soon as possible after onset of illness if it is to have an optimal effect. Morris WDT: p. 5, lines 2-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1330.

648. It usually takes three to four days after a patient sees the doctor for a definitive diagnosis of *Campylobacter* infection to be made, based on the time required for the organism to grow and be identified on a stool culture. Morris WDT: p. 5, lines 6-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it takes 3 days or less to identify *Campylobacter* in a stool culture. Thielman WDT: P.4, ¶ 7. In addition, a recently introduced test allows the identification of *Campylobacter* within 2 hours. B-1143 P.1-3.

649. Physicians generally resort to empiric therapy while awaiting culture results. Morris WDT: p. 5, lines 8-10

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no evidentiary basis is provided for it.

650. The average stool culture costs in excess of $100. Morris WDT: p. 5, lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no evidentiary basis is provided for it and because the ALJ has ruled against the use of economic data or arguments.

651. Physicians often initiate empiric therapy, and skip the culture. Morris WDT: p. 5, lines 11-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the unpublished study on which it is based concerns practices in 1997, while at the present time, 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 WDT: 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 WDT: P.3 L.15-18; B-857 P.2; G-253 P.5; G-707 P.9).

652. Conn's Current Therapy, published annually, is widely used by clinicians as a practical guide to management of medical problems seen in their day-to-day practice. Morris WDT: p. 5, lines 18-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no evidentiary basis is provided for it and of the numerous physicians testifying in this proceeding, only the witness (who writes for it) mentions this reference.

653. Conn's Current Therapy recommends ciprofloxacin empiric therapy for diarrheal disease cases in which a bacterial etiology is suspected. Morris WDT: p. 5, lines 21-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the reference is not in evidence and cannot be reviewed.

654. Ciprofloxacin has a broad-spectrum clinical activity against a number of enteric pathogens. Morris WDT: p. 5, line 23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

655. Erythromycin has limited activity against some enteric pathogens other than *Campylobacter*. Morris WDT: p. 6, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

656. Erythromycin is a poor choice for empiric therapy. Morris WDT: p. 6, lines 1-2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although Bayer/AHI agree that ciprofloxacin may treat for a broader spectrum of bacteria than erythromycin, this does not mean that erythromycin is a "poor" choice. In certain circumstances, particularly when *C. jejuni* infection is suspected, erythromycin is preferred for empiric therapy due to the lower rate of macrolide resistance observed among *C. jejuni* isolates in the United States and the narrow spectrum of erythromycin therapy against *C. jejuni*. The narrow spectrum confers minimal risk of empirically treating *Salmonella* or Shiga toxin-producing *E. coli* infections. B-1909 P.8 L.7-16. Furthermore, infants and children account for a significant percentage of campylobacteriosis cases, and in situations where antibiotic therapy is indicated for children, fluoroquinolones are not recommended or approved for that use, and macrolides such as erythromycin or azithromycin are the preferred treatment for campylobacteriosis B-1905 P.4 L.9-16.

657. Kelly's Textbook of Internal Medicine recommends ciprofloxacin for use in patients before culture results are known because of its broad-spectrum activity against a number of bacterial enteric pathogens. Morris WDT: p. 6, lines 3-5

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the reference is not in evidence and cannot be reviewed.

658. Ciprofloxacin tends to be better tolerated by patients than erythromycin. Morris WDT: p. 6, line 6

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that azithromycin, a macrolide like erythromycin, also is well-tolerated and has low resistance. See Bayer/AHI responses to proposed findings of fact 1338 and 1342.

659. Erythromycin can cause gastrointestinal discomfort. Morris WDT: p. 6, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

660. The recent rapid emergence of ciprofloxacin resistance in *Campylobacter* is of clear concern. Morris WDT: p. 6, lines 11-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As previously stated, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. 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, and resistance to erythromycin and azithromycin, the preferred antimicrobials, remain low. Analysis of United

States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

661. Ciprofloxacin has demonstrated great utility in management of diarrheal illness. Morris WDT: p. 6, line 17 – p. 7, line 1

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1322.

Irving Nachamkin (G-1470)

662. Dr. Nachamkin is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

663. *Campylobacter jejuni* is the most common cause of bacterial diarrhea in the United States. Nachamkin WDT: p. 2, lines 31-32

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject.

664. *Campylobacter jejuni* is one of the most common causes of bacterial diarrhea worldwide. Nachamkin WDT: p. 2, lines 32-33

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but disagree with this PFOF as relates to the current status in the United States, which is the relevant time and location for the issues in this hearing. As relates to the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject.

665. People acquire *Campylobacter* from contaminated food. Nachamkin WDT: p 2, L 34-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF as ambiguous and potentially misleading. If the PFOF means only that some people eat some food with some *Campylobacter*, then we do not object to it. If it means that all or most cases of campylobacteriosis are acquired from food (as opposed to water), then we disagree with this PFOF as being misleading. While Bayer/AHI agree that some people acquire *Campylobacter* from contaminated food, numerous other risk factors have been identified for campylobacteriosis, including ingestion of

inadequately treated water via drinking water sources and recreational waters, foreign travel, contact with farm animals and pets, consumption of raw milk, taking medication, having an underlying disease, and contact with humans via fecal-oral transmission and ill food handlers. G-1483 P.15 L.13-18; G-1483 P.20 L.11-12; G-1475 P.5 L.43 – P.6 L.1; G-1743; B-1908 P.21 L.16-19; B-1900 P.9 L.28-30; G-1470 P.4 L.22-29; G-1452 P.9 L.28-29.

666. Symptoms of campylobacteriosis include fever, abdominal pain and diarrhea (bloody or watery). Nachamkin WDT: p. 2, lines 35-36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because, although campylobacteriosis can include such symptoms, it does not always do so, most cases are so mild that people do not even consult a physician, and *Campylobacter* infections may be asymptomatic in up to 25% of cases. B-1909 P.4 L.4-9; G-70 P.4.

667. 5% - 10% of untreated patients with campylobacteriosis may experience relapse of illness. Nachamkin WDT: p. 2, lines 40-41

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI disagree with this PFOF as misleading, ambiguous and unsupported. The PFOF does not specify whether the relapse being described is clinical or biological, provides no firm basis to support the estimate of 5 to 10% (other than citing other literature that does not support the estimate), and perhaps suggests. that patients with campylobacteriosis that are treated may not experience clinical or biological relapse, or at least not at the percentages stated for untreated patients. Bayer/AHI agree that clinical and biological relapses occur in patients with campylobacteriosis, whether untreated or treated with fluoroquinolones. B-1906 P.13 L.15-21; G-1616 P.3; G-422 P.3; B-127 P.2; G-497 P.2-4.

668. Fluoroquinolones such as ciprofloxacin are widely used to treat *Campylobacter* infections. Nachamkin WDT: p. 2, lines 44-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF as misleading. First of all, only a very small percentage of people with campylobacteriosis seek treatment [G-615 P.3; B-1909 P.4 L.4-6] and secondly, antimicrobials, including ciprofloxacin, are not widely used [G-1485 P.9 L.46, P.10 L.1-7; B-1909 P.7 L.17-22, P.18 L.15-18; G-70 P.6; B-1905 P.5 L.9-12; G-1468 P.3 L.21] nor should be widely used [B-1905 P.3 L.15-18; G-1485 P.9 L.36-46, P.10 L.1-7; B-127 P.1; G-172 P.5,6; G-292 P.1] to treat *Campylobacter* enteritis. For the limited numbers of people that do require an antibiotic, the antibiotic of choice for treatment of *Campylobacter* enteritis is a macrolide such as erythromycin or azithromycin or the new rifaximin [B-1905 P.4 L.8-11; B-1909 P.14 L.1-16; G-1457 P.6 L.44-45; G-1477 P.2 ¶ 4; G-1469 P.5 L. -5; G-557 P.3; B-816 P.2]. Ciprofloxacin is another antibiotic frequently used for treatment of *Campylobacter* enteritis in the small percentage of patients that require an antibiotic [B-1905 P.4 L.3-11; G-1485 P.13 L.20-38; G-191 P.6].

669. Some patients with *Campylobacter* may go on to develop reactive arthritis and Guillain-Barre syndrome, both the result of the body's immune response to the *Campylobacter* infection. Nachamkin WDT: p. 3, lines 6-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF as misleading and not relevant to this proceeding since there are no data associating complications such as reactive arthritis and Guillain-Barre with fluoroquinolone-resistant *Campylobacter* infections, as compared to infections with susceptible *Campylobacter*. CVM Interrogatory Answer 60; 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.

670. In some patients, reactive arthritis, with pain and joint swelling, occurs within 2 weeks following *Campylobacter* infections. Nachamkin WDT: p. 3, lines 8-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although the statement is true, it is misleading and not relevant to this proceeding since there are no data associating complications such as reactive arthritis with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. CVM Interrogatory Answer 60; 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.

671. It is estimated that 1 per 1000 *Campylobacter* infections results in Guillain-Barre syndrome. Nachamkin WDT: p. 3, lines 9-10

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being potentially misleading and as being not relevant to this proceeding since there are no data associating complications such as, Guillain-Barre with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter*. CVM Interrogatory Answer 60; 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

672. Guillain-Barre syndrome is characterized by a sudden onset of paralysis (polio like). Most patients, however, recover from the paralysis and return to a normal life function within 1 year of the onset of the disease. Nachamkin WDT: p. 3, lines 10-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is misleading and not relevant to this proceeding since there are no data associating complications such as Guillain-Barre 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 Bayer/AHI also object to the term "polio-like" since polio is a disease caused by a virus, not a bacteria, is completely unrelated to Guillain-Barré Syndrome (GBS), and, unlike GBS, results much more often in permanent paralysis.

673. The overall health burden from *Campylobacter* infection is considerable. Nachamkin WDT: p. 3, line 15

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being vague and as being an unsubstantiated opinion rather than a statement of fact. The terms "overall health burden" and "considerable" are not defined. Campylobacteriosis is generally a self-limiting disease and in this sense is usually not a considerable health burden. In addition, the health burden of relevance to this hearing is restricted to infections from *Campylobacter jejuni* and/or *Campylobacter coli* that are fluoroquinolone-resistant due to use of Baytril in poultry in the United States, to the

extent they: (a) result in less effective treatment in people treated with fluoroquinolones, (b) result in more protracted illness because the *Campylobacter* are resistant, and/or (c) result in increased hospitalizations. In this regard, for the reasons stated in their response to PFOF 1342, fluoroquinolone-resistant campylobacteriosis is not a significant health problem in the United States in and of itself. Finally, CVM does not have any facts or data demonstrating any increase in the rate or extent of complications from infections caused by fluoroquinolone-resistant *Campylobacter* as compared to infections caused by fluoroquinolone-susceptible *Campylobacter*. [CVM Interrogatory Answer 60].

674. A recent analysis of more than 16,000 patients with *Campylobacter* infection in Denmark suggests mortality following *Campylobacter* infection is 4/1000 within 30 days with a 1.9 times excess mortality within 2 years. Nachamkin WDT: p. 3, lines 17-23

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. It is refuted by B-1900 P.49 L.23-31 and B-1901 P.26. It is not a correct statement of what was found if "excess" means "in excess of what would have occurred in the absence of campylobacteriosis infection." Rather, the Danish study found that AIDS patients, leukemia patients, etc. have elevated mortality rates and also elevated rates of bacterial infections. There is no demonstration of any facts proving or suggesting that bacterial infections (rather than AIDS, leukemia, etc.) cause any excess mortality rates. (Cox, 2003 letter to BMJ, http://bmj.com/cgi/eletters/326/7385/357#29767, (B-1922) with response by Dr. Molbak acknowledging that "Nonetheless, we agree with Jacobs and Cox that the causal direction of our observations needs to be carefully investigated in future studies. It is possible that gastrointestinal infection may be a marker of increased vulnerability for some individuals. It is also likely that the events in the causal chain that led to the diagnosis of the infection and further death were very complex and insufficiently described by our approach for a subset of the cases.")

In addition, the scope of this hearing is the United States and therefore *Campylobacter*-related statistics from Denmark are not relevant to the issue of this hearing. This PFOF, in which Nachamkin paraphrases the findings of the recent Danish study by Helms, Molbak and others, is misleading because it only partially quotes his testimony. Nachamkin's testimony subsequently states that the excess mortality "was partly due to other concurrent illnesses such as HIV infection and other chronic diseases, but they attributed 26% of the excess deaths to *Campylobacter* infection." (G-1470 P.3 L.24-26). Most important, however, is that the relevance to this proceeding of the *Campylobacter*-related mortality inferences drawn by Molbak himself (G-1468) [see Bayer FOF 773 which is G-444 P.323-324] and paraphrased by Nachamkin are 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.

675. People can die from campylobacteriosis. Nachamkin WDT: p. 3, lines 21-26

Bayer/AHI Response: Bayer/AHI dispute this PFOF. It is also misleading and not relevant to this proceeding since the issue is not about all *Campylobacter* infections, it is only about fluoroquinolone-resistant *Campylobacter* infections. Also, 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] The phrase "die from campylobacteriosis" is therefore potentially misleading and inaccurate, as the underlying cause of death may be something entirely different that is statistically associated with campylobacteriosis, e.g., AIDS. See our response to PFOF #674.

676. *Campylobacter jejuni* is a gram-negative bacteria. Nachamkin WDT: p. 3, lines 28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

677. *Campylobacter* is microaerophillic. It requires about 5% oxygen to grow and does not grow well in the presence of atmospheric levels of oxygen. Nachamkin WDT: p. 3, lines 31-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

678. *Campylobacter jejuni* is the major *Campylobacter* species to cause human infection. Nachamkin WDT: p. 3, lines 37-38

Bayer/AHI Response: Bayer/AHI agrees with the PFOF although "human gastrointestinal infection" would be more accurate.

679. Approximately 90 – 95% of human *Campylobacter* infections are caused by *C. jejuni*. Nachamkin WDT: p. 3, lines 39-40

Bayer/AHI Response: Bayer/AHI agrees with the PFOF although "gastrointestinal infections" would be more accurate.

680. *Campylobacter coli* is thought to cause about 5 - 10% of the infections reported as *Campylobacter jejuni*. Nachamkin WDT: p. 3, lines 40-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

681. *C. coli* causes a disease identical to *C. jejuni* in terms of gastroenteritis. Nachamkin WDT: p. 3, lines 42-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

682. *Campylobacter jejuni* is primarily associated with poultry. Nachamkin WDT: p. 4, lines 8-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. It is an incorrect and unsubstantiated claim. Evidence in the record disputes the contention that chicken or turkey is a principle source of campylobacteriosis in humans. (If the statement means only that *Campylobacter jejuni* in poultry is primarily associated with *Campylobacter jejuni* in poultry, we have no objection other than tautology.) Chicken is not major source of campylobacteriosis in

humans B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or suggest that poultry is a principle source of campylobacteriosis, but refutes this supposition.

Bayer/AHI also disagrees with this PFOF as being vague, misleading and inaccurate. Although the primary cause of *Campylobacter* enteritis in humans has not been definitively determined and may vary from one time and place to another, ingestion of water containing *Campylobacter* is probably the most significant single cause of *Campylobacter* enteritis in humans (Bayer FOF 162-164). Contact with pets, livestock, and humans are also causes of *Campylobacter* enteritis.

683. Handling raw poultry is a risk factor for sporadic cases of campylobacteriosis. Nachamkin WDT: p. 4, lines 16-17

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and unsubstantiated. This statement is taken out of context and misrepresents the risks for campylobacteriosis. 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. B-1901 P.29 (citing G-1644). In a recent extensive CDC *Campylobacter* case-control study, Friedman et al. found that none of the reported kitchen and food preparation practices was associated with increased risk of illness. G-1452 P.88.

684. Ingestion of contaminated poultry/poultry products is a risk factor for sporadic cases of campylobacteriosis. Nachamkin WDT: p. 4, lines 16-17

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and incomplete. Recent epidemiological data, particularly in the U.S., demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that ingestion of contaminated poultry/poultry products by consumers at home is a risk factor for sporadic cases of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or suggest that contaminated poultry/poultry products is a risk factor for sporadic cases of campylobacteriosis, but tends to refute this supposition.

685. Eating poultry at restaurants is a risk factor for campylobacteriosis. Nachamkin WDT: p. 4, lines 19-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being inaccurate and misleading. Evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the risk factor for campylobacteriosis. B-1901 P.29, 30 (citing U.S. studies G-1644, G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

686. Contamination of food products via cross-contamination (i.e., cutting boards) is also a risk factor for infection. This cross contamination with poultry may account for 10 – 50% of human *Campylobacter* infections. Nachamkin WDT: p. 4, lines 20-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate, unsubstantiated, speculative, and as giving an unjustified causal interpretation to data (assuming that "account for" means "cause" in this context.) This PFOF fails to control for confounding by poor kitchen hygiene, i.e., the possibility that people with poor kitchen hygiene are less likely to wash cutting boards and also more likely to get food poisoning, but not because of cross-contamination with poultry. Indeed, in the CDC case-control data set, failure to wash the cutting board is a risk factor for campylobacteriosis, but handling raw chicken is not (Cox, 2002). This argues against the speculation asserted here that "This cross contamination with poultry may account for 10 – 50%. of human *Campylobacter* infections" – it appear that 0% is more consistent with the data. In any case, we dispute this PFOF as being speculation rather than fact.

687. Since January 2000, in Iceland, *Campylobacter* culture-positive poultry were frozen before sale to the general public and culture-negative poultry were allowed to be sold as fresh. Nachamkin WDT: p. 4, lines 34-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

688. Iceland has experienced a 60% reduction in campylobacteriosis cases from 1999 levels. Nachamkin WDT: p. 4, lines 36-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

689. Since January 2000, in Norway, *Campylobacter* culture-positive poultry were frozen before sale to the general public and culture-negative poultry were allowed to be sold as fresh. Nachamkin WDT: p. 4, lines 34-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

690. In Norway, cases of campylobacteriosis in 2002 were reduced to 50% of the levels of campylobacteriosis in 2001. Nachamkin WDT: p. 4, lines 39-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

691. Poultry consumption is one of the most important sources for human *Campylobacter* infection. Nachamkin WDT: p. 4, lines 40-41

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and as being based on an unjustified causal inference. The validity of the inference leading to this conclusion has been refuted in [Cox, B-1901 P.52] as follows:

Some of CVM's witnesses seem also not to have fully recognized the importance of ruling out threats to validity of causal inference in interrupted time series data before such data can be interpreted as evidence of causal relations (Campbell and Stanley, 1963). For example, Dr. Nachamkin (G-1478 P.4 ¶ 12) interprets the reductions in CP rates in Iceland and Norway following changes in chicken processing as justification for an opinion that "poultry consumption is one of the most important sources for human *Campylobacter* infection" (presumably, at least in those two countries). (See also Dr. Tauxe's testimony, G-1475 P.17 ¶ 51). However, to properly assess the impacts of these interventions, *it is necessary to adjust for the impacts of other simultaneous interventions,* such as a massive public education effort to improve kitchen hygiene. An unexamined attribution of improvements in CP rates to interventions in chicken-freezing policy may over-state the impact caused by that intervention if other simultaneous interventions were also reducing CP rates. Indeed, as noted by Dr. Norm Stern for the Iceland study, "Clearly there may be other interventions (e.g. changes in consumption and consumer handling practices) or natural phenomena (e.g. chances in the environmental sources of *Campylobacter* in the period 1999-2000) which could also explain the dramatic decrease in the human health burden" (Stern et al., 2002).

Evidence in the record shows that poultry consumption is *not* "one of the most important sources for human *Campylobacter* infection", and indeed is not even a major source. Chicken is not even a major source of campylobacteriosis in humans B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or suggest that poultry is a principle source of campylobacteriosis, but refutes this supposition.

692. Estimates from experimental human *Campylobacter* infection suggest an infective dose of as few as 500 - 800 *Campylobacter* organisms. Nachamkin WDT: p. 4, lines 45-46; G-67

Bayer/AHI Response: Bayer/AHI disagree with this PFOF, preferring the wording of their related PFOF (657): "Based on experimental data, the minimum number of *Campylobacter*

capable of causing campylobacteriosis has been estimated to be about 500 - 800 organisms (minimum infectious dose)." CVM's PFOF may be interpreted to mean that the infective dose for all people is between 500 to 800 organisms, which is not accurate. B-1901 P.23, citing B-748/G-629 and G-628; G-67.

693. Dose does not appear to be the only factor contributing to campylobacteriosis. Nachamkin WDT: p. 5, lines 1-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

694. In *Campylobacter*, there appears to be strain to strain variation in virulence to humans. Nachamkin WDT: p. 5, line 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

695. In industrialized nations, such as the U.S., there does not appear to be a carrier state for *Campylobacter jejuni*. Nachamkin WDT: p. 5, lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Many persons with campylobacteriosis - perhaps as many as 25% of all persons infected - do not exhibit clinical symptoms and are therefore "asymptomatic" carriers. Pasternack (B-1909) P.3 L.23, P.4 L.1-3. .

696. "Carrier state" refers to a situation in which infected individuals harbor the organisms and may shed them in their feces, but are not ill. Nachamkin WDT: p. 5, lines 11-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

697. In the U.S. and other developed countries, there is a low occurrence of human-to-human transmission of infection. Nachamkin WDT: p. 5, lines 13-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214. Human-to-human transfer of *C. jejuni* and *C. coli*, either by direct or indirect pathways, has been well-documented. For example, G-1697 describes an outbreak of *C. jejuni* infections associated with food handler contamination, G-1692 describes the intrafamilial spread of *Campylobacter* in five separate households, G-580 describes a "persistent" outbreak of *Campylobacter* infection in a day care nursery in Israel, and B-213 reviews nine different studies that point to person-to-person contact as being the main transmission route. The rate of human-to-human transmission in the United States is unknown, but such transmission is not necessarily as uncommon as has been supposed. G-1452 P.9 L.28-29. In addition, sewage treatment plants which process domestic, commercial, and industrial wastewaters that received human waste discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of bacteria, including fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9.

698. Patients with untreated campylobacteriosis may shed *Campylobacter* organisms in their stool for 2-3 weeks following infection. Nachamkin WDT: p. 5, lines 17-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

699. Diagnosis of campylobacteriosis is made by stool culture. Nachamkin WDT: p. 5, lines 37-38

Bayer/AHI Response: Bayer/AHI dispute this PFOF as incomplete. Although diagnosis of *Campylobacter* enteritis is typically made by stool culture, the ProSpecT *Campylobacter* Microplate Assay is a new test that is being used to identify *Campylobacter* infections within two hours (B-1143 P. 1-3) and that test is not technically a "stool culture". Bayer/AHI also disagree with this PFOF because *Campylobacter* bacteremia, a rare form of campylobacteriosis, is typically diagnosed with a blood sample, and never a stool culture.

700. The number of cases of campylobacteriosis is grossly underestimated. Nachamkin WDT: p. 5, lines 43-44

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being potentially misleading. They agree that a consensus exists that the vast majority of *Campylobacter* infections are unreported; however, they point out that this under-reporting is due in substantial part to the fact that most *Campylobacter* infections are mild and resolve in less than 5 days without treatment G-1477 P.2, Para. 3; G-615 P.3; B-1909 P.r L.4-6; B-1485 P.5 L.30-31.

701. Stool cultures are probably performed on only 1 patient for every 20 with infection. Nachamkin WDT: p. 5, lines 44-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is vague, not substantiated, and is a speculation, not a fact. Nachamkin does not provide a reference for this statement. In a FoodNet population survey of persons with diarrheal illness, a stool sample was obtained from approximately 19% (about 1 in 5) persons who visited a health care provider. G-1790 P.7. In another FoodNet study, 43% of physicians who had seen a patient with diarrhea had ordered a stool culture on their most recent patient. Morris WDT: P.5 L.13-15.

702. Erythromycin may not be tolerated well by patients. Nachamkin WDT: p. 6, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to the proposed finding of fact; however, they point out that azithromycin, a macrolide like erythromycin, is well-tolerated and has low resistance. See Bayer/AHI responses to proposed findings of fact 1338 and 1342.

703. Fluoroquinolone agents, such as ciprofloxacin, have very good activity against susceptible *C. jejuni*, as well as for the other major causes of gastroenteritis. Nachamkin WDT: p. 6, lines 5-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being meaningless, inaccurate, and misleading. If a bacteria is "susceptible" to a particular antibiotic as determined by *in vitro*

testing, it is considered that this antibiotic has "activity" against that bacteria, not "very good activity". Substituting "*C. jejuni* against which they have activity" for the equivalent phrase "susceptible *C. jejuni*" shows that the PFOF is meaningless (a logical tautology), i.e., it asserts that: "Fluoroquinolone agents, such as ciprofloxacin, have activity against *C. jejuni* against which they have activity," If the proposed finding of fact is referring to *in vivo* activity, the actual studies are conflicting. 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.

704. Fluoroquinolone treatment is a standard to treating patients with suspected bacterial gastroenteritis because of good tolerance to the drug and its effectiveness against a broad range of bacteria capable of causing diarrhea. Nachamkin WDT: p. 6, lines 7-10

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as being inaccurate and an overstatement. First of all, the only "standard" treatment for bacterial gastroenteritis is the administration of fluids to correct or prevent dehydration [B-1906 P.9 L.17-20]. Most cases of *Campylobacter* enteritis are self-limiting and are not treated with antimicrobials. Lastly, although Bayer/AHI agree that ciprofloxacin may be used to empirically treat a limited number of cases of gastroenteritis, including *Campylobacter* enteritis [B-1905 P.4 L.3-11; G-1485 P.13 L.20-38; G-191 P.6], the antibiotic of choice for treatment for the small number of individuals that truly would benefit from antibiotics is a macrolide such as erythromycin or azithromycin or the new rifaximin [B-1905 P.4 L.8-11; B-1909 P.14 L.1-16; G-1457 P.6 L.44-45; G-1477 P.2 ¶. 4; G-1469 P.5 L.3-5; G-557 P.3; B-816 P.2]

705. Fluoroquinolones are commonly used to treat serious *Campylobacter* infections and are also used as empiric therapy for travelers' diarrhea and diarrhea of unknown etiology. Nachamkin WDT: p. 6, lines 11-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI disagrees with this PFOF because it is an overstatement. Antimicrobials such as erythromycin, azithromycin, or the new rifaximin are the main drugs of choice to treat *Campylobacter* infections. [B-1905 P.4 L.8-11; B-1909 P.14 L.1-16; G-1457 P.6 L.44-45; G-1477 P.2 ¶ 4; G-1469 P.5 L.3-5; G-557 P.3; B-816 P.2] Fluoroquinolones are being re-evaluated for treatment of diarrhea of unknown etiology because of concerns with *Salmonella* [B-1909 P.5 L.18-20, P.8 L.17-18] and life-threatening complications of hemorragic *E. coli* [B-1905 P.3 L.19-21, P.4 L.1-2; B-1909 P.5 L.8-17, P.8 L.18-21; B-1559 P.1, 3, 4, 6] As stated in a recent FoodNet population study, "Antibiotics are not essential in the treatment of most acute diarrhoeas. Treatment with antibiotics does not reduce the duration or severity of the illness when it is viral in origin, and antibiotic treatment may even prolong asymptomatic carriage of *Salmonella*. In addition, antimicrobial therapy might make persons more susceptible to infection with antimicrobial-resistant pathogens, and unnecessary antibiotic usage can select for antibiotic resistance." G-1790 P.8. Similarly, the recent IDSA guidelines state, "Because of increasing threats from antimicrobial-resistant infections, side effects of treatment with antimicrobial agents, suprainfections when normal flora are eradicated by antimicrobial agents, and the possibility of induction of disease-producing phage by antibiotics (such as Shiga toxin phage induced by quinolone antibiotics), any consideration of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences." G-261 P.11.

706. From 1982-1992, no fluoroquinolone-resistant *Campylobacter jejuni* were detected at the University of Pennsylvania Medical Center. Nachamkin WDT: p. 6, lines 33-34; G-440

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because it is misleading, ambiguous and unsupported. "Not detecting" something can mean that no one looked, or that detection methods used were poor, or that the thing not detected was not there. The intended interpretation is not specified. The reader must assume that the PFOF refers to isolates from human beings, and cannot determine the accuracy or relevancy of the statement. The PFOF provides no details, such as the number of isolates tested between 1982 and 1992, and the sampling, analytical, and reporting procedures employed. Certainly, fluoroquinolone-resistant *Campylobacter jejuni* was detected elsewhere in the US and abroad in those years, so the significance of the non-detection at the University of Pennsylvania Medical Center is unclear.

707. From 1982-1992, erythromycin resistance in *Campylobacter* was 2% overall. Nachamkin WDT: p. 6, line 36; G-440

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because it is ambiguous, vague and unsupported. The reader must assume that the PFOF refers to isolates from human beings, and cannot determine the accuracy or relevancy of the statement because the PFOF provides no relevant details, such as the number of isolates tested between 1982 and 1992, and the sampling, analytical, and reporting procedures employed.

708. At the University of Pennsylvania Medical Center fluoroquinolone resistance rates ranged from a low of 8.3% in 1996 to a high of 40.5% in 2001. Nachamkin WDT: p. 6, lines 42-43;G-1517

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being unsupported and misleading. The reader cannot determine the relevancy or accuracy of the PFOF because details such as the number of isolates tested and the sampling, analytical and reporting procedures have not been provided. The PFOF is also misleading because ciprofloxacin resistance in 1995, the year before Baytril was approved for use in poultry, as reported in the same study by Nachamkin, was 21%. A-200 P.58 L.12-13. Nachamkin also acknowledges that the risk factors for resistant *Campylobacter* identified in his study "were unknown". G-1470 P.7 L.5-6.

We also disagree with this PFOF as being inaccurate, ambiguous, and as failing to distinguish between reported and true values. The true fluoroquinolone resistance rates at the University of Pennsylvania Medical Center between 1996 and 2001 are unknown, as most cases presumably were not reported. Moreover, the reported rates "at the University of Pennsylvania Medical Center" presumably include contributions from a highly transient student population in which an increasing proportion of foreign students with recent foreign travel are expected (based on local demographics) to have been represented over those years. Since changes in the composition of the population being observed have not been specified (i.e., how many cases occurred among students with recent foreign travel vs. among others), claiming that the "fluoroquinolone resistance rates ranged from a low of 8.3% in 1996 to a high of 40.5% in 2001" is ambiguous. It could simply mean that the rate in each group (domestic vs. foreign) stayed constant (or even

went down), but that the composition of the total population changed (higher proportion of foreign students). (Thus, the unconditional rate would go up while the conditional rates would not.) Since the composition of the denominator of the rate is not specified, the PFOF is ambiguous, i.e., the reported rates conflate demographic factors and groups-specific ("conditional") resistance rates in unspecified ways. Thus, the numbers presented in the PFOF are uninterpretable without further information, and the meaning of the PFOF is ambiguous.

709. All but one of the fluoroquinolone-resistant isolates studies at the University of Pennsylvania Medical Center between 1996 – 2001 had a ciprofloxacin MIC $\geq$ 32 μ/mL. Nachamkin WDT: p. 6, lines 43-45;G-1517

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as using the term "fluoroquinolone-resistant isolates", which has no officially agreed-to definition. The PFOF is potentially misleading because ciprofloxacin MICs for *Campylobacter* have not been validated to affirm that clinical resistance correlates with these levels. B-1900 P.4 L.22-24. Having a MIC $\geq$32 ug/ml is usually not relevant to the clinical management of *Campylobacter* enteritis and does not define "fluoroquinolone-resistant isolates" in any generally agreed-to or clinically relevant sense B-1909 P.17 L.4-6.

710. There is a temporal relationship between the approval of fluoroquinolones for use in poultry in the U.S. and the rise in the level of fluoroquinolone-resistant *Campylobacter* in humans in the United States. Nachamkin WDT: p. 7, lines 12-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and unsubstantiated. It is specifically refuted by [Cox, B-1901 P.29], which shows that no such "temporal relationship" has been demonstrated in available data; moreover, there are not sufficient data representing the general US population to support such a general claim about trends or to justify the claim for a "rise in the level of fluoroquinolone-resistant *Campylobacter* in humans in the United States" [Bayer/AHI response to CVM's PFOF #78]. This statement is also taken out of context, is misleading, inaccurate and is presented as an unsubstantiated opinion. The full context is a statement by Nachamkin that it his belief that his study also supports the conclusion originally drawn by Smith. The term "temporal relationship" is not defined, but is usually used by CVM and its witnesses to mean "follows", rather than indicating a causal relationship [Cox, B-1901 P.26]. Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source

infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

711. Fluoroquinolone resistance has not been appreciably observed in New South Wales, Australia, where fluoroquinolones are not permitted for veterinary use. Nachamkin WDT: p. 7, lines 16-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement in taken out of context, is misleading, and inaccurate. The term "appreciably" has not been defined, therefore Bayer cannot accept this statement as fact. Moreover, a contradictory phenomenon has been reported in a number of other countries, where fluoroquinolone resistance is elevated despite the fact that fluoroquinolones are not permitted for veterinary use. Australia also has very low use of fluoroquinolones in humans.

712. In genetic fingerprinting to determine bacterial strain similarity, it is impractical to determine the DNA sequence of the enteric bacterial chromosome of each strain for comparison. Nachamkin WDT: p. 7, lines 28-32

Bayer/AHI Response: Bayer/AHI do not dispute the general intent of this PFOF, but object to the use of the term "genetic fingerprinting" in this context, as it suggests an unrealistic degree of precision in a very ambiguous process.

713. Methods successfully used for fingerprinting *Campylobacter* include pulsed-field gel electrophoresis (PFGE), restriction-fragment length polymorphism (RFLP), ribotyping, multilocus sequence typing (MLST), and restriction endonuclease digestion analysis (REA). Nachamkin WDT: p. 7, lines 34-38

Bayer/AHI Response: Bayer/AHI do not dispute the general intent of this PFOF, but object to the use of the term "genetic fingerprinting" in this context, as it suggests an unrealistic degree of precision in a very ambiguous process. Bayer also objects to the term "successfully". See reply to CVM PFOFs 714-717.

714. PFGE and RFLP have been used to show a link between *Campylobacter jejuni* strains found in turkeys and in humans. Nachamkin WDT: p. 8, lines 1-4

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as vague and potentially misleading. What kind of link, specifically, is being referred to? (Obviously, all *Campylobacter* strains are "linked" to the extent that they are all strains of *Campylobacter*, but presumably something more is meant here. What more is meant has not been specified.) If the statement means that PFGE and RFLP have been used to show that *Campylobacter jejuni* strains found in turkeys originate in humans, or vice versa, it is inaccurate. In general, the subtypes found in humans and poultry do *not* have "identical DNA fingerprints"; they simply have the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line

of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444).

715. RFLP-fla typing is accurate in identifying *Campylobacter* strains. Nachamkin WDT: p. 6, lines 6-8

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. There is a very large difference between (fully and uniquely) identifying *Campylobacter* strains and identifying fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a unique "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444).

716. In *Campylobacter*, the fla gene is highly variable and can be used to discriminate between strains. Nachamkin WDT: p. 8, line 14

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. There is a very large difference between (fully and uniquely) identifying *Campylobacter* strains and identifying fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a unique "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444).

717. Studies have shown that human and poultry *Campylobacter* isolates share similar biochemical and genetic characteristics. Nachamkin WDT: p. 8, line 36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being so vague that it is meaningless, as well as being potentially misleading. If human and poultry *Campylobacter* isolates did not "share similar biochemical and genetic characteristics", they would not both be *Campylobacter* isolates. If the intent is to suggest that PFGE and RFLP have been used to show that *Campylobacter jejuni* strains found in poultry originate in humans, or vice versa, it is inaccurate. In general, the subtypes found in humans and poultry do *not* have "identical DNA fingerprints"; they simply have the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444).

718. Piffaretti showed human and poultry isolates were similar. Nachamkin WD: p. 8, lines 38-39

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being so vague as to be meaningless, as well as being potentially misleading. If human and poultry *Campylobacter* isolates were not somewhat "similar", they would not both be *Campylobacter* isolates. If the intent is to suggest that Piffaretti showed that *Campylobacter jejuni* strains found in poultry originate in humans, or vice versa, it is inaccurate. In general, the subtypes found in humans and poultry do *not* have "identical DNA fingerprints"; they simply have the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444).

719. Nachamkin found poultry isolates showed strong similarity to strains from humans. Nachamkin WDT: p. 8, lines 42-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague, misleading, and inaccurate. It is vague because "strong similarity" is not defined. This statement is misleading given that the cited article G-1768 and testimony relate to chickens strains found in Denmark and two different patients one from Canada the other from China. Moreover, Bayer/AHI dispute the significance of this PFOF because genetic typing analysis showing "similar" *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

720. K. Smith found retail poultry isolates that exhibited fluoroquinolone resistance were also of the same type as from humans. Nachamkin WDT: p. 9, lines 4-7; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and misleading. "Of the same type" is a vague phrase. They are of the same general type (e.g., both are *C. jejuni*, and they share some more specific similarities with each other and with isolates from lamb and other sources.) They are *not* of fully identical ("the same") type, as claimed. It is more accurate to say that Smith found retail poultry isolates that exhibited fluoroquinolone resistance were also of the same fla-A PCR/RFLP subtype as from humans. Bayer/AHI dispute the significance of this

PFOF because genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

721. Fitzgerald found turkeys are a reservoir for similar *Campylobacter* strains found among human clinical *Campylobacter* isolates. Nachamkin WDT: p. 9, lines 8-11; G-218

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is vague in that. "similar" is undefined. It is misleading in suggesting that turkeys may serve as a reservoir source of *Campylobacter* infection for humans. The turkey *Campylobacters* referred to in this study were isolated from the environment of growing turkeys and not from turkey products. Certainly the turkey's growing environment is significantly removed from providing sources of human infections. Additionally, turkeys are not a source of human campylobacteriosis. Moreover, Bayer/AHI dispute the significance of this PFOF because genetic typing analysis showing "similar" *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

722. Stern found some *Campylobacter* isolates from poultry in the production houses had the same fla types as commonly identified in human strains. Nachamkin WDT: p. 9, lines 12-15; B-715

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but Bayer/AHI dispute the significance of this PFOF. Genetic typing analysis showing overlapping *Campylobacter* fla types between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

723. Poultry is a major source of human campylobacteriosis. Nachamkin WDT: p. 9, line 18

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. It is an incorrect and unsubstantiated claim. Evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis in humans B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or suggest that poultry is a principle source of campylobacteriosis, but refutes this supposition.

724. *Campylobacter* strains isolated from humans are similar to those isolated from contaminated poultry. Nachamkin WDT: p. 9, line 24-25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being so vague that it is meaningless, as well as being potentially misleading. Of course human and poultry *Campylobacter* isolates "are similar" in some respects (e.g., they are both *Campylobacter* isolates and both of fairly common types.) If the intent is to suggest that the similarities are such that they prove or make it likely that *Campylobacter jejuni* strains found in poultry originate in

humans, or vice versa, it is inaccurate. In general, the subtypes found in humans and contaminated poultry do *not* have "identical DNA fingerprints"; they simply have the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Moreover, both lamb and chicken share a significant proportion of *Campylobacter jejuni* subtypes with humans (presumably meeting the unspecified criteria for "similar" in the PFOF), suggesting the possibility of a common environmental source and indicating that shared subtypes need not arise from consumption of one species by another. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

725. Fluoroquinolone-resistant *Campylobacter jejuni* causing human infections has increased dramatically in the United States and is temporally associated with the introduction of fluoroquinolones for use in poultry in the United States. Nachamkin WDT: p. 9, lines 25-28

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. The statement that the introduction of fluoroquinolones for use in poultry is temporally associated with human resistance is refuted by B-1901 P.26, P.27, P.41, P.44, P.45, P.52, P.53. The assertion that "fluoroquinolone-resistant *Campylobacter jejuni* causing human infections has increased dramatically" is mistaken. In truth, the incidence of fluoroquinolone-resistant campylobacteriosis incidence has *decreased* dramatically in the United States since 1996, though less dramatically than the decrease in fluoroquinolone-susceptible (e.g., chicken-associated) campylobacteriosis incidence [CVM proposed finding of fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10. B-1901, P.85].

Geraldine Ransom (G-1472)

726. Ms. Ransom is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

727. USDA Food Safety and Inspection Service conducted two one-year baseline studies on poultry carcass rinsates to determine the prevalence and levels of *Campylobacter*

jejuni/coli on young chicken carcasses sampled in USDA-inspected poultry establishments. Ransom WDT: p. 2, line 8-11.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

728. In the 1994-1995 FSIS baseline study in chickens, the in-plant FSIS inspector randomly selected post-chiller young chicken carcasses for submission to one of three pre-assigned FSIS field laboratories (Athens, GA, St. Louis, MO and Alameda, CA); the entire carcass was shipped via FedEx and analysis was initiated the next day; and the laboratory aseptically rinsed the carcass in 400 ml of Buffered Peptone Water and analyzed the rinsate sample. Ransom WDT: p. 2, line 17-22.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

729. In the 1999-2000 FSIS baseline study in chickens, the in-plant FSIS inspector rinsed the carcass; a portion of the rinsate was submitted via FedEx to assigned laboratories (i.e., the same laboratories used in the 1994-1995 FSIS baseline study) for testing. Ransom WDT: p. 2, line 22-24.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

730. In the 1994-1995 and 1999-2000 FSIS baseline studies in chickens, the rinsate samples were tested using a Most Probable Number format of the FSIS *Campylobacter* method. Ransom WDT: p. 2, line 26-28; G-1472, Attachments 1, 2, 6.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

731. In the 1994-1995 and 1999-2000 FSIS baseline studies in chickens, the FSIS *Campylobacter* method consists of two-stage enrichment in Hunt Broth followed by plating onto Modified *Campylobacter* Charcoal Differential Agar where suspect *Campylobacter* colonies were then confirmed based on the following criteria: typical morphology and motility by microscopic examination, oxidase positive, catalase positive, glucose non-fermentative, resistance to cephalothin, and susceptible to nalidixic acid. Ransom WDT: p. 2, line 31-36.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

732. Suspect *Campylobacter* colonies that were resistant to nalidixic acid were not identified as C. *jejuni/coli* in the 1994-1995 or 1999-2000 FSIS baseline studies in chickens. Ransom WDT: p. 2, line 36-38.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

733. In the 1999-2000 FSIS baseline study in chickens, laboratories were asked to submit suspect nalidixic acid resistant colonies that were encountered to the FSIS Special Projects and Outbreak Support Laboratory in Athens, GA, where they were passed to Dr. Paula Cray

(USDA/Agricultural Research Service, Athens, GA) for speciation and antibiotic resistance profiling. Ransom WDT: p. 2, line 38-43; G-1472, Attachments 3, 4, 5.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

734. As part of the 1999-2000 FSIS baseline study in chickens, all samples were also analyzed using a method developed by Dr. Eric Line (USDA/Agricultural Research Service, Athens, GA), i.e., the modified ARS method; this part of the study was called "The *Campylobacter* Methods Comparative Study." Ransom WDT: p. 3, line 1-4.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

735. The *Campylobacter* Methods Comparative Study consisted of direct plating onto Campy-Line Agar for enumeration of C. *jejuni/coli*, with backup qualitative test (i.e., enrichment in Bolton Broth followed by plating onto Campy-Line Agar) and colonies were identified as C. *jejuni/coli* using the FSIS confirmation protocol where suspect *Campylobacter* colonies were then confirmed based on the following criteria: typical morphology and motility by microscopic examination, oxidase positive, catalase positive, glucose non-fermentative, resistance to cephalothin, and susceptible to nalidixic acid. Ransom WDT: p. 2 line 33-36; p. 3, line 4-8; G-1472, Attachments 3, 4, 5.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

736. Laboratories were instructed to submit suspect nalidixic acid resistant *Campylobacter* colonies from Campy-Line Agar to the FSIS Special Projects and Outbreak Support Laboratory in Athens, GA, where they were passed to Dr. Paula Cray (USDA/Agricultural Research Service, Athens, GA) for speciation and antibiotic resistance profiling. Ransom WDT: p. 3, line 8-11.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

737. From August 1996 through July 1997, FSIS conducted a baseline study on young turkey carcasses. Ransom WDT: p. 3, line 15-16.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

738. In the August 1996 – July 1997 FSIS baseline study in turkeys, whole carcasses were shipped to FSIS laboratories where rinsate samples were prepared using 600 ml of Butterfields Phosphate Diluent and quantitative C. *jejuni/coli* analyses were conducted. Ransom WDT: p. 3, line 16-19; G-651.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Kirk Smith (G-1473)

739. Dr. Smith is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, except where Dr. Smith testifies on matters related to causality, causal interpretations of data, or statistical analysis of data.

740. K. Smith's study evaluated 91 percent of all *Campylobacter* isolates from cases of clinical illness in humans from Minnesota in 1996 through 1998. K. Smith WDT: p. 3, lines 3-5; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being incomplete and inaccurate. The 91% number is an estimate based on assumptions not stated in this PFOF about the accuracy of reporting. The true percent of all *Campylobacter* isolates from cases of clinical illness in humans from Minnesota in 1996 through 1998 evaluated in the Smith may be lower due to possible under-reporting.

741. The 1996-1998 sample in K. Smith's study was population-based. K. Smith WDT: p. 3, line 6; G-589

Bayer/AHI Response: The term "population-based" is vague and is not defined in this PFOF. Bayer/AHI do not agree and there is no evidence in the record that the sample in K. Smith's study represents a random sample of the general US population or of the general Minnesota population.

742. In the K. Smith case-comparison study, the comparison group was selected from Minnesota residents infected with *C. jejuni* isolates that were sensitive to quinolones. To be eligible to be chosen as one of the two persons with sensitive *C. jejuni* to be matched to a person with resistant *C. jejuni,* the person with sensitive *C. jejuni* had to meet three criteria: (a) be within ten years of age of the person with resistant *C. jejuni*; (b) live in the same region of Minnesota as the person with resistant *C. jejuni* (either in the seven county Minneapolis St. Paul metropolitan area or elsewhere in Minnesota); and (c) have a date of stool collection that yielded their *C. jejuni* isolate that was as close as possible to the date of stool collection to the person with resistant *C. jejuni.* K. Smith WDT: p. 5, lines 5-17.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

743. Nalidixic acid is an antibiotic which belongs to the quinolone family. K. Smith WDT: p. 3, line 20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

744. Nalidixic acid is not a fluoroquinolone like ciprofloxacin, but rather is the building block upon which fluoroquinolones are built, i.e., all of the fluoroquinolones are also quinolones. K. Smith WDT: p. 3, lines 20-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

745. If bacteria develop resistance to a fluoroquinolone they are exposed to, they will usually also be resistant to nalidixic acid, the building block base component of all fluoroquinolones. K. Smith WDT: p. 3, lines 23-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

746. Resistance to nalidixic acid was a reliable marker for resistance to fluoroquinolones in the K. Smith study. K. Smith WDT: p. 3, lines 32-33; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being overly broad, vague, and misleading. "Reliable" is a vague and undefined term (just how reliable was it?) and the specific fluoroquinolones for which resistance to nalidixic acid is considered reliable, along with the degree of reliability for specific fluoroquinolones (especially ciprofloxacin) have not been specified in this PFOF. There are no official interpretive criteria for what constitutes clinical or in vitro "resistance to fluoroquinolones" for *Campylobacter* (CVM PFOF #747, citing K. Smith WDT: p. 4, lines 4-5). Thus, the claim that "Resistance to nalidixic acid was a reliable marker for resistance to fluoroquinolones" asserts that a reliable marker has been found for a condition that has no generally or officially accepted definition. This is misleading by conveying the impression that Smith was able to make a reliable determination of "fluoroquinolone resistance" (presumably including ciprofloxacin resistance) from resistance to nalidixic acid, when in reality, no such reliable determination can be made before "fluoroquinolone resistance" is defined.

747. There are no official interpretive criteria for what constitutes resistance to fluoroquinolones for *Campylobacter*. K. Smith WDT: p. 4, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

748. K. Smith used an MIC of 4 μg/ml to define resistance to ciprofloxacin, enrofloxacin and sarafloxacin in *Campylobacter*. K. Smith WDT: p. 4, lines 10-12; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Smith used an MIC of ≥4 μg/ml to define resistance. G-589.

Bayer/AHI agree to this PFOF, provided that "define" means only "define for purposes of his analysis" (rather than referring to any legal or scientific or clinically relevant definition) and provided that "resistance" means only "resistance in vitro." The in vitro resistant definitions have not been validated to affirm that clinical resistance correlates with these levels [Burkhart (B-1900) P. 4 L. 22-24]. No data link in vitro MICs conducted on *Campylobacter* spp. to clinical resistance in humans. [Burkhart (B-1900) p. 10 L. 1-2]. 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]

749. In the K. Smith study, the vast majority (96%) of isolates that were resistant to fluoroquinolones (MIC of ≥4 μg per milliliter) actually had MICs of ≥32 μg per milliliter. K. Smith WDT: p. 4, lines 19-21; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as misrepresenting what was learned and known based on the tests performed in the Smith study. The E-test, used in this study (G-589) is not a NCCLS approved method for determination of MIC's *in vitro* for *Campylobacter*. It is not necessarily valid or appropriate for this purpose. Moreover, the assertion that isolates "actually had MICs of ≥32 μg per milliliter" ignores well-known variability in the distribution of MICs estimated via the E-test. G-1481 P.5 ¶ 10; B-1913 P.19 L.15-19.

750. An MIC of 32 μg/ml represents a stronger resistance than 4 μg/ml. K. Smith WDT: p. 4, lines 23-25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being meaningless and misleading. The crucial term "a stronger resistance" is not defined and has no generally understood meaning in this context. The statement does not clarify whether resistance refers to *in vivo* or *in vitro* resistance. Relative "strength" of resistance is undefined and/or meaningless from a human health perspective since no clinical significance has been demonstrated for *Campylobacter* isolates defined by Smith or others as "fluoroquinolone resistant" *in vitro*. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation #14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). For bacteria that are either resistant or not to clinical treatment, the claim that some resistance is "stronger than" other resistance is inaccurate.

751. *C. jejuni* is by far the most common species causing human illness. K. Smith WDT: p. 4, lines 32-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF, assuming species modifies "*Campylobacter*".

752. In Minnesota, *Campylobacter jejuni* accounts for 95% of human *Campylobacter* infections. K. Smith WDT: p. 4, lines 33-34

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

753. K. Smith's case-comparison study enrolled 96% of Minnesota residents with a quinolone-resistant *Campylobacter jejuni* during 1996-1997. K. Smith WDT: p. 4, line 36-40; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. The true percentage of Minnesota residents with a quinolone-resistant *Campylobacter jejuni* during 1996-1997 enrolled in K. Smith's case-comparison study is much smaller than 96%, as most such cases are probably not detected or enrolled (see e.g., Bartholomew (G-1454) P.10 L.13-16).

754. Poultry is a major food reservoir of *Campylobacter* for humans. K. Smith WDT: p. 5, lines 26-27

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being vague and inaccurate. What is meant by "major food reservoir of *Campylobacter* for humans" is not specified. If it means that a major fraction (e.g., more than 10%) of human campylobacteriosis cases are caused by *Campylobacter* from chicken, then the statement is inaccurate. Poultry is only one of many sources of *Campylobacter* for humans, and based on the most recent and relevant data appears to be at most a very small contributor. Bayer/AHI also dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record shows that contact with and consumption of chicken and turkey is not a major source of *Campylobacter* infection in humans. So, we disagree that "Poultry is a major food reservoir of *Campylobacter* for humans."

755. K. Smith's retail chicken study tested 91 domestic chicken products purchased in Minnesota between September 8, 1997 to November 3, 1997 from 16 retail markets representing 11 franchises. The chicken products came from 15 poultry processing plants in nine states. K. Smith WDT: p. 5, lines 39-42; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

756. K. Smith performed molecular subtyping on 91 *C. jejuni* isolates from retail chicken products to compare them with molecular subtyping on human *C. jejuni* isolates to see if chicken was a source of quinolone-resistant *Campylobacter jejuni* infections in humans. K. Smith WDT: p. 6, lines 16-19; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as embodying a false assumption that molecular subtyping can enable one "to see if chicken was a source of quinolone-resistant *Campylobacter jejuni* infections in humans". In fact, the comparison of molecular subtypes in chicken products and human isolates does not identify whether one was the source of the other, or where both have a common (e.g., environmental, such as ciprofloxacin-contaminated water) source (Cox, WDT: B-1901, pp 20-21, citing G-1670). There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out by molecular subtyping. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

757. The DNA fingerprinting method used to evaluate *C. jejuni* from retail chicken in the K. Smith study is called restriction-fragment-length polymorphism of the flagellin gene amplified by polymerase chain reaction (PCR-RFLP). K. Smith WDT: p. 6, lines 19-21; G-589

Bayer/AHI Response: Bayer/AHI disagrees that the term "PCR-RFLP" applies specifically or only to the flagellin gene. We disagree that "PCR-RFLP" stands for "restriction-fragment-length polymorphism of the flagellin gene amplified by polymerase chain reaction". Instead, it stands for "Polymerase chain reaction-restriction fragment length polymorphism".

758. PCR-RFLP involves a single gene from the bacteria, the flagellin gene, which is amplified and then cut up with an enzyme; the resultant pieces of the gene are spread out using a process known as gel electrophoresis, creating a pattern of bands that represents a DNA fingerprint. K. Smith WDT: p. 6, lines 21-25

Bayer/AHI Response: Bayer/AHI disagrees that PCR-RFLP necessarily involves the flagellin gene.

759. In 1997, the PCR-RFLP method was the most widely accepted method of molecular subtyping of *Campylobacter*. K. Smith WDT: p. 6, lines 25-26

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being vague, inaccurate and misleading. The specific PCR-RFLP method referred to by Smith was applied to *Campylobacter* isolates that were exposed to several antimicrobials prior to susceptibility testing. [White (G-1484); G-589]. Bayer/AHI disagrees that application of PCR-RFLP specifically as practiced by Smith "was the most widely accepted method of molecular subtyping of *Campylobacter.*"

760. K. Smith's study found that the percentage of *C. jejuni* isolates from Minnesota residents that were resistant to nalidixic acid increased from a low of 1.3% in 1992 to 10.2% in 1998; this increase was statistically significant using a chi-square test for linear trend. K. Smith WDT: p. 7, lines 9-12; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate, incomplete, and misleading. It is incomplete because it does not describe or adjust for the effects of changes in isolation procedures, in exposures of *Campylobacter* isolates to various antimicrobials prior to susceptibility testing [White (G-1484); G-589], or in the criteria used to submit and select isolates for testing, between 1992 and 1998 [B-1901, p. 80]. It is inaccurate and misleading because it attributes the combined effect of all these changes solely to an increase in "the

percentage of *C. jejuni* isolates from Minnesota residents that were resistant to nalidixic acid". In reality, Smith has not shown that an increase in *reported* resistance to nalidixic acid from "from a low of 1.3% in 1992 to 10.2% in 1998" corresponds to a change in the *actual* levels of resistance. Moreover, this PFOF is inaccurate in referring to "the percentage of *C. jejuni* isolates from Minnesota residents" rather than to "the percentage of *C. jejuni* isolates from sampled Minnesota residents".

761. K. Smith found that if an isolate was resistant to nalidixic acid, it is almost always was resistant to ciprofloxacin as well, and vice versa. K. Smith WDT: p. 8, lines 7-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

762. In the K. Smith study, 285 nalidixic acid resistant isolates were confirmed to be resistant to ciprofloxacin: 1 in 1993, 16 in 1994, 41 in 1995, 44 in 1996, 98 in 1997, and 85 in 1998. K. Smith WDT: p. 8, lines 13-15; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

763. In the K. Smith study, 20 randomly selected ciprofloxacin-resistant isolates from humans were tested for resistance to a variety of fluoroquinolones, including enrofloxacin and sarafloxacin (the two veterinary fluoroquinolones in use in the United States at that time); of the 20 isolates, all were also resistant to enrofloxacin, sarafloxacin, grepafloxacin, and trovafloxacin. K. Smith WDT: p. 8, line 33 – p. 9, line 1; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

764. During K. Smith's study period in Minnesota, fluoroquinolones are the most popular choice of antibiotics for treating patients with *Campylobacter* infections. K. Smith WDT: p. 10, lines 21-22; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This proposed finding of fact is taken out of context and is misleading. It implies that the "most popular choice" applies beyond Minnesota. This statement is not supported by the citation.

765. Over 80% of people with *Campylobacter jejuni* infections (both fluoroquinolone-resistant and fluoroquinolone sensitive) were treated with an antibiotic in the K. Smith case-comparison study. K. Smith WDT: p. 10, lines 23-25; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

766. Over 60% of people in Minnesota with *Campylobacter jejuni* infections (either fluoroquinolone-resistant or fluoroquinolone sensitive) who received an antibiotic received a fluoroquinolone in the K. Smith case-comparison study. K. Smith WDT: p. 10, lines 25-28; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The people referred to in this statement not only received an antibiotic, but the antibiotic received could be identified. As stated, the denominator would be higher which would give a different percentage and lower than presented. The statement as presented is inaccurate. G-589 P.5.

767. Travel to Mexico, Spain, and Asia were risk factors for acquiring fluoroquinolone-resistant *Campylobacter* infections in K. Smith's study. K. Smith WDT: p. 9, lines 23-42; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

768. Among the patients from 1997 in the K. Smith case-comparison study who were treated with a fluoroquinolone after the collection of stool specimens, the duration of diarrhea was statistically significantly longer for the patients with quinolone-resistant *C. jejuni* infections (median, 10 days) than for the patients with quinolone-sensitive *C. jejuni* infections (median, 7 days). K. Smith WDT: p. 10, lines 31-35; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is specifically refuted by [Cox, B-1901, pages 31-33]. The claimed statistically significant difference disappears when effects of confounding, especially by foreign travel, are removed [Cox, B-1901, P. 26, 30]. This PFOF is specifically refuted for data from Smith et al. (as well as of data from the CDC 1998-1999 *Campylobacter* case-control study) showing that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

769. K. Smith found that fluoroquinolones were not as effective in treating patients with quinolone-resistant infections as they are in treating patients with quinolone-sensitive infections. K. Smith WDT: p. 10, lines 35-37

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is specifically refuted by [Cox, B-1901, pages 31-33]. The claimed difference in effectiveness disappears when the analysis removes the effects of confounding, especially by foreign travel [Cox, B-1901, P. 26, 30]. This PFOF is further refuted by analysis of United States data from Smith et al. (as well as of data from the CDC 1998-1999 *Campylobacter* case-control study) showing that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

770. In K. Smith's study, patients with quinolone-resistant infections suffered a significantly longer course of illness because the antibiotic provided to them (a fluoroquinolone) did not work against the resistant *C. jejuni*. K. Smith WDT: p. 10, lines 38-40; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is specifically refuted by [Cox, B-1901, pages 31-33]. The claimed statistically significant difference disappears when the analysis is set up correctly to remove the effects of confounding, especially by foreign travel [Cox, B-1901, P. 26]. The PFOF is further refuted by analysis of United States data from Smith et al. (as well as of data from the CDC 1998-1999 *Campylobacter* case-control study) showing that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

771. In the Goodman randomized double-blinded study, treatment at the time of presentation with ciprofloxacin compared with placebo shortened the duration of diarrhea (2.4 vs. 3.4 days), and increased the percentage of patients cured or improved by treatment days 1, 3, 4, and 5. K. Smith WDT: p. 11, lines 8-11; G-250

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. The proposed finding of fact is misleading and not relevant to this proceeding. The Goodman study does not evaluate the impact of fluoroquinolone resistant infections nor does it adjust for the confounders such as foreign travel. The duration of diarrhea cannot be correctly evaluated without accounting for foreign travel. Cox (B-1901) P.39-40; Feldman (B-1902) P.8 L.25-29.

772. In the Wistrom randomized, double-blinded, multicenter clinical trial, a significant difference was noted between norfloxacin and placebo in median time to cure patients with campylobacteriosis (three days compared with five days, p=0.05). K. Smith WDT: p. 11, lines 30-34; G-705

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as misleading and not relevant to this proceeding. The Wistrom study does not evaluate the impact of fluoroquinolone resistant infections nor does it adjust for the confounders such as foreign travel. The duration of diarrhea cannot be correctly evaluated without accounting for foreign travel. Cox (B-1901) P.39-40; Feldman (B-1902) P.8 L.25-29.

773. The percentage of all laboratory-confirmed *C. jejuni* infections in Minnesota residents that were quinolone-resistant and domestically acquired increased from 0.8% in 1996 to 4.5% in 1999. K. Smith WDT: p. 12, lines 20-24; G-589

Bayer/AHI Response: Bayer/AHI Response: Bayer/AHI disagrees with this PFOF. The wording of this PFOF (a) uses an ambiguous and misleading term ("resistant") which is routinely interpreted by CVM and its witnesses, including Dr. Smith, to mean and/or imply "resistant to clinical doses" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). Given that CVM routinely uses this meaning, the term "quinolone-resistant" is inappropriate here, as no clinical relevance of such resistance has been established. See our response to PFOF #408. (b) The term "increased" implies or suggests a continuous, monotonic increase, which has not been shown. We believe that a more accurate wording would be "The percentage of all laboratory-confirmed *C. jejuni* infections in Minnesota residents with MICs of at least 4 and domestically acquired was 0.8% in 1996 and 4.5% in 1999."

774. The increase of domestically acquired fluoroquinolone-resistant *Campylobacter jejuni* in Minnesota from 1996-1998 was a statistically significant increase. K. Smith WDT: p. 12, lines 19-24; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate, overly broad, ambiguous, and misleading. First, "statistical significance" can be assessed only for specific hypotheses and for specified models or assumptions. No specific hypothesis has been stated here. The claimed increase may be statistically significant for the hypothesis "The rate in 1998 was greater than the rate in 1996" while being non-significant for the hypothesis "The rate increased steadily from 1996-1998" or for the hypothesis "The rate increased more quickly from 1996-1998 than from 1992-1994". If the intended meaning of this PFOF is that a statistically significant change in the long-term resistance trend occurred when enrofloxacin was introduced, then we disagree with this PFOF as being inaccurate [Cox, B-1901, P. 29] and unsubstantiated by any supporting facts or data. We also disagree with this PFOF because it draws a conclusion about true infections ("domestically acquired resistant infections increased") in an entire state ("in Minnesota") from a sample taken in a single area that did not represent the entire state and that did not represent a random sample of all cases (non-reported and untreated as well as treated) even in the Minneapolis-St. Paul area. Thus, the conclusion is far more general than the data on which it is based permit. Thus, the PFOF constitutes an invalid extrapolation from a sharply limited, non-representative sample, and in this sense must be regarded as speculation. rather than as a fact.

775. In K. Smith's study, 85% of patients with fluoroquinolone-resistant *Campylobacter jejuni* infections between 1996-1998 did not use a quinolone before culture. K. Smith WDT: p. 13, lines 4-7; G-589

Bayer/AHI Response: Bayer/AHI disputes this PFOF, to the extent the use of the term "resistant" means "clinical" resistance. There are no official interpretive criteria for what constitutes "fluoroquinolone-resistant *Campylobacter jejuni* infections" (CVM PFOF #347 and #747, citing K. Smith WDT: P.4 L.4-5). CVM and its witnesses, including Dr. Smith, routinely use the term to mean "resistant to fluoroquinolone therapy with in vivo", which makes its usage in this PFOF inappropriate. See our response to CVM's PFOF #85 on this point. We also note that "did not use a quinolone before culture" does not mean or imply "did not ingest a quinolone before culture" (e.g., in drinking water, unbeknownst to the patient). See our response to CVM's PFOF #367 on this point.

776. In K. Smith's retail chicken study *Campylobacter* was obtained from 80 (88%), including *C. jejuni* from 67 (74%) and *C. coli* from 19 (21%) of the 91 retail chicken products tested. K. Smith WDT: p. 13, lines 13-15; G-589

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

777. In K. Smith's retail chicken study, ciprofloxacin-resistant *Campylobacter* was isolated from 18 products (20%), including resistant *C. jejuni* from 13 (14%) and resistant *C. coli* from five (5%). K. Smith WDT: p. 13, lines 16-18; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and potentially misleading. There are no official interpretive criteria for what constitutes "ciprofloxacin-resistant *Campylobacter*" (CVM PFOF #347 and #747, citing K. Smith WDT: p. 4, lines 4-5). Thus, asserting that "ciprofloxacin-resistant *Campylobacter* was isolated from 18 products (20%)" uses a term that lacks any accepted definition (i.e., "ciprofloxacin-resistant *Campylobacter*") to suggest a condition ("resistance") which has not been demonstrated and is untrue: e.g., that the CFUs in question were resistant to clinically relevant doses of fluoroquinolones. Indeed, other CVM witnesses put exactly this mistaken interpretation on the term "resistant" (e.g., Tollefson WDT: page 2, lines 40-43; Levy, PFOF #408, Smith, G-1473, p. 10, paragraph 22). For example, Levy testifies that "The emergence of increasing resistance to the fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." [Levy WDT: p. 10, lines 1-4] Given that CVM and its witnesses repeatedly use "fluoroquinolone-resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "ciprofloxacin-resistant *Campylobacter* was isolated" is vague and misleading.

778. *Campylobacter* from retail chicken products in K. Smith's retail chicken study had a MIC for ciprofloxacin of $\geq$32 μg per milliliter for all resistant isolates, indicating very strong resistance. K. Smith WDT: p. 13, lines 21-23; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as subjective and unsubstantiated. The statement does not clarify whether resistance refers to *in vivo* or *in vitro* resistance. "Very strong" is not defined. Relative "strength" of resistance is meaningless from a human health perspective because the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation #14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). The proposed finding of fact is also meaningless in that a bacterium is either "resistant" (not inhibited by therapeutic concentrations of the drug) or it is not.

779. Of eight *Campylobacter* isolates from retail chicken that were tested by K. Smith for resistance to other fluoroquinolones, all eight were resistant to enrofloxacin, sarafloxacin, grepafloxacin, and trovafloxacin; six of the eight were resistant to levofloxacin, and the other two had intermediate resistance to levofloxacin. K. Smith WDT: p. 13, lines 23-26; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and potentially misleading. There are no official interpretive criteria for what constitutes "resistant to enrofloxacin" (CVM PFOF #347 and #747, citing K. Smith WDT: p. 4, lines 4-5). Thus, asserting that "all eight were resistant to enrofloxacin" uses a term that lacks any accepted definition. Indeed, other CVM witnesses use the term "resistant" to mean "resistant to fluoroquinolones administered *in vivo*" (e.g., Tollefson WDT: page 2, lines 40-43; Levy, PFOF #408, Smith, G-1473, p. 10, paragraph 22). For example, Levy testifies that "The emergence of increasing resistance to the

fluoroquinolones among *Campylobacter* and other bacterial pathogens seriously compromises human chemotherapy and can lead to increased morbidity and mortality associated with *Campylobacter* infections." [Levy WDT: p. 10, lines 1-4] Given that CVM and its witnesses repeatedly use "resistant" to mean and/or imply "resistant to clinical doses of ciprofloxacin", the statement in this PFOF that "all eight were resistant to enrofloxacin" is vague and potentially misleading.

780. Six of the seven subtypes of quinolone-resistant *C. jejuni* recovered from retail chicken products by K. Smith were also identified among quinolone-resistant *C. jejuni* isolates from humans; 6 of 7 had an identical DNA fingerprint as strains found in humans. K. Smith WDT: p. 13, lines 38-41; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. The subtypes found in humans and poultry did *not* have "identical DNA fingerprints"; they simply had the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, four of the seven subtypes also occurred in quinolone sensitive *C. jejuni*. G-589.

781. K. Smith found that, in human isolates from 1997 in Minnesota (the same year the poultry products were collected in Minnesota), excluding patients who had taken a quinolone prior to culture, 12 of 13 human *Campylobacter jejuni* isolates were of the same subtype found among *Campylobacter jejuni* from the chickens. K. Smith WDT: p. 13, lines 41-45; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. In emphasizing that the poultry product isolates and human case isolates were from the same year, the statement seems to suggest a temporal overlap between the two samples. This is established to be untrue from the facts stated in G-589. Poultry samples were collected during only a brief period in 1997 (between September 8th & November 3, 1997). It is clear that human cases for roughly three quarters of the year in 1997 could not possibly share any overall temporally with the chicken products sampled only in the Minneapolis/ St. Paul (MSP) area since the poultry samples were collected after the human samples. It is also likely that many of the human cases were from occurrences outside the MSP area and therefore also could not have shared any geographical relationship with the chicken sample isolates. The phrase "of the same subtype" is also vague and misleading; see our response to CVM PFOF #780.

782. Identical subtypes/DNA fingerprints of quinolone-resistant *C. jejuni* were found by K. Smith in domestically acquired human campylobacteriosis cases and domestic retail chicken products in Minnesota. K. Smith WDT: p. 13, line 46 – p. 14, line 1; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. The subtypes found in humans and poultry did *not* have "identical subtypes/DNA fingerprints"; they

simply had the same fla-A PCR/RFLP band patterns. There is a very large difference between "identical DNA fingerprint" and the same fla-A subtypes. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, four of the seven subtypes also occurred in quinolone sensitive C. jejuni. G-589.

783. Chicken is a source of quinolone-resistant *C. jejuni* for humans in Minnesota. K. Smith WDT: p. 14, lines 2-4

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being inaccurate and an unsubstantiated and speculative opinion rather than a fact. It is not substantiated by data and indeed is specifically refuted by Smith's own data (Cox, B-1901, pages 15, 27, and especially 33]. In addition, evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis, fluoroquinolone resistant or otherwise . Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a source of quinolone-resistant *C. jejuni* for humans in Minnesota.

Bayer/AHI also object to the wording of this PFOF as using an ambiguous and misleading term ("resistant") which is routinely interpreted by CVM and its witnesses, including Dr. Smith, to mean and/or imply "resistant to clinical doses" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). Given that CVM routinely uses this meaning, the term "quinolone-resistant" is inappropriate here, as no clinical relevance of such resistance has been established. See our response to PFOF #408 on this point.

784. In K. Smith's study, patients with domestically acquired quinolone-resistant *C. jejuni* infections were 15 times more likely to have a *C. jejuni* subtype that was also found among quinolone-resistant *C. jejuni* isolates from domestic chicken products collected in 1997 than were patients with domestically acquired quinolone-sensitive *C. jejuni* isolates. This link is statistically significant. K. Smith WDT: p. 14, lines 8-12 and 16-18; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being inaccurate. This statement is scientifically unjustified and inconsistent with the reported data of study G-589. Statistical inferences from a selected sample to its related population are valid only if the components of the

sample are randomly chosen and independent. When sampled data groups are not independent valid statistical inferences cannot be made because pre-existing associations prevent testing of whether the association may have occurred by chance alone. It is clear that FQ-R variants in humans and poultry represent small subsets within their respective and much larger FQ-S populations. This is true because FQ-R variants are selected clones arising from their FQ-S progenitors. This means that FQ-R populations from both humans and poultry are entirely dependent upon their respective FQ-S populations so that independence and statistical inference testing between these groups is invalid. Additionally, probability associations establish that the biological plausibility of finding FQ-R associations before finding FQ-S associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that an FQ-R chicken strain will cause an FQ-R human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a C. jejuni from chicken is FQ-R X probability that a domestically acquired human case is FQ-R for 1998). Conversely, the same conditional probability for a chicken FQ-S strain causing a human FQ-S infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that FQ-S associations would be found over FQ-R associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

785. In K. Smith's study, patients with domestically acquired resistant *C. jejuni* infections were 22.3 times more likely to have a *C. jejuni* subtype that was also found among resistant *C. jejuni* isolates from domestic chicken products than were patients with foreign travel-. associated quinolone-sensitive *C. jejuni* isolates. This link is statistically significant. K. Smith WDT: p. 14, lines 12-16; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being inaccurate and unjustified. This statement is scientifically unjustified and inconsistent with the reported data of study G-589. Statistical inferences from a selected sample to its related population are valid only if the components of the sample are randomly chosen and independent. When sampled data groups are not independent valid statistical inferences cannot be made because pre-existing associations prevent testing of whether the association may have occurred by chance alone. It is clear that FQ-R variants in humans and poultry represent small subsets within their respective and much larger FQ-S populations. This is true because FQ-R variants are selected clones arising from their FQ-S progenitors. This means that FQ-R populations from both humans and poultry are entirely dependent upon their respective FQ-S populations so that independence and statistical inference testing between these groups is invalid. Additionally, probability associations establish that the biological plausibility of finding FQ-R associations before finding FQ-S associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that an FQ-R chicken strain will cause an FQ-R human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a C. jejuni from chicken is FQ-R X probability that a domestically acquired human case is FQ-R for 1998). Conversely, the same conditional probability for a chicken FQ-S strain causing a human FQ-S infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that FQ-S associations would be found over FQ-R associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

786. When a large number of subtypes are generated by a subtyping method, two isolates that share an identical subtype are more likely to be related to a common source than if the method yields a small number of subtypes. K. Smith WDT: p. 14, lines 22-25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. The number of subtypes generated by a typing method may not be related at all to the ability of the method to discriminate genetic similarity (G-444). The discriminatory ability of the method, not the number of subtypes, is the most important factor in a subtyping methodology. This statement cannot be accepted as fact.

787. The use of comparison groups to statistically link domestically acquired quinolone-resistant human cases and retail chicken products renders the exact method of subtyping unimportant. K. Smith WDT: p. 14, lines 26-28

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. The comparison groups are wholly dependent upon the typing methodology used and therefore cannot be rendered "unimportant".

788. If the link between domestically acquired quinolone-resistant human cases and retail chicken products was an artifact of the subtyping method used, then the statistically significant finding that domestically acquired sensitive human isolates and foreign travel-associated resistant human isolates were less similar to domestic resistant chicken isolates would not be present. K. Smith WDT: p. 14, lines 28-33

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. This statement is scientifically unjustified and inconsistent with the reported data of study G-589. Statistical inferences from a selected sample to its related population are valid only if the components of the sample are randomly chosen and independent. When sampled data groups are not independent valid statistical inferences cannot be made because pre-existing associations prevent testing of whether the association may have occurred by chance alone. It is clear that FQ-R variants in humans and poultry represent small subsets within their respective and much larger FQ-S populations. This is true because FQ-R variants are selected clones arising from their FQ-S progenitors. This means that FQ-R populations from both humans and poultry are entirely dependent upon their respective FQ-S populations so that independence and statistical inference testing between these groups is invalid. Additionally, probability associations establish that the biological plausibility of finding FQ-R associations before finding FQ-S associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that an FQ-R chicken strain will cause an FQ-R human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a C. jejuni from chicken is FQ-R X probability that a domestically acquired human case is FQ-R for 1998). Conversely, the same conditional probability for a chicken FQ-S strain causing a human FQ-S infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that FQ-S associations would be found over FQ-R associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

789. Smith found that in Minnesota, there was an increase in quinolone resistance among human *Campylobacter jejuni* isolates from 1.3% in 1992 to 10.2% in 1998. K. Smith WDT: p. 14, lines 35-37; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This statement is misleading insofar as it implies that the total of the resistance measured over this period had its origin in Minnesota. In reality, approximately 70% of the resistance found in Minnesota residents was acquired in a foreign country (G-589). Bayer/AHI also object to the wording of this PFOF as using an ambiguous and misleading term ("resistant"); see our responses to PFOF #408 and #783 on this point. We also object to the term "increased" as it implies or suggests a continuous, monotonic increase, which has not been shown. We believe that a more accurate wording would be "Smith found that in non-representative samples from one metropolitan area in Minnesota, the fraction of MICs that were 4 or greater among sampled human *Campylobacter jejuni* isolates was 1.3% in 1992 and 10.2% in 1998."

790. Smith found that domestically acquired resistant infections increased in statistically significant (i.e., the increase likely was not due to chance) fashion from 1996 to 1998 in Minnesota. K. Smith WDT: p. 14, lines 43-45; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate, overly broad, ambiguous, and misleading. First, "statistical significance" can be assessed only for specific hypotheses and for specified models or assumptions. No specific hypothesis has been stated here. The claimed increase may be statistically significant for the hypothesis "The rate in 1998 was greater than the rate in 1996" while being non-significant for the hypothesis "The rate increased steadily from 1996-1998" or for the hypothesis "The rate increased more quickly from 1996-1998 than from 1992-1994". If the intended meaning of this PFOF is that a statistically significant change in the long-term resistance trend occurred when enrofloxacin was introduced, then we disagree with this PFOF as being inaccurate [Cox, B-1901, P. 29] and unsubstantiated by any presentation of supporting facts or data. We also disagree with this PFOF because it draws a conclusion about true infections ("domestically acquired resistant infections increased") in an entire state ("in Minnesota") from a sample taken in a single area that did not represent the entire state and that did not represent a random sample of all cases (non-reported and untreated as well as treated) even in the Minneapolis-St. Paul area. Thus, the conclusion is far more general than the data on which it is based permit. Thus, the PFOF constitutes an invalid extrapolation from a sharply limited, non-representative sample, and in this sense must be regarded as speculation rather than as a fact.

791. Smith found that domestic chicken products obtained from Minnesota retail markets in 1997 had high rates of contamination with ciprofloxacin-resistant *C. jejuni*. K. Smith WDT: p. 14, lines 46 – p. 15, line 1; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as vague and inaccurate. Of the 91 retail chicken products sampled, on 13 or 14% were C. jejuni that were resistant to ciprofloxacin. This is not a high rate of contamination and the statement misrepresents the facts as reported by Smith. G-589 P. 5. As stated, this PFOF is misleading and misrepresents the sampling location. The retail samples were all taken in the Minneapolis-St. Paul metropolitan

area of Minnesota only and do not constitute a representative sample for the entire state (G-589 P. 2).

792. Smith found that the vast majority of resistant strains from domestically acquired human cases in Minnesota in 1997 were identical to resistant strains from the chicken products using a DNA fingerprinting method. K. Smith WDT: p. 15, lines 2-4; G-589

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF. This statement is misleading and scientifically incorrect. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". The frequent genetic rearrangements which occur at the fla locus make any conclusions about clonality or relatedness from isolates disparate in time and space (typing FOF's) speculative at best. Additional genetic typing to establish that chromosomal DNA regions outside the fla region is similar are required to establish that the examined *Campylobacters* are indeed similar. No such analysis was performed in this study. The statement that strains were "identical" is incorrect. It can only be said that the strains share the same fla types. It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, if the most sophisticated and exacting genetic subtyping showed *Campylobacters* to be "indistinguishable", it would not by itself, imply any causal relationship, since common sources for human and chicken *Campylobacters.* (such as water) could not be ruled out. In the absence of epidemiological data no causal inferences can be drawn (typing FOF's). In the Smith study (G-589), there is no epidemiological data establishing any causal relationship between chicken *Campylobacters* and human *Campylobacters*. Only foreign travel and prior use of a fluoroquinolone are found to risks associated with FQ-R infections in the case-comparison study. This statement must be wholly rejected.

793. Chicken is a major source of resistant *C. jejuni* for people. K. Smith WDT: p. 15, line 4-13; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is a major source of *C. jejuni* (resistant or otherwise) for people. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the

record does not show or even merely suggest that poultry is a major source of resistant *C. jejuni* for people.

794. K. Smith found a statistically significant link between domestically acquired fluoroquinolone-resistant *Campylobacter jejuni* in human and chicken strains. K. Smith WDT: p. 15, lines 6-7; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This statement is scientifically unjustified and inconsistent with the reported data of study G-589. Statistical inferences from a selected sample to its related population are valid only if the components of the sample are randomly chosen and independent. When sampled data groups are not independent valid statistical inferences cannot be made because pre-existing associations prevent testing of whether the association may have occurred by chance alone. It is clear that FQ-R variants in humans and poultry represent small subsets within their respective and much larger FQ-S populations. This is true because FQ-R variants are selected clones arising from their FQ-S progenitors. This means that FQ-R populations from both humans and poultry are entirely dependent upon their respective FQ-S populations so that independence and statistical inference testing between these groups is invalid. Additionally, probability associations establish that the biological plausibility of finding FQ-R associations before finding FQ-S associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that an FQ-R chicken strain will cause an FQ-R human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a C. jejuni from chicken is FQ-R X probability that a domestically acquired human case is FQ-R for 1998). Conversely, the same conditional probability for a chicken FQ-S strain causing a human FQ-S infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that FQ-S associations would be found over FQ-R associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

795. Chicken is an important source of fluoroquinolone-resistant *C. jejuni*. K. Smith WDT: p. 15, line 13 and lines 36-37

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that chicken or turkey is an important source of *C. jejuni* (resistant or otherwise). Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of fluoroquinolone-resistant *C. jejuni*.

Additionally, this statement is misleading and scientifically incorrect. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". The frequent genetic rearrangements which occur at the fla locus make any conclusions about clonality or relatedness from isolates disparate in time and space (typing FOF's) speculative at best. Additional genetic typing to establish that chromosomal DNA regions outside the fla region is similar are required to establish that the examined *Campylobacters* are indeed similar. No such analysis was performed in this study. It can only be said that the strains share the same fla types. It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, if the most sophisticated and exacting genetic subtyping showed *Campylobacters* to be "indistinguishable", it would not by itself, imply any causal relationship, since common sources for human and chicken *Campylobacters* (such as water) could not be ruled out. In the absence of epidemiological data no causal inferences can be drawn (typing FOF's). In the Smith study (G-589), there is no epidemiological data establishing any causal relationship between chicken *Campylobacters* and human *Campylobacters*. Only foreign travel and prior use of a fluoroquinolone are found to risks associated with FQ-R infections in the case-comparison study. There are no studies to date adequately demonstrating that poultry are a source of FQ-R *Campylobacters* for people. This statement must be wholly rejected.

796. The use of fluoroquinolones in poultry has had a primary role in increasing resistance to quinolones among *C. jejuni* isolates from humans. K. Smith WDT: p. 15, lines 39-40

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This statement is misleading and scientifically incorrect. The fla-A PCR/RFLP typing method examines a region of the *Campylobacter* genome equivalent to between one ten thousandths and one one-hundred thousandths of the total *Campylobacter* DNA. It is no more of a "DNA fingerprint" than one line of one swirl on the little finger constitutes an actual "fingerprint". The frequent genetic rearrangements which occur at the fla locus make any conclusions about clonality or relatedness from isolates disparate in time and space (typing FOF's) speculative at best. Additional genetic typing to establish that chromosomal DNA regions outside the fla region is similar are required to establish that the examined *Campylobacters* are indeed similar. No such analysis was performed in this study. It can only be said that the strains share the same fla types. It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, if the most sophisticated and exacting genetic subtyping showed *Campylobacters* to be "indistinguishable", it would not by itself, imply any causal relationship, since common sources for human and chicken *Campylobacters* (such as water) could not be ruled out. In the absence of epidemiological data no causal inferences can be drawn (typing FOF's). In the Smith study (G-589), there is no epidemiological data establishing any causal relationship between chicken *Campylobacters* and human *Campylobacters*. Only foreign travel and prior use of a fluoroquinolone are found to be risks associated with FQ-R infections in the case-comparison study. There are no studies to date adequately demonstrating that poultry are a source of FQ-R *Campylobacters* for people. This statement must be wholly rejected.

797. Treatment with enrofloxacin of broiler chickens infected with quinolone-sensitive *C. jejuni* does not eradicate these bacteria; rather, it readily selects for quinolone-resistant strains of *C. jejuni*. K. Smith WDT: p. 15, lines 42-45

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This finding of fact is incorrect as written. By definition, quinolone-sensitive *C. jejuni* would be eliminated by treatment with enrofloxacin. Additionally, this statement is misleading. Study A-190 demonstrates that *Campylobacter* is in fact eradicated in approximately 80% of the pre-colonized chickens which were subsequently treated with enrofloxacin in a pen study. Resistant clones were selected for in a small percentage of the remaining chickens. These chickens may have served as a recontamination source of FQ-R *Campylobacters* for chickens from whom *Campylobacter* was eradicated in earlier treatment. This statement cannot be accepted as fact.

798. At most, 15% of domestically acquired fluoroquinolone-resistant *Campylobacter jejuni* infections were due to prior fluoroquinolone therapy in humans during 1996-1998 in K. Smith's study. K. Smith WDT: p. 15, lines 25-26; G-589

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as expressing an unjustified assumption. The assertion that "At most, 15% of domestically acquired fluoroquinolone-resistant *Campylobacter jejuni* infections were due to prior fluoroquinolone therapy in humans" is limited by what the respondents knew. For example, if, as is certainly plausible, some percentage of the cases interviewed had drunk water contaminated by ciprofloxacin-resistant *Campylobacter* caused by prior fluoroquinolone therapy in humans, none of this would have been captured in Dr. Smith's data. Dr. Smith took the reported use of ciprofloxacin cases as an upper bound on the contribution of quinolone use to reported resistance, but this is an unjustified inference.

799. There has been a temporal relationship between the licensure of fluoroquinolones for use in food animals, particularly poultry, and a subsequent increase in quinolone-resistant *Campylobacter* isolates from humans in the United States, the Netherlands, Spain, the United Kingdom, Taiwan and Mexico. K. Smith WDT: p. 15, line 45 – p. 16, line 4

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as inaccurate, misleading and vague. It is vague because the term "temporal relation" is not defined. (Is "comes before" what is meant by "temporal relation"? It is not clear. *Any* two events stand in some "temporal relation". Asserting an unspecified "temporal relation" between "licensure of fluoroquinolones for use in food animals, particularly poultry, and a subsequent increase in quinolone-resistant *Campylobacter* isolates" is misleading, as it suggests the possibility of a causal relation between these events, where no such causal relation exists [B-1901, pages 26-28, 41-45]. To be balanced, the PFOF should equally point out that it is equally true that "There has been a temporal relationship between the increase in quinolone-resistant *Campylobacter* isolates from humans and subsequent licensure of fluoroquinolones for use in food animals, particularly poultry."

Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter*

rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

800. Quinolone resistance in *Campylobacter* from humans follows closely after the use of fluoroquinolones in veterinary medicine. K. Smith WDT: p. 16, lines 5-7

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. Reported fluoroquinolone resistance in *Campylobacter* from humans *preceded* the use of fluoroquinolones in veterinary medicine by over a decade [Cox, B-1901, p. 79, citing (Karmali et al., 1981; Svedhem et al., 1981; testimony of Dr. Barrett, G-1451, p. 3, line 6)]. A 1997 review noted that "The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized soon after the introduction of these compounds for clinical use more than 10 years. ago" Acar JF, Goldstein FW. Trends in bacterial resistance to fluoroquinolones. Clin Infect Dis. 1997 Jan;24 Suppl 1:S67-73, cited in [Cox and Popken, 1993]. B-119. These authors also contributed to and cited a 1993 review of resistance that found that "The new fluoroquinolones have been in use for nearly 10 years in the treatment of community- and nosocomially-acquired infections. Resistant clones may be selected during therapy and disseminate if favorable epidemiological conditions prevail. ... Resistance has been reported in methicillin-susceptible Staphylococcus aureus, *Campylobacter jejuni/coli*, *Salmonella*, *Shigella* and *Escherichia coli*. (Acar JF, O'Brien TF, Goldstein FW, Jones RN. The epidemiology of bacterial resistance to quinolones. Drugs. 1993;45 Suppl 3:24-8.) B-120.

In Minnesota specifically, it is not true that "Quinolone resistance in *Campylobacter* from humans follows closely after the use of fluoroquinolones in veterinary medicine", as claimed in this PFOF. This is specifically refuted in [B-1901, p. 29]: "Nonparametric nonlinear regression analysis of the 1996-1999 MN data suggests that there was an increase in the slope of the FQ-r rate (a change point) in early 1998, years *after* the introduction of FQ in chickens. Such change points... are not clearly related to anything that happened in 1995 or 1996, including enrofloxacin introduction. ... Other parts of the temporal pattern suggest that human FQ-r CP rates are *not* caused by enrofloxacin use."

801. Fluoroquinolones had been used in human medicine for years, but significant increases in resistant *Campylobacter* infections in humans did not happen following this use. K. Smith WDT: p. 16, lines 8-10

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. For example, a 1997 review noted that "The emergence of resistance to fluoroquinolones in virtually all species

of bacteria was recognized soon after the introduction of these compounds for clinical use more than 10 years ago" B-119. These authors also contributed to and cited a 1993 review of resistance that found that "The new fluoroquinolones have been in use for nearly 10 years in the treatment of community- and nosocomially-acquired infections. Resistant clones may be selected during therapy and disseminate if favorable epidemiological conditions prevail. ...Resistance has been reported in methicillin-susceptible Staphylococcus aureus, *Campylobacter jejuni/coli*, *Salmonella*, *Shigella* and *Escherichia coli*. B-120. Nachamkin, for example identifies 21% resistance in *Campylobacter* isolates in 1995, prior to approval of enrofloxacin. See reply to CVM PFOF 708.

802. The increase in fluoroquinolone resistance is particularly striking in Spain, where the percentage of ciprofloxacin-resistant *Campylobacter* isolates increased from 0-3% in 1989 to 30-50% in 1991 following the licensure of enrofloxacin for veterinary use in 1990. K. Smith WDT: p. 16, lines 12-16

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. It uses a term ("ciprofloxacin-resistant *Campylobacter* isolates") with no official or generally accepted definition. For Spain, specifically, this PFOF refers to "the percentage of ciprofloxacin-resistant *Campylobacter* isolates" without specifying the population (the denominator) to which this percentage refers (e.g., patients with foreign travel, patients visiting physicians who have recently been trained to search for ciprofloxacin-resistant *Campylobacter* isolates, etc.). No. evidence is presented suggesting that "licensure of enrofloxacin for veterinary use in 1990" had any relation to the time series or trend reported, i.e., that "percentage of ciprofloxacin-resistant *Campylobacter* isolates increased from 0-3% in 1989 to 30-50% in 1991"; thus, the phrase "following the licensure of enrofloxacin for veterinary use" seems gratuitous and inserted only to suggest a possible causal connection where none has been shown to exist. Also, human and animal fluoroquinolones are extensively used in Spain in an unregulated fashion.

More generally, evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

803. There is strong evidence from independent studies in numerous countries throughout the world that fluoroquinolone use in veterinary medicine (not in human medicine) is the

primary force behind the increase in fluoroquinolone-resistance in *Campylobacter* infections of humans. K. Smith WDT: p. 16, lines 18-22

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being a sheer statement of Dr. Smith's opinion, unsubstantiated by any facts or data. We are not aware of any evidence (strong or otherwise) that supports the frequently raised hypothesis "that fluoroquinolone use in veterinary medicine (not in human medicine) is the primary force behind the increase in fluoroquinolone-resistance in *Campylobacter* infections of humans". In fact, available data seem to contradict this hypothesis, which after more than 10 years remains unvalidated and unsupported by data (other than the occasional coincidence that veterinary uses of fluoroquinolones are sometimes approved in countries with increasing resistance trends.)

Bayer/AHI disagrees with this PFOF as being misleading and vague. It is vague because the term "temporal relation" is not defined. (Is "comes before" what is meant by "temporal relation"? It is not clear. *Any* two events stand in some "temporal relation" to each other. Asserting an unspecified "temporal relation" between "licensure of fluoroquinolones for use in food animals, particularly poultry, and a subsequent increase in quinolone-resistant *Campylobacter* isolates" is misleading, as it suggests the possibility of a causal relation between these events, where no such causal relation exists [B-1901, pages 26-28, 41-45]. To be balanced, the PFOF should point out that it is equally true that "There has been a temporal relationship between the increase in quinolone-resistant *Campylobacter* isolates from humans and subsequent licensure of fluoroquinolones for use in food animals, particularly poultry."

Bayer/AHI also disagree with this PFOF as being inaccurate. Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

In the United States and elsewhere, reported fluoroquinolone resistance in *Campylobacter* from humans *preceded* the use of fluoroquinolones in veterinary medicine, often by over a decade [Cox, B-1901, p. 79, citing (Karmali et al., 1981; Svedhem et al., 1981; testimony of Dr. Barrett, G-1451, p. 3, line 6)]. Smith's denial that fluoroquinolone use in human medicine "is the primary force behind the increase in fluoroquinolone-resistance in *Campylobacter* infections of humans" is unsubstantiated by facts and data. For example, a 1997 review noted that "The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized

soon after the introduction of these compounds for clinical use more than 10 years ago". B-119. Trends in bacterial resistance to fluoroquinolones. Clin Infect Dis. 1997 Jan;24 Suppl 1:S67-73, cited in [Cox and Popken, 2003]. These authors also contributed to and cited a 1993 review of resistance that found that "The new fluoroquinolones have been in use for nearly 10 years in the treatment of community- and nosocomially-acquired infections. Resistant clones may be selected during therapy and disseminate if favorable epidemiological conditions prevail. ... Resistance has been reported in methicillin-susceptible Staphylococcus aureus, *Campylobacter jejuni/coli*, *Salmonella*, *Shigella* and *Escherichia coli*. (Acar JF, O'Brien TF, Goldstein FW, Jones RN. The epidemiology of bacterial resistance to quinolones. Drugs. 1993;45 Suppl 3:24-8.) B-120. Nachamkin, for example identifies 21% resistance in *Campylobacter* isolates in 1995, prior to approval of enrofloxacin. See reply to CVM PFOF 708.

804. Studies from Spain demonstrate a temporal relationship between the use of fluoroquinolones in veterinary medicine and an increase in fluoroquinolone-resistant *Campylobacter* isolates in humans. K. Smith WDT: p. 16, lines 34-36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as vague, misleading, and inaccurate. It uses a term ("fluoroquinolone-resistant *Campylobacter* isolates") with no official or generally accepted definition. For Spain, specifically, no evidence is presented suggesting (let alone "demonstrating") that "use of fluoroquinolones in veterinary medicine" had any impact on the time series or trend of "fluoroquinolone-resistant *Campylobacter* isolates in humans". Thus, the phrase "temporal relationship" used in this context seems gratuitous and inserted only to suggest a possible causal connection where none has been established. The PFOF fails to specify what "temporal relationship" it is referring to or how studies from Spain "demonstrate" this unspecified temporal relationship. Since any two events have some "temporal relationship" to each other, the PFOF is vacuous. If it means to assert that evidence from Spain suggests that use of fluoroquinolones in veterinary medicine caused an increase in fluoroquinolone-resistant *Campylobacter* isolates in humans, then we object that this assertion is inaccurate and unsubstantiated [B-1901, pages 26-28, 41-45].

More generally, evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. There are no temporal and epidemiologic associations in multiple countries showing that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. Furthermore, there are no temporal and epidemiologic associations in any country that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

809. Reina found cross-resistance between nalidixic acid and ciprofloxacin in 89.1% of the *Campylobacter* strains isolated from pediatric patients during 1987-1993 tested. K. Smith WDT: p. 17, lines 13-15; G-532

Bayer/AHI Response: Bayer/AHI do not dispute that this is what was reported.

810. In 1987, none of the *Campylobacter* isolated from pediatric patients by Reina were resistance to either nalidixic acid or ciprofloxacin. K. Smith WDT: p. 17, lines 16-17; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

811. In 1988 and 1989, Reina found both nalidixic acid and ciprofloxacin resistance to 2.3% and 3.4% of *Campylobacter* isolates from pediatric patients tested, respectively. K. Smith WDT: p. 17, lines 17-19; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

812. In 1990, Reina found 19% of the *Campylobacter* isolates from pediatric patients tested were resistant to nalidixic acid and 13% were resistant to ciprofloxacin. K. Smith WDT: p. 17, lines 19-20; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

813. In 1991, Reina found 31.8% of the *Campylobacter* isolates from pediatric patients tested were resistant to nalidixic acid and 30.5% were resistant to ciprofloxacin. K. Smith WDT: p. 17, lines 20-21; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

814. In 1992, Reina found 36.7% of the *Campylobacter* isolates from pediatric patients tested were resistant to nalidixic acid and 32.9% were resistant to ciprofloxacin. K. Smith WDT: p. 17, lines 22-23; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

815. In 1993, Reina found 55.2% of the *Campylobacter* isolates from pediatric patients tested were resistant to nalidixic acid and 48.8% were resistant to ciprofloxacin. K. Smith WDT: p. 17, lines 23-24; G-532

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

816. Reina found the rate of nalidixic acid resistance in *Campylobacter jejuni* isolated from humans rose from 0% in 1987 to 2.3% in 1988, to 3.4% in 1989, to 13% in 1990, to 30% in 1991 in Spain. K. Smith WDT: p. 17, lines 27-30; G-529

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

817. In a study from Spain, Ruiz found 47.5% of human *Campylobacter jejuni* isolates tested were resistant to both nalidixic acid and ciprofloxacin in 1991; 63.5% of human *Campylobacter jejuni* isolates studied were resistant to both nalidixic acid and ciprofloxacin in 1992; 73% of human *Campylobacter jejuni* isolates studied were resistant to both nalidixic acid and ciprofloxacin in 1993; and 88% of *Campylobacter jejuni* isolates studied were resistant to both nalidixic acid and ciprofloxacin in 1994. K. Smith WDT: p. 17, lines 32-39; G-544

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

818. In a study from Spain, Sanchez found 0% of human *Campylobacter* isolates studied were resistant to ciprofloxacin and ofloxacin and 2.6% were resistant to norfloxacin and nalidixic acid in 1988. K. Smith WDT: p. 17, line 46 – p. 18, line 1; G-557

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

819. In a study from Spain, Sanchez found, 6.1% of human *Campylobacter* isolates tested were resistant to ciprofloxacin and ofloxacin, 8.1% were resistant to norfloxacin, and 20.4% were resistant to nalidixic acid in 1989. K. Smith WDT: p. 18, lines 2-3; G-557

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

820. In a study from Spain, Sanchez found 8.6% of human *Campylobacter* isolates tested were resistant to ciprofloxacin, 8.7% were resistant to ofloxacin, 10.8% were resistant to norfloxacin, and 17.4% were resistant to nalidixic acid in 1990. K. Smith WDT: p. 18, lines 3-5; G-557

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

821. In a study from Spain, Sanchez found 50.7% of human *Campylobacter* isolates tested were resistant to ciprofloxacin, 47.6% were resistant to ofloxacin, 52.3% were resistant to norfloxacin, and 58.7% were resistant to nalidixic acid in 1991. K. Smith WDT: p. 18, lines 5-7; G-557

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

822. In a study in Spain, Sanchez found 49.5% of human *Campylobacter* isolates tested were resistant to ciprofloxacin, 45.6% were resistant to ofloxacin, 55.5% were resistant to norfloxacin, and 56.8% were resistant to nalidixic acid in 1992. K. Smith WDT: p. 18, lines 7-9; G-557

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

823. In a study in Spain, Saenz found that 81% of broilers tested carried *Campylobacter* in 1997-1998. K. Smith WDT: p. 18, line 15; G-549

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

824. Testing of 5,800 isolates of *Campylobacter* isolated from humans in 1996 and 1997 in the United Kingdom revealed that 12% were resistant to ciprofloxacin (at a level of >8 μg/ml). K. Smith WDT: p. 18, lines 31-33; G-632

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the exception that NCCLS has not approved this as an acceptable breakpoint.

825. Studies from Mexico demonstrate a temporal relationship between fluoroquinolone use in veterinary medicine and an increase in fluoroquinolone-resistant *Campylobacter* isolates in humans. K. Smith WDT: p. 18, lines 37-39

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as vague, misleading, and inaccurate. It uses a term ("fluoroquinolone-resistant *Campylobacter* isolates") with no official or generally accepted definition. For Mexico, specifically, this PFOF refers to "an increase in fluoroquinolone-resistant *Campylobacter* isolates in humans." without specifying the population (the denominator) to which this increase applies (e.g., patients with foreign travel, patients visiting physicians who have recently been trained to search for ciprofloxacin-resistant *Campylobacter* isolates, etc.). No evidence is presented suggesting let alone "demonstrating"). that "fluoroquinolone use in veterinary medicine" had any impact on the time series or trend of "increase in fluoroquinolone-resistant *Campylobacter* isolates in humans"; thus, the phrase "temporal relationship" seems gratuitous and inserted only to suggest a possible causal connection where none has been established. The PFOF fails to specify what "temporal relationship" it is referring to or how studies from Mexico "demonstrate" this unspecified temporal relationship. Since any two events have some "temporal relationship" to each other, the PFOF is vacuous. If it means to assert that evidence from Mexico suggests that use of fluoroquinolones in veterinary medicine *caused* an increase in fluoroquinolone-resistant *Campylobacter* isolates in humans, then we object that this assertion is inaccurate and unsubstantiated [B-1901, pages 26-28, 41-45].

826. Mexico produces a substantial amount of poultry meat; production increased from 1.7 x 10^9 lbs. in 1990 to 3.2 x 10^9 lbs. in 1997. K. Smith WDT: p. 19, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

827. Sales of quinolones for use in poultry, including ciprofloxacin, enrofloxacin, and danofloxacin, increased dramatically in Mexico, from 86 x 10^6 medicated liters in 1993 to 326 x 10^6 medicated liters in 1997. K. Smith WDT: p. 19, lines 8-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF with the exception that this fact does not apply to the legal proceedings related to this case.

828. In a study by Chung-Chen in Taiwan, 92% of 12 *C. jejuni* and 91% of 23 *C. coli* isolates from retail chicken products were resistant to ciprofloxacin. K. Smith WDT: p. 19, lines 28-30; G-376

Bayer/AHI Response: Bayer/AHI do not dispute that this is what was reported.

829. Large amounts of fluoroquinolones are used in poultry in Taiwan. K. Smith WDT: p. 19, lines 30-31

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. Bayer U.S.A. has no direct knowledge of legal and/or illegal use of fluoroquinolone use in poultry in Taiwan.

830. Fluoroquinolone-resistant *Campylobacter* has been isolated in retail chicken and in humans in the United States, the Netherlands, Spain, the United Kingdom, and Taiwan. K. Smith WDT: p. 19, lines 33-36

Bayer/AHI Response: Bayer/AHI dispute this PFOF, to the extent it uses an ambiguous and misleading term ("fluoroquinolone-resistant") which is routinely interpreted by CVM and its witnesses, including Dr. Smith, to mean and/or imply "resistant to clinical treatment with fluoroquinolones" (e.g., Tollefson WDT: P.2 L.40-43; Levy, PFOF #408, Smith, G-1473 P.10 ¶ 22). Given that CVM routinely uses this meaning, the term "fluoroquinolone-resistant" is inappropriate here, as no clinical relevance of such resistance has been established. See our response to PFOF #408 on this point.

831. Fluoroquinolone use in poultry and livestock is widespread in most regions of the world, including Europe, the United States, Asia, Latin America, and South Africa. K. Smith WDT: p. 19, lines 42-44

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. Bayer U.S.A. has no direct knowledge of use of fluoroquinolone use in Europe, Asia, Latin America, and South America. Joint Stipulation 49. Additionally, use of fluoroquinolones in Europe, Asia, Latin America, and South America is not relevant to the pending legal case in the U.S. In the U.S., enrofloxacin use is not widespread in poultry. Joint Stipulations 15, 16, 17, 46; A-201 P.20 L.9; A-192.

832. The use of fluoroquinolones in poultry in foreign countries is an important contributor to infections with resistant *C. jejuni* among travelers to those countries. K. Smith WDT: p. 19, line 46 – p. 20, line 2

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. This statement is merely speculative opinion without basis in established fact. Only the use of enrofloxacin in the United States bears significantly on the issues at hearing. This statement cannot be accepted as fact.

833. Domestically acquired quinolone-resistant *C. jejuni* infections in Minnesota residents increased significantly after fluoroquinolones were licensed for use in poultry in the United States. K. Smith WDT: p. 20, lines 13-15

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being vague and overly broad. It uses a term ("quinolone-resistant *C. jejuni* infections") with no official or generally accepted definition. (Smith has proposed an in vitro definition for resistance, not a definition for in vivo infections.) The PFOF refers to "infections in Minnesota residents", but no representative sample of Minnesota residents was taken that could justify inferences for the general Minnesota population. It asserts that "infections in Minnesota residents increased significantly" without specifying the tests and assumptions used to define "significantly" and without specifying the population (the denominator) to which this increase applies (e.g., patients with foreign travel, patients visiting physicians who have recently been trained to search for ciprofloxacin-resistant *Campylobacter* isolates, etc.).

Bayer/AHI also disagrees with this PFOF as being inaccurate, incomplete, and misleading. It is incomplete because it does not describe or adjust for the effects of changes in isolation procedures, in exposures of *Campylobacter* isolates to various antimicrobials prior to susceptibility testing [White (G-1484); G-589], or in the criteria used to submit and select isolates for testing over the (unspecified) time frame in question [B-1901, p. 80]. It is inaccurate and misleading because it attributes the combined effect of all these changes solely to an increase in "Domestically acquired quinolone-resistant *C. jejuni* infections". In reality, Smith has not shown that an increase in *reported* resistant infections corresponds to a change in the *actual* levels of resistant infections. Moreover, this PFOF is inaccurate in referring to "infections in Minnesota residents" rather than to "infections in sampled Minnesota residents".

No evidence is presented suggesting let alone "demonstrating" that fluoroquinolone use in veterinary medicine had any impact on the time series or trend of increase in fluoroquinolone-resistant *Campylobacter* isolates in humans; thus, the phrase "after fluoroquinolones were licensed for use in poultry in the United States." seems gratuitous and inserted only to suggest a possible causal connection where none has been established.

We further object to the use of the phrase "increased significantly after fluoroquinolones were licensed for use" as being ambiguous and potentially misleading. Although there were some years after 1995 in which rates were higher than in some years prior to 1995, nonparametric nonlinear regression analysis of the 1996-1999 MN data suggests that there was an increase in the slope of the FQ-resistance rate (a change point) in early 1998, years *after* the introduction of FQ in chickens. Such change points occurring at *any* time in the interval between 1995 and 2001 can explain the types of "temporal relations" and "trends" that Smith refers to. But they are *not* clearly related to anything that happened in 1995 or 1996, including enrofloxacin introduction. [Cox, B-101, p, 29]

834. The temporal relationship between the use of fluoroquinolones in veterinary medicine and the subsequent increase in fluoroquinolone resistance in human *Campylobacter* isolates has been born out again and again in different countries around the world. K. Smith WDT: p. 20, lines 17-21

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being vague and incorrect. The PFOF fails to specify what "temporal relationship" it is referring to or how this unspecified temporal relationship has been "born out again and again in different countries around the

world". Since any two events have some "temporal relationship" to each other, the PFOF is vacuous. If it means to assert that evidence from multiple countries suggests that use of fluoroquinolones in veterinary medicine *caused* a subsequent increase in fluoroquinolone-resistant *Campylobacter* isolates in humans, then we object that this assertion is inaccurate and unsubstantiated and is refuted by data [B-1901, pages 26-28, 41-45].

Evidence in the record shows that in many instances, the emergence and trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Thus, there is no temporal evidence for a causal relationship between the use of fluoroquinolones in veterinary medicine and the subsequent increase in fluoroquinolone resistance in human *Campylobacter* isolates [B-1901, pages 26-28, 41-45]. Furthermore, there are no temporal and epidemiologic associations in any country indicating that fluoroquinolone approvals in poultry have led to fluoroquinolone-resistant disease in people. The only instance in which there is a documented, plausible relationship comes from Taiwan (G-1775) and common source infections for swine, poultry and humans cannot be ruled out in that instance. Additionally, fluoroquinolones are extensively used in an unregulated fashion in Taiwan.

835. The presence of fluoroquinolone-resistant *Campylobacter* on retail chicken products has been documented in numerous countries around the world. K. Smith WDT: p. 20, lines 21-23

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as using a term ("fluoroquinolone-resistant *Campylobacter*") with no official or generally accepted definition.

836. In K. Smith's study of retail chicken purchased in Minnesota in 1997, there is a statistically significant link between resistant *C. jejuni* isolates from retail chicken products and domestically acquired resistant *C. jejuni* in humans. K. Smith WDT: p. 20, lines 24-26; G-589

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as vague and potentially misleading. What kind of link, specifically, is being referred to? (Obviously, all *Campylobacter* strains are "linked" to the extent that they are all strains of *Campylobacter*, but presumably something more is meant here. What more is meant has not been specified.) If the statement means or suggests that Smith's study showed that *Campylobacter jejuni* strains found in retail chicken products are a source of domestically acquired resistant *C. jejuni* in humans, or vice versa, it is inaccurate [Cox, B-1901 P. 28].

We also object to this PFOF as being scientifically unjustified and inconsistent with the reported data of study G-589. Statistical inferences from a selected sample to its related population are valid only if the components of the sample are randomly chosen and independent. When sampled data groups are not independent valid statistical inferences cannot be made because pre-existing associations prevent testing of whether the association may have occurred by chance alone. It is

clear that FQ-R variants in humans and poultry represent small subsets within their respective and much larger FQ-S populations. This is true because FQ-R variants are selected clones arising from their FQ-S progenitors. This means that FQ-R populations from both humans and poultry are entirely dependent upon their respective FQ-S populations so that independence and statistical inference testing between these groups is invalid. Additionally, probability associations establish that the biological plausibility of finding FQ-R associations before finding FQ-S associations in human and poultry sub-populations given that a subtyping system is valid is highly unlikely. For example, the conditional probability that an FQ-R chicken strain will cause an FQ-R human, domestically acquired case is 0.14 X 0.03 or 0.0042 (probability that a C. jejuni from chicken is FQ-R X probability that a domestically acquired human case is FQ-R for 1998). Conversely, the same conditional probability for a chicken FQ-S strain causing a human FQ-S infection is 0.86 X 0.97 or 0.83. It is nearly 200 times more likely that FQ-S associations would be found over FQ-R associations if a subtyping system is able to correctly identify the most likely occurrences (G-589). This statement cannot be accepted as fact.

837. Retail poultry is a primary source of fluoroquinolone-resistant *Campylobacter* for humans in the Unites States and elsewhere in the world. K. Smith WDT: p. 20, lines 29-31

Bayer/AHI Response: Bayer/AHI dispute this PFOF as being inaccurate and as being unsubstantiated speculative opinion. Smith's own data show no positive association between fluoroquinolone-resistant campylobacteriosis in humans and recent chicken consumption [Cox,. B-1901, P. 33, L 2; Cox, 2002]. Evidence in the record disputes the contention that chicken or turkey is a primary source of fluoroquinolone-resistant *Campylobacter* for humans in the United States and elsewhere in the world. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a primary source of fluoroquinolone-resistant *Campylobacter* for humans in the Unites States and elsewhere in the world. Additionally, this statement is erroneous on its face. Retail poultry which is purchased by the consuming public and cooked in their homes in the United States has been shown to be protective for Campylobacteriosis. (G-228).

838. Treatment of bacterial gastroenteritis with fluoroquinolones shortens the duration of illness, if the infecting bacteria is susceptible to fluoroquinolones. K. Smith WDT: p. 20, lines 32-35

Bayer/AHI Response: Bayer/AHI object to this PFOF on the grounds that is refers to treatment of bacterial gastroenteritis, in general, and not campylobacteriosis. As relates to campylobacterioisis, Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is specifically refuted by B-1901 P.31-33. The claimed reduction in duration of illness disappears when effects of confounding, especially by foreign travel, are removed B-1901 P.26, 30. This PFOF is specifically refuted for data from Smith et al. (as well as of data from the CDC 1998-1999 *Campylobacter* case-control study) showing that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

839. When the infecting *Campylobacter* strain is resistant to fluoroquinolones, and fluoroquinolones are used to treat these infections, the result (on a population level) is treatment failure and a longer duration of illness. K. Smith WDT: p. 20, lines 35-38

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is specifically refuted by [Cox, B-1901, pages 31-33]. The claimed reduction in duration of illness disappears when effects of confounding, especially by foreign travel, are removed [Cox, B-1901, P. 26, 30]. This PFOF is specifically refuted for data from Smith et al. (as well as of data from the CDC 1998-1999 *Campylobacter* case-control study) showing that there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

840. *Campylobacter* infections can become invasive and life threatening, particularly in the elderly and those immunocompromised for other reasons. K. Smith WDT: p. 20, lines 39-41

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being vague: no "other reasons" are specified. This proposed finding of fact is also misleading, as a fatal outcome of campylobacteriosis is rare and is almost always confined to those 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]

841. It often takes 2 days until stool culture and sensitivity results come back. K. Smith WDT: p. 21, lines 4-5

Bayer/AHI Response: Bayer/AHI disagree with this PFOF. The meaning of "come back" is not defined and thus Bayer/AHI is unable to adequately interpret the sentence. If FDA means that it is necessary to wait 2 days to obtain culture results in order to have a definitive diagnosis of campylobacteriosis, this has been refuted by B-1906, P.6 L.1-5.

Robert Tauxe (G-1475)

842. Dr. Tauxe is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI dispute this PFOF because Dr. Tauxe classifies himself as a "medical epidemiologist" (p. 2, line 34), yet he purports to testify at length as an expert on poultry industry and food processing practices and their effects. See Tauxe WDT: P.15 L.32-46, P.16 L.1-46, P.17 L.1-40. For the same reason, the witness also lacks competence to testify as an expert concerning genetic typing, as he also does at some length. See WDT: P.11 L.35-46 – P.13 L.1-5.

843. Foodborne illness in the United States affects 1 in 4 Americans every year. Tauxe WDT: p. 2, lines 6-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is based on a survey published in 1999, and as the witness himself acknowledges, the annual incidence of foodborne illnesses such as *Campylobacter* is declining significantly due to a variety of factors. See Tauxe WDT: P.16 L.24-46.

844. CDC has estimated there are 76 million cases of foodborne illnesses that occur each year from all different causes of foodborne infections. Tauxe WDT: p. 2, lines 7-8; G-410.

Bayer/AHI Response: Bayer/AHI do not dispute that CDC estimated this in the past; however, the proposed finding of fact is outdated, misleading and irrelevant to this proceeding. The figures cited are based on 1996 information and reveal nothing concerning *Campylobacter*.. In fact, this publication estimated that *Campylobacter* only accounted for 3% of these foodborne infections and the incidence since then has decreased 27% from 1996 to 2001 according to CDC. G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. Angulo (G-1452) P.7 L.13-14, L.16-18, P.17 L.10.

845. Many people who become ill with a diarrheal illness do not visit a physician, either because the symptoms are relatively mild, or because they lack access to affordable care. Tauxe WDT: p. 2, lines 19-21

Bayer/AHI Response: Bayer/AHI does not generally dispute this PFOF; howeverthe witness has misquoted the supporting literature. Although not specifically referenced, it is clear that the intended basis for PFOF 845 is G-1790 and that the article has been misquoted by the witness. G-1790 at page 7 states: "The most commonly expressed reasons for not visiting a health-care provider were that the illness 'did not last long enough' (38%) and that the illness 'was too mild' (28%)." - nothing is said in G-1790 about a "lack of affordable care". Although G-1790 at page 7 also says that "The prevalence of calling or visiting a health-care provider was higher among respondents with medical insurance than among respondents without medical insurance (Table 2)", Table 2 shows that people without medical insurance called and then visited a medical person. The witness provides no other basis for his claim that "many" people with diarrheal illness do not visit a physician because they lack access to affordable care, and G-1790 does not support that statement.

846. Many people who do not visit a physician with a diarrheal illness are not asked to provide a specimen for culture. Tauxe WDT: p. 2, lines 22-23; G-1790

Bayer/AHI Response: While Bayer/AHI generally agree with this PFOF, it is Bayer's and AHI's understanding that stool samples are only provided upon request from a physician during the examination. In addition, the witness cites to G-1790, which indicates that for the one study described in the exhibit, stool samples were only requested from people that visited a medical person.

847. Many specimens that are cultured are not reported, because the infection is not a reportable illness in many states. Tauxe WDT: p. 2, lines 24-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

848. *Campylobacter jejuni* is the most common type of *Campylobacter* that causes illness in humans. Tauxe WDT: p. 2, lines 40-42; G-1475

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

849. Between 1982 and 1986, among 37,713 human isolates of *Campylobacter* reported through the national *Campylobacter* surveillance system with species data, 37,556, or 99.6% were *Campylobacter jejuni* or *Campylobacter coli,* and of those that were either of the two 99.8% were *Campylobacter jejuni.* Tauxe WDT: p. 3, lines 2-5; G-617

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

850. Among human *Campylobacter* isolates reported to FoodNet between 1996 and 2000, 97% of *Campylobacter* infections for which a species was reported were either *Campylobacter jejuni* or *Campylobacter coli,* and of those that were either of those two, 95% were *Campylobacter jejuni; Campylobacter jejuni* represented 93% of all reported *Campylobacter* infections for which the species was reported. Tauxe WDT: p. 3, lines 7-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

851. People who become infected with *Campylobacter jejuni* typically become ill after 2-4 days. Tauxe WDT: p. 3, lines 15-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it appears to be based on the "Skirrow 2000" reference which is exhibit G-580, and that reference estimates the incubation period to be 1 to 7 days, after removing outliers.

852. *Campylobacter jejuni* illnesses cause crampy abdominal pain and diarrhea, often with fever and some nausea. The diarrhea often becomes bloody and the cramps severe. Tauxe WDT: p. 3, lines 16-18

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the vast majority of persons with *Campylobacter* infections to do not seek treatment or report their symptoms, most of these unreported cases are mild, up to 25% of *Campylobacter* infections are asymptomatic, and Dr.

Thielman points out in his testimony that bloody stools are "less frequent symptoms" of campylobacteriosis, B-1909 P.4 L.5; G-70 P.4; G-1477 P.2 ¶ 3.

853. *Campylobacter jejuni* illnesses usually last 5-7 days. Tauxe WDT: p. 3, lines 18-19 and p. 13, lines 7-8; G-580

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Dr. Tauxe cites G-580, but the range of 5-7 days is not mentioned in G-580. First, the reference clarifies that the "clinical consequences depend in part on the virulence of the infecting strain, the challenge dose, and the susceptibility of the patient" and that "the disease described below is that experienced by patients sufficiently ill to seek medical attention, but unrecorded milder illness is undoubtedly common" (Page 2). Second, page 3 goes on to state that "after a variable period [in those who are "sufficiently ill"], usually about 3 to 4 days into the illness, the diarrhea begins to ease and the patient's condition improves, although the abdominal pain may persist for several more days." Finally, page 4 states that the "average duration of illness is difficult to measure", because there are so many variables.

854. In 1991, a ten-site collaborative survey of persons with diarrheal illness showed that among those from whom *Campylobacter* was isolated, including both inpatients and outpatients, 97% reported diarrhea, 80% reported abdominal cramps, 59% reported fever, 37% reported bloody diarrhea, 34% reported vomiting, and 21% were hospitalized. These symptoms are caused by the direct effect of the *Campylobacter* on the intestines. Tauxe WDT: p. 3, lines 21-28

Bayer/AHI Response: Bayer/AHI agree that the survey makes the statements in this PFOF; however this PFOF is misleading to the extent that it is intended to generalize to all cases of campylobacteriosis since it omits the qualification in the witness's testimony that this survey concerned only persons who sought medical care from whom fecal specimens were obtained.,As Bayer/AHI have pointed out, and the witness acknowledges, persons with such infections do not seek care because their illness is mild. Furthermore, as Bayer/AHI have also pointed out, up to 25% of *Campylobacter* infections may be asymptomatic. B-1909 P.4 L.1-3

855. *Campylobacter* infections can be complicated if the *Campylobacter* moves out of the intestinal tract into the person's bloodstream, causing severe septic illness and sometimes reaching other organs of the body and causing localized infections there. Tauxe WDT: p. 3, lines 30-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is not relevant to this case as no relationship between fluoroquinolone resistance and ability to cause extraintestinal disease has been demonstrated. B-1908 P.46, L.18-19, L.13-24, P.47 L.1-2. The PFOF is also misleading. *Campylobacter* infections of the blood (bacteremia) are uncommon, occurring in only about 1% of *Campylobacter* cases, and campylobacteremia is a prerequisite for all other extra-intestinal infections, which are rarer still. Furthermore, most campylobacteremia infections are self-resolving without treatment. 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. G-1485 P.7 L.1-3; G-580 P.7, 8. However, in the rare

instances of bacteremia and extraintestinal infections requiring antibiotic treatment, particularly among those patients with underlying immunodeficiency states, parenteral (intramuscular or intravenous, not oral, treatment) combination therapy with imipenem and gentamicin is the recommended treatment. B-1909 P.8 L.21-22, P.9 L.1-3; B-1905 P.5 L.6-8; B-273 P.7; B-742 P.5.

856. In approximately 1 per 1000 infections, the person who is recovering from *Campylobacter* infection develops a severe paralysis that affects the major muscles of the limbs and trunk, starting with the feet, and ascending to affect more and more of the body until the person may be completely paralyzed, including the muscles they need to breathe. Tauxe WDT: p. 3, lines 39-43; G-444

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it refers to Guillain-Barre Syndrome, and there is no evidence connecting this complication of campylobacteriosis to antibiotic treatment or to fluoroquinolone resistance. CVM Interrogatory Answer 60; Kist WDT: P.8 L.12-16, P.14 L.18-19, P.16 L.6-7; Pasternack WDT: P.19, 6-8.

857. The Neal study found that 13% of persons with documented *Campylobacter* infection developed symptoms of reactive arthritis, a very high rate that was specific to *Campylobacter*, more so than other enteric infections. Tauxe WDT: p. 4, lines 19-22; G-1475, p. 50-51

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the only report of the "study" on which the proposed finding and the witness's testimony is based is a short abstract showing no information about study methods or underlying data; refers variously and indiscriminately to "joint symptoms", "reactive arthritis like symptoms" and "reactive arthritis symptoms"; shows no correlation with undefined *Campylobacter* "illness" lasting 1-4, 5-9 or 10-14 days; and a barely statistically significant association with undefined *Campylobacter* "illness" lasting "> 15 days". Tauxe WDT: P.50. Neil also acknowledged that his hypothesis, that antibiotics could prevent this complication, would need to be evaluated. Tauxe WDT: P.4 L.34.

858. In Neal's study, the arthritis symptoms were correlated with the duration of illness. Persons that had a reactive arthritis were 2.7 times more likely to have had an acute illness lasting more than 15 days than were persons without joint symptoms, a difference that was statistically significant. Neal's study suggests that antibiotic treatment which shortens the duration of illness and thus decreases the stimulation of the immune system could help prevent this complication, though this would need to be evaluated with a formal clinical treatment trial. Tauxe WDT: p. 4, lines 23-34

Bayer/AHI Response: Bayer/API dispute this PFOF because the variously and indiscriminately described symptoms in the Neal abstract did not correlate with any illness durations except undefined "illness" "> 15 days", and then only barely so; the abstract makes no mention of antibiotic treatment; and there is no evidence that this complication of campylobacteriosis (or any other complication) is related to antibiotic treatment. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1909 P.17 L.1-4, P.19 L.6-8. Moreover, the studies concerning the effectiveness of antibiotic treatment of campylobacteriosis are conflicting and at best show effectiveness during the illness durations with which no correlation to joint symptoms was shown in the Neal study. See Bayer/AHI

responses to proposed findings of fact 1322, 1330. Lastly, Neil specifically acknowledged that his hypothesis, that antibiotics could prevent reactive arthritis, would need to be evaluated. Tauxe WDT: P.4 L.34.

859. People become infected with *Campylobacter* by swallowing them. This usually occurs because *Campylobacter* was present on food or in water or other drinks that they consumed. It may also occur if *Campylobacter* is on their hands after contact with something that was contaminated and they put their hands on food or directly in their mouth. Tauxe WDT: p. 4, lines 43-46 and p. 5, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

860. In a volunteer feeding trial conducted at the University of Maryland, 800 organisms, the smallest number tested, were sufficient to cause disease in some of the volunteers. Tauxe WDT: p. 5, lines 3-6; G-67

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that the 800 organisms dose, as stated in the PFOF, only caused disease in some, not all, of the volunteers.

861. *Campylobacter* are microscopic organisms, far smaller than can be seen with the human eye, and millions would fit on the heads of a pin. Tauxe WDT: p. 5, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

862. A very small amount of contamination in food may contain enough organisms to cause illness. Tauxe WDT: p. 5, lines 8-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF addresses "contamination in food" with "organisms". If the witness is referring to the infectious dose of food borne bacteria a more precise definition of "a very small amount" is necessary. The infectious dose is normally given as number of organisms, and for ***Campylobacter,*** based on experimental data, the minimum number capable of causing campylobacteriosis has been estimated to be about 500 - 800 organisms (minimum infectious dose). G-70 P.3; G-441 P.3; G-1470 P.4 L.43-46, P.5 L.1-8. Moreover, the risk that a given meal will lead to clinical campylobacteriosis depends only in part on the number of bacteria ingested.

863. *Campylobacter* does not spread easily from person-to-person. Tauxe WDT: p. 5, lines 36-37

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because the human-to-human transfer of *C. jejuni* and *C. coli*, either by direct or indirect pathways, has been documented. For example, G-1697 describes an outbreak of *C. jejuni* infections associated with food handler contamination, G-1692 describes the intrafamilial spread of *Campylobacter* in five separate households, G-580 describes a "persistent outbreak of *Campylobacter* infection in a day care nursery in Israel, and B-213 reviews nine different studies that point to person-to-person contact

as being the main transmission route. The rate of human-to-human transmission in the United States is unknown, but such transmission is not necessarily as uncommon as has been supposed. G-1452 P.9 L.28-29. In addition, sewage treatment plants which process domestic, commercial, and industrial wastewaters that received human waste discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of bacteria, including fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9; G-580 P.14. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214.

864. Most *Campylobacter* infections are related to consuming food or water that is contaminated with animal feces. Tauxe WDT: p. 6, lines 1-3

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF; however, they point out that recreational and drinking water is the predominant source of *Campylobacter* infections. B-1910 P.6 L.8-11, P.28 L.1-2

865. *Campylobacter* infection has been associated with direct contact with infected animals that may or may not be ill. Tauxe WDT: p. 6, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

866. The vast majority of *Campylobacter* infections occur sporadically, not as part of an outbreak. Tauxe WDT: p. 6, lines 14-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

867. A typical epidemiological study would involve interviewing patients with *Campylobacter* infection about things they had to eat or drink or other exposures they had in the week before they became ill, and comparing the frequency of those exposures with those of another group of people, who lived in the same area and were otherwise similar, but did not have *Campylobacter* infections. This technique, known as the case-control study, had been used to identify specific risk factors and specific exposures for a number of different infections. Tauxe WDT: p. 7, lines 25-31

Bayer/AHI Response: Bayer/AHI agree that such methods may be typical; however, they do not agree that the proposed finding of fact accurately or completely describes the methodology of a proper case-control study. B-1912 P.13-17.

868. The case-control study is a standard epidemiologic approach for defining those exposures that precede illness and are likely to be associated with getting the illness. Tauxe WDT: p. 7, lines 31-34

Bayer/AHI Response: Bayer/AHI disagree with this PFOF; only a properly designed and implemented case-control study that produces statistically significant results can identify exposures that precede illness and are likely to be associated with getting the illness.

869. Case-controlled studies of sporadic *Campylobacter* infections in the United States and other countries typically identify exposure to undercooked poultry as a source of *Campylobacter* infections. Tauxe WDT: p. 8, lines 5-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because evidence in the record disputes the contention that exposure to undercooked poultry is a source of *Campylobacter* infections. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that exposure to undercooked poultry is a source of *Campylobacter* infections.

870. In the Washington State study, illness was associated with eating chicken, turkey and Cornish hens, particularly as undercooked. Tauxe WDT: p. 8, lines 10-12; G-268

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because the Washington State study was too flawed to support a conclusion that illness was associated with eating chicken, turkey and Cornish hens, particularly as undercooked; in addition, as the witness's actual testimony points out, this study also purported to find an association with undercooked fish and shellfish, as well as poultry. See Bayer/AHI response to proposed finding of fact 875.

871. In the Deming study conducted among University of Georgia students, most illness was associated with eating undercooked and even raw chicken. Tauxe WDT: p. 8, lines 13-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF because of the limitations in the Deming study. G-162 (Deming 1987) is outdated and epidemiologically flawed. Deming (G-162) study did not isolate 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. B-1901 P.38-39, P.57-64. Moreover, Bayer/AHI disagree with the applicability of the Deming study to the issues in this hearing. The population in the Deming study is not representative of the current U.S. population in terms of age, income, travel habits, dietary habits, and other relevant risk factors. B-1901 P.38, P.57-64. The attributable fractions calculated in Deming cannot correctly be applied to U.S. population case rates. B-1901 P.38, P.57-64.

872. *Campylobacter* on chickens, turkeys or other meats is easily transferable in the kitchen to other foods. This can happen via unwashed hands of food handlers, by the use of utensils, first on raw poultry and then on other foods such as fresh fruits or vegetables that might not be eaten before cooking, or because raw poultry drips onto another food. Tauxe WDT: p. 9, lines 29-34

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by the fact that contact with and consumption of chicken in the home is protective (negatively correlated to campylobacteriosis). Evidence in the record refutes that retail poultry eaten by consumers at home is a major source of campylobacteriosis (B-1901 P.19, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24). This PFOF is also refuted by evidence 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. B-1901 P.29 (citing G-1644).

873. In Hopkins's study in Colorado, *Campylobacter* infection was associated with handling raw chicken, as opposed to eating undercooked chicken, and it is likely that the persons became infected as a result of handling the raw chicken in the kitchen, even before it was cooked. Tauxe WDT: p. 9, lines 34-37; B-412

Bayer/AHI Response: Bayer/AHI dispute this PFOF. It is speculative, misleading, and draws conclusions only permissible by the main investigator of the study. This PFOF is refuted by the fact that contact with and consumption of chicken in the home is protective (negatively correlated to campylobacteriosis). Evidence in the record more recent than Hopkin's outdated 1983 study refutes that retail poultry eaten by consumers at home is a major source of campylobacteriosis B-1901 P.29-30; G-1644P.10;G-185 P.1,3; G-1711 P.1,3,4,5,6; B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24). This PFOF is also refuted by recent epidemiological evidence in the record 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. B-1901 P.29; G-1644P.10; G-185 P.1,3 ; G-1711 P.1,3,4,5,6.

874. In Great Britain, an outbreak was reported at a school for chefs after a training exercise in how to pluck and slaughter a whole chicken. Tauxe WDT: p. 9, lines 38-40; G-1704

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it does not identify any disease for which there was a purported outbreak.

875. In Harris's case-control study in Seattle, infection among those eating chicken was strongly associated with not washing the kitchen cutting board and other indicators of cutting board hygiene, suggesting that practices in the kitchen can easily transfer the organisms to other foods. Tauxe WDT: p. 9, lines 41-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF. It is speculative in that it makes suggestions outside the scope of the original research. This PFOF is refuted by the fact that contact with and consumption of chicken in the home is protective (negatively correlated to campylobacteriosis). Evidence in the record more recent than Harris's outdated 1986 study

refutes that retail poultry eaten by consumers at home is a major source of campylobacteriosis (B-1901 P.19, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24). This PFOF is also refuted by recent epidemiological evidence in the record 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. B-1901 P.29 (citing G-1644). Moreover, the Harris study did not isolate 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. B-1901 P.38-39. P.57-64.

876. Most poultry meat is contaminated with *Campylobacter* by transferring chicken feces to the carcass during the slaughter process. Tauxe WDT: p.10, lines 30-31

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness is not qualified to offer an expert opinion on poultry processing.

877. In one study in the United Kingdom, the number of *Campylobacter* organisms on the surface of a fresh chicken carcass, was estimated at 1,000-1,000,000 organisms per chicken. Tauxe WDT: p. 10, lines 37-39; G-1656

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the study in question was published in 1988, and data regarding 15 year-old *Campylobacter* contamination levels in the United Kingdom are not relevant to this proceeding. As the witness himself testifies, between 1996 and 2001 there was a 25% decline in the frequency of *Campylobacter* infections in the United States, and this decline occurred at the same time as several major changes in the food safety system, including efforts within the poultry industry to reduce contamination at slaughter, which have been reinforced by implementation of the HACCP/Pathogen Reduction regulation. Tauxe WDT: P.16 L.24-40.

878. A drop of raw chicken juice would often include an infectious dose of 500 organisms. Tauxe WDT: p. 10, lines 40-41

Bayer/AHI Response: Bayer/AHI dispute this proposed PFOF. Dr. Tauxe's testimony states as a premise for this PFOF that because the surface of a fresh chicken carcass, can contain an estimated at 1,000-1,000,000 organisms per chicken, a drop of raw chicken juice would often include an infectious dose of 500 organisms. The conclusion does not follow. Whether a drop of raw chicken juice would often include an infectious dose of 500 organisms would depend on factors such as the extent and frequency of the original *Campylobacter* load, whether the chicken has been frozen and then thawed, among many other factors. In any event, the witness is not qualified to offer an expert opinion on these factors.

879. The optimal temperature for growth of *Campylobacter jejuni* is the body temperature of a bird. Tauxe WDT: p. 11, lines 2-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

880. In a study from Israel, the most common serogroup isolated from humans was also the most common serogroup isolated from chicken meat. Tauxe WDT: p. 11, lines 35-36; G-1713

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11). In addition, the witness is not qualified to offer an expert opinion on these factors.

881. In the Netherlands, comparison of biotypes and serotypes of human and animal isolates of *C. jejuni* showed that five of the six most common types present in human isolates were also common in chicken isolates, while there was little overlap with the types found in swine; testing the strains by hippurate hydrolysis, a laboratory test used to separate *C. jejuni* from *C. coli* also showed that poultry strains resembled human strains, while strains from pigs did not. This was particularly noteworthy as the Dutch were reported to eat four times as much pork as chicken. Tauxe WDT: p. 11, line 44-p.12, lines 6; G-1698

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11). In any event, the witness is not qualified to offer an expert opinion on this subject.

882. In New Zealand, whole cell DNA restriction digest patterns were used to compare *Campylobacter* from a variety of sources, and it was reported that 50% of human isolates had patterns that were indistinguishable from those isolated from poultry. Tauxe WDT: p. 12, lines 9-12; G-1666

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11). In any event, the witness is not qualified to offer an expert opinion on this subject.

883. *Campylobacter* infections typically last approximately 5-7 days. Tauxe WDT: p. 13, lines 7-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 853.

884. For persons with defective immune systems, including people with congenital defects in their immune system and people with human immunodeficiency virus infections, *Campylobacter* bacteremia can be a severe, debilitating febrile illness requiring multiple and prolonged courses of antibiotic treatment. Tauxe WDT: p. 13, lines 23-29

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because it is misleading and not relevant to this proceeding. *Campylobacter* infections of the blood (bacteremia) occurs in 1% or less of campylobacteriosis cases and is usually self-resolving without treatment. In very rare cases, campylobacteriosis can cause systemic illness in the blood stream (sepsis), and in extremely rare cases, infections can become present in extra-intestinal organs as a result. G-1485 P.7 L.1-3; G-580 P.7, 8. In the rare instances of bacteremia and extraintestinal infections requiring antibiotic treatment, however, and particularly among those patients with underlying immunodeficiency states, parenteral (intramuscular or intravenous, not oral, treatment) combination therapy with imipenem and gentamicin is the recommended treatment, not oral

administration of fluoroquinolones. [Pasternack (B-1909) P.8 L.21-22, P.9 L.1-3; Iannini (B-1905) P.5 L.6-8, L.18-20; (B-273) P.7; (B-742) P.5] In addition, there is no relationship between fluoroquinolone-resistant *Campylobacter* and the development of bacteremia in these patients. B-1906 P.16 L.6-7, P.18 L.6-7, 12-13; B-1908 P.47 L.23-24, P.48 L.1-2; B-1909 P.8 L.21-22, P.9 L.1-3; B-1905; P.5 L. 6-8; B-273 P.7; B-742 P.5.

885. Practice guidelines issued by the Infectious Diseases Society of America and CDC recommend considering empiric treatment of diarrheal illness with antibiotics if the diarrhea is visibly bloody, or is associated with fever, while waiting for the results of stool culture. Tauxe WDT: p. 14, lines 8-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the IDSA guidelines say, "for patients with febrile diarrheal illnesses, especially those believed to have moderate to severe invasive disease, empirical treatment should be considered (after a fecal specimen is obtained for the performance of the studied noted above)." G-261 P.11-13. The introduce this recommendation with a lengthy cautionary statement: "Because of increasing threats from antimicrobial-resistant infections , side effects of treatment with antimicrobial agents, and the possibility of induction of disease-producing phage by antibiotics (such as Shiga-toxin phage induced by quinolone antibiotics), any consideration of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences." Id. at 11. In addition, the guidelines point out that "[s]ome experts recommend avoiding administration of antimicrobial agents to persons in the United States with bloody diarrhea." Id. at 4.

886. In a survey of the physicians in FoodNet about when they ordered stool cultures, they reported that they ordered a stool culture from 79% of patients with bloody stools, and 40% of those without bloody stools. Tauxe WDT: p. 14, lines 17-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is supported by a reference (Hennessy 1998) that is not in evidence and cannot be reviewed.

887. CDC reported that among persons with diarrhea who consulted a physician, 40% were treated with an antimicrobial agent. Tauxe WDT: p. 14, lines 20-22

Bayer/AHI Response: Bayer/AHI do not dispute that the journal article on which the proposed finding of fact is based includes a table showing that 40% of persons with diarrheal illness who "[v]isited a medical person" "[t]ook antibiotics"; however, the proposed finding of fact and the witness neglect to point out that the authors concluded that "[a]ntibiotics are not essential in the treatment of most acute diarrhoeas. Treatment of antibiotics does not reduce the duration or severity of the illness when it is viral in origin, and antibiotic treatment may even prolong asymptomatic carriage of *Salmonella*. In addition, antimicrobial therapy might make persons more susceptible to infection with antimicrobial-resistant pathogens, and unnecessary antibiotic usage can select for antibiotic resistance." G-1790 P.6, 8.

888. The principal textbook of infectious disease used in the U.S. states that treatment with antibiotics seems prudent in those patients with high fever, bloody diarrhea, or more than eight stools per day; in patients whose symptoms have not lessened or are worsening at the

time the diagnosis is made; or in those in whom symptoms have persisted for more than 1 week. Tauxe WDT: p.14, lines 42-45, and p. 15, line 1; B-205

Bayer/AHI Response: Bayer/AHI agree with this PFOF, but want to place it in the context in which the author of the "principal textbook" intended. The cited text appears in a section entitled "Therapy" (B-205 P.6), and that section begins by stating that fluid and electrolyte replacement constitutes the cornerstone of treatment". The author then goes on to state that "persons infected with *C. jejuni* who are ill enough to seek medical attention and from whom a fecal culture is obtained represent only a subset of all those infected. Nevertheless, even among these patients, less than half are candidates for specific antimicrobial therapy."

889. The persons at greatest risk for invasive bloodstream infection with *Campylobacter* are the elderly and the immunocompromised. Tauxe WDT: p. 15, lines 4-5

Bayer/AHI Response: Bayer/AHI do not dispute the PFOF; however, they point out that only 1% or fewer of *Campylobacter* infections results in such infections (bacteremia), that such infections usually are self-resolving without treatment, and that when they require treatment with antibiotics, the recommended treatment is with antibiotics other than quinolones. See Bayer/AHI response to proposed finding of fact 884.

890. In the laboratory-based surveillance for *Campylobacter* from 1982-1986, 102/29468 or 0.03% of the infections were diagnosed by blood culture. Infection in the bloodstream 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 WDT: p. 15, lines 5-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF. They point out, however, that this proposed finding of fact is of little to no relevance here, for the reasons stated in their responses to proposed findings of fact 884 and 889.

Fred Tenover (G-1476)

891. Dr. Tenover is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

892. PFGE uses the fragments produced by restriction enzyme digestion of the chromosomal DNA in the bacterial cell as means of strain identification. Tenover WDT: p. 2, lines 27-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

893. PFGE involves embedding organisms in an agarose gel matrix, lysing (breaking open) the organisms within the gel, and cleaving the chromosomal DNA into 15-20 fragments using enzymes called restriction endonucleases, then inserting slices of agarose containing

the chromosomal DNA fragments into the wells of an agarose gel slab, and separating the DNA restriction fragments into a pattern of discrete bands by applying an electric current to the agarose gel. Tenover WDT: p. 2, lines 28-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

894. In PFGE the DNA restriction patterns of the isolates are compared with one another to determine the genetic relatedness of the bacterial isolates. Tenover WDT: p. 2, lines 38-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

895. Genotype is the genetic makeup of an organism encoded in its DNA. Tenover WDT: p. 3, line 14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

896. Phenotype is the external manifestations of an organism's genetic makeup, i.e., how the organism's genes are expressed. Tenover WDT: p. 3, lines 16-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

897. Isolate is a general term for a pure culture of bacteria presumed to be derived from a single organism, for which no information is available aside from its genus and species. Tenover WDT: p. 3, lines 19-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

898. Genetically related isolates (clones) are isolates that are indistinguishable from each other by a variety of genetic typing tests (e.g., PFGE, multilocus enzyme electrophoresis, or ribotyping) or that are so similar that they are presumed to be derived from a common parent. Tenover WDT: p. 3, lines 28-31

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

899. A strain is an isolate or group of isolates that can be distinguished from other isolates of the same genus and species by biochemical characteristics or genetic characteristics or both. Tenover WDT: p. 3, lines 39-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

900. A strain is a descriptive subdivision of a species. Tenover WDT: p. 3, line 41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

901. Genotyping techniques are essential for epidemiologic investigations of the sources of infection and routes of transmission in human and animal illnesses associated with nosocomial and foodborne bacterial pathogens. Tenover WDT: p. 10, lines 4-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

902. PFGE is a good method for strain delineation of many common bacterial pathogens, and is one of several techniques that have been validated for *Campylobacter* species. Tenover WDT: p. 10, lines 6-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

903. The concentration of an antimicrobial agent (usually in μg/ml) that is required to inhibit the growth of the bacteria in the laboratory test is given is known as the minimal inhibitory concentration, or MIC, of the antimicrobial agent. Tenover WDT: p. 13, lines 9-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

904. In the United States, the National Committee for Clinical Laboratory Standards, or NCCLS, establishes the criteria that are used to interpret the results of antimicrobial susceptibility testing. Tenover WDT: p. 13, lines 13-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

905. The interpretive criteria developed by NCCLS are known as breakpoints. Tenover WDT: p. 13, lines 23-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

906. Breakpoints are used by microbiology laboratories to report the results of their antimicrobial susceptibility tests to physicians. Tenover WDT: p. 13, lines 23-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

907. PK/PD parameters include measurements such as protein binding, the peak serum concentration of the antimicrobial agent in the body (C_{max}) and the total concentration of the drug achievable in the serum over a given time period (as measured by the area under the serum concentration curve, or AUC). Tenover WDT: p. 15, lines 12-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

908. The peak MIC ratio and the 24-h AUC/MIC ratio are major determinants of the activity of fluoroquinolones (e.g., ciprofloxacin). Tenover WDT: p. 16, lines 3-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

909. Peak/MIC ratios should exceed 8, and 24-h AUC/MIC values should be >100, to successfully treat gram-negative infections and to prevent the emergence of resistant organisms during therapy with fluoroquinolones. Tenover WDT: p. 16, lines 5-7

Bayer/AHI Response: Bayer/AHI object to this PFOF because it does not specify whether the treatment is in humans or animals, does not specify the target organism, and does not specify whether it is referring to gut, serum or tissue peak/MIC ratios. Evidence in the record demonstrates that for fluoroquinolones, the best clinical outcomes are associated with peak/MIC ratios >/= 10. B-1913 attachment # 1 P.50 2. If a high enough peak/MIC ratio can be achieved then not only will the parent organism be killed but also the "resistant" mutant. B-1913 attachment # 1 P.51 1. Peak/MIC ratios can easily exceed 10 in the gastrointestinal tract of patients with *Campylobacter* infections that have an MIC of 32 when patients are treated with 500mg ciprofloxacin BID. B-1913 attachment # 1 P.51 1, 2.

Nathan M. Thielman (G-1477)

910. Dr. Thielman is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

911. Patients with campylobacteriosis characteristically present for medical care with an acute diarrheal illness that is clinically indistinguishable from that caused by *Salmonella, Shigella*, and some *E. coli* bacteria. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is an overstatement; as shown in the IDSA guidelines, the clinical features of these diseases are similar but do vary somewhat. G-261 P.10 Table 7. In addition, as Bayer/AHI point out in their responses to proposed findings of fact 1297 and 1304, most persons with *Campylobacter* infections (17 out of 18) do not "present for medical care" at all, most cases are mild, and up to 25% of *Campylobacter* infections may be asymptomatic.

912. In addition to diarrhea, patients with campylobacteriosis frequently complain of abdominal pain, fever, and headaches. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 911.

913. Less frequent symptoms of campylobacteriosis are muscle aches, vomiting and bloody stools. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

914. Untreated, the usual duration of campylobacteriosis is less than five days, but in several outbreaks the duration of illness was considerably longer. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

915. Campylobacteriosis lasting longer than one week has been documented in around 10-20% of patients seeking medical attention, and relapse occurs in about 5-10% of those who do not receive treatment. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

916. Complications from campylobacteriosis, such as associated blood stream infections occur more frequently in the elderly, the very young, or those who are immunocompromised by hypogammaglobulinemia or AIDS. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is misleading. Such complications rarely occur in normal hosts. B-1909 P.6 L.12-16. In addition, although three of the four literature references cited by Thielman are not in evidence, the article that is in evidence, G-581, which pertains to *Campylobacter* bacteremia in England and Wales, indicates (at Page 2) that the occurrence of bacteremia was highest in patients aged 65 years or more and second highest in young adults. The authors of that study stated that the low incidence in children (aged 1 to 14) was not predictable, and noted a similar pattern of age distribution in the USA (Page 6).

917. Short-term complications of campylobacteriosis include colitis, sometimes complicated by toxic megacolon, septic abortion, cholecystitis, pancreatitis, and septic arthritis. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, it is misleading and not relevant to this proceeding for the reasons stated in the response of Bayer/AHI to proposed finding of fact 1350, as well as the fact that these complications are rare.

918. Late complications from campylobacteriosis include rare cases of reactive arthritis and Guillain-Barré syndrome, a serious neurological condition resulting in ascending paralysis and sensory nerve changes. Thielman WDT: p. 2, ¶ 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, it is misleading and not relevant to this proceeding for the reasons stated in their response to proposed findings of fact 917 and 1350.

919. There are no clear-cut clinical features of *Campylobacter*-associated diarrhea that distinguish it from other inflammatory diarrheal illnesses. Thielman WDT: p. 2, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 911; moreover, they note that this concern will become obsolete as the new ProSpecT test, which can identify *Campylobacter* within 2 hours, becomes widely used. B-1143 P.1-3

920. When a given patient presents with an inflammatory diarrheal illness, the microbiologic cause of the patient's illness is unknowable without appropriate culture test results. Thielman WDT: p. 2, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 911; moreover, they note that obtaining an individual patient's medical history can assist in identifying suspected causes (G-1485 P.11 L.31-38) and that use of the new ProSpecT test allows *Campylobacter* infections to be identified within 2 hours. (B-1143 P.1-3)

921. Rather than awaiting culture results, most practicing physicians will initiate empirical antibiotics in an effort to mitigate symptoms promptly and decrease associated complications. Thielman WDT: p. 2, ¶ 4

Bayer/AHI Response: Although Bayer/AHI agree that for moderate to severe cases of inflammatory diarrhea, some medical care providers may start treatment with an antibiotic before stool culture results are available (Ohl WDT: P.10 L.28-30), 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 2 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 (Pasternack WDT: P.13 L.11-21, P.14 L.1-16; Iannini WDT: P.4. L.9-16, P.6 L.1-5). In addition, 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. 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, L1-2, Iannini P.3 L.15-18.

922. Empiric treatment means prescribing a drug that is effective for any number of possible causative pathogens. Thielman WDT: p. 2, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it neglects the importance of considering the characteristics of the host (e.g., fluoroquinolones are not appropriate for patients under 18, pregnant women, and lactating women). JS 25; B-1909 P.4 L.19; G-529 P.3: B-121 P.2.

923. Since early initiation of therapy may have greater impact on resolution of symptoms than delayed treatment, it is often important to start a patient on therapy prior to getting a culture result. Thielman WDT: p. 2-3, ¶ 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness's testimony expressly relates only to perceptions (Thielman WDT: P.2-3 ¶ 4), and actual studies are in conflict with one another on the effectiveness of antibiotic therapy (Pasternack WDT: P.11 L. 19-22, P.12 L.1-22, P.13 L.1-8; B-44 P.7; G-705 P.1; B-816 P.2-3; G-188 P.1, 3, 4, 5; G-172 P.3. For example, the most significant treatment effect was seen in a study in which the patients received treatment on average 4 or more days after the onset of diarrhea. B-1127 P.1; G-172 P.3; Pasternack WDT: P.12 L.14-20. In addition, the IDSA guidelines classify the evidence underlying even their recommendation for selective antibiotic treatment for *Campylobacter* as

being "moderately" supportive and not based on a properly randomized, controlled clinical trial. G-261 P.2-3.

924. The Sanford Guide to Antimicrobial Therapy specifically recommends either ciprofloxacin 500 mg (a fluoroquinolone) by mouth twice daily or azithromycin 500 mg by mouth daily for three days for diarrhea associated with *Campylobacter jejuni*. Thielman WDT: p.3, ¶ 5

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the cited reference in fact recommends antimotility agents and fluids, not antibiotics, as the empiric treatment for moderate cases of *Campylobacter* diarrhea. G-244. Furthermore, for treatment of severe diarrhea, the guide issues cautions in prescribing ciprofloxacin, stating that if a patient has had recent antibiotic therapy, that "Metro 500 mg bid po x 10-14 days" should be added as a "primary suggested regimen". G-244 P.2

925. The Pocket Book of Infectious Disease Therapy lists erythromycin and fluoroquinolones as the preferred agents for diarrheal illnesses associated with *Campylobacter jejuni*. Thielman WDT: P.3, ¶ 6

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the cited reference is not in evidence and available for review, and they cannot assume that the witness's characterization is accurate and not misleading due to the witness's mischaracterization of the Sanford and IDSA references. See Bayer/AHI responses to proposed findings of fact 924 and 926.

926. The Infectious Diseases Society of America "Practice Guidelines for the Management of Infectious Diarrhea" recommends fluoroquinolones for adults with diarrheal illnesses. Thielman WDT: p 3, ¶ 6; G-261

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the IDSA guidelines in fact recommend other drugs, too, and do not recommend the use of fluoroquinolones for all adults with diarrheal illness. G-261 P.11-13.

927. In a study supported by Bayer Corporation and designed to evaluate the safety and efficacy of ciprofloxacin as empirical treatment for children with acute inflammatory diarrhea, the authors concluded that ciprofloxacin was as safe as intramuscular ceftriaxone. Thielman WDT: p 3, ¶ 6

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they note that the conclusions of the report specifically stated: "In conclusion oral ciprofloxacin was as safe and effective as intramuscular ceftriaxone for the empiric treatment of ambulatory children with acute invasive diarrhea requiring an emergency room visit." Moreover, they point out that ciprofloxacin is not approved for use in children under 18 in the United States. Joint Stipulation 25.

928. Fluoroquinolones are generally well tolerated and easily prescribed on an outpatient basis. Thielman WDT: p.4, ¶ 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although Bayer/AHI agree that fluoroquinolones are generally well tolerated, the statement "easily prescribed" is unclear and connotes the potentially imprudent dispensing of the antibiotic.

929. Fluoroquinolone therapy typically consists of ciprofloxacin 500 mg administered twice daily for three to five days for diarrheal illnesses. Thielman WDT: p.4, ¶ 7

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that the Sanford Guide to Antimicrobial Therapy recommends antimotility agents and fluids, not antibiotics, as the empiric treatment for moderate cases of *Campylobacter* diarrhea. The guide also cautions that if a patient has had recent antibiotic therapy, that "Metro 500 mg bid po x 10-14 days" should be added as a "primary suggested regimen". G-244 P.2

930. Because it takes up to 3 days to identify *Campylobacter* in a stool culture and would take several additional days to document resistance (particularly since resistance-testing is not routinely performed), practicing clinicians have no way of knowing whether the *Campylobacter* associated with a particular illness is fluoroquinolone-resistant for approximately one week - an interval during which the illness will either resolve on its own, persist or progress with complications, particularly in immunocompromised patients. Thielman WDT: p. 4, ¶ 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. With the availability of the new ProSpecT test, clinicians can now identify *Campylobacter* within 2 hours (B-1143 P.1-3) and prescribe an antibiotic, if prudent, on that basis. Furthermore, if the new ProSpecT test is not available, azithromycin is an effective, broad-spectrum alternative that is well-tolerated and to which resistance is low. B-1905 P.4 L.8-11; B-1909 P.13 L. 11-21, P.14 L.1-16; G-1457 P.6 L.44-45; G-1469 P.5 L.3-5; G-557 P.3; B-816 P.2; Iannini WDT: P.4 L.9-16, P.6 L.1-5.

931. While fluoroquinolones are not approved for the treatment of gastroenteritis in children in the U.S., physicians sometimes use drugs, including fluoroquinolones, in an off-label manner. Thielman WDT: p. 4, ¶ 8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it the witness's testimony is based only on his personal experience and is not specific to any off-label use of ciprofloxacin to treat gastroenteritis. Moreover, it is inconsistent with the ISDA guidelines, of which the witness was a co-author, regarding the treatment of gastroenteritis in children. G-261 p. 13;

932. Macrolides, such as erythromycin and azithromycin, can produce undesirable side effects including gastrointestinal distress. Thielman WDT: p. 4, ¶ 9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although erythromycin can produce undesirable side effects, azithromycin is generally quite well-tolerated, and is usually tolerated by individuals who are intolerant to erythromycin. B-1909 P.13 L.20-21

933. Although *Campylobacter*-associated diarrhea can be treated with a macrolide antibiotic such as erythromycin, fluoroquinolones are commonly, and appropriately, prescribed as first-line therapy for patients suffering with this illness especially since most gastroenteritis is treated empirically and fluoroquinolones are a broad spectrum antimicrobial that can be effective against most pathogenic gastrointestinal bacteria. Thielman WDT: P.4, ¶ 10

Bayer/AHI Response: Bayer/AHI dispute this PFOF. While the empiric use of fluoroquinolones may have been a popular first-line therapy, 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 2 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. B-1909 P.13 L.11-21, P.14 L.1-16; B-1905 P.4 L.9-16, P.6 L.1-5 More importantly, routine empiric antimicrobial treatment is generally not recommended at all for diarrheal illness (B-1905 P.3 L.15-18; G-1485 P.9 L.36-46, P.10 L.1-7); and more recent treatment guidelines are more cautious about recommending the use of such therapy (Pasternack WDT: 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 WDT: P.3 L.15-18; B-857 P.2; G-253 P.5; G-707 P.9).

934. Practice guidelines and reference books, recognize that illness associated with *Campylobacter* are indistinguishable clinically from illness caused by other pathogens which are unresponsive to macrolides but easily treated with fluoroquinolones. Thielman WDT: p.4, ¶ 10

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 911 and 939.

935. Fluoroquinolone antibiotics remain a critical first line therapy for *Campylobacter*-associated diarrhea. Thielman WDT: p. 5, ¶ 11

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1342 and because the actual studies are in conflict with one another on the effectiveness of antibiotic therapy (Pasternack WDT: P.11 L.19-22, P.12 L.1-22, P.13 L.1-8; B-44 P.7; G-705 P.1; B-816 P.2-3; G-188 P.1, 3, 4, 5; G-172 P.3. In addition, the IDSA guidelines classify the evidence underlying even their recommendation for selective antibiotic treatment for *Campylobacter* as being "moderately" supportive and not based on a properly randomized, controlled clinical trial. G-261 P.2-3. Lastly, 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 2 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. B-1909 P.13 L.11-21, P.14 L.1-16; B-1905 P.4 L.9-16, P.6 L.1-5.

Linda Tollefson (G- 1478)

936. Dr. Tollefson is qualified as an expert to testify as to the matters set forth in her written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

937. The National Antimicrobial Resistance Monitoring System (NARMS) for zoonotic enteric pathogens in animals and humans became operational in January 1996 but planning began in 1995. Tollefson WDT: page 2, lines 16-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

938. NARMS is an antimicrobial resistance monitoring system that helps ensure the continued safety and effectiveness of antimicrobial drugs for use in both animals and humans. Tollefson WDT: page 2, lines 19-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although a goal of the NARMS system may be to ensure the continued safety and effectiveness of antimicrobial drugs for use in both animals and humans, it problems with both the human NARMS and animal NARMS arms of the *Campylobacter* resistance monitoring lead to inaccurate results. This PFOF is refuted by A-200 P.5 L.18- P.6 L.15, P.7 L.16-19, P.8 L.11-13, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9, P.17 L.23-24 – P.18 L.1-2, P.19 L.21-23, P.19 L.23 – P.20 L.1-2, P.20 L.14-15, P.20 L.18-21, P.21 L.10-13, P.21 L.14-15, P.25 L.18-22, P.25 L.22-23, P.27 L.5-24, P.54 L.17-21, P.55 L.6-7, P.30 L.1 – P.33 L.17; A-199 P6. L.21-26, P.11 L.14-19, P.11 L.22 – P.12 L.2, P. 12 L. 16 – P. 15 L. 15; B-1900 P. 44 L. 2-3, P.50 L.8-10; B-1901 P.43; B-1913 P.45 Attachment 1 ¶ 8, P.55 Attachment 1 ¶ 4; G-1478 P.9 L.36-46.

939. Development of antimicrobial resistant bacteria is a hazard associated with drug use in both human and veterinary medicine. The selection of antimicrobial resistant bacterial populations is a consequence of exposure to antimicrobial drugs and can occur from human, animal, and agricultural uses. Tollefson WDT: page 2, lines 27-32

Bayer/AHI Response: Bayer/AHI object to this PFOF as a compound of two proposed facts. Bayer/AHI agree with the second sentence but dispute the first sentence. The first sentence is refuted by the fact that clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

940. The use of antimicrobial drugs in food-producing animals is sometimes necessary to treat illnesses caused by bacteria. Unfortunately, food-producing animals can become reservoirs of bacteria capable of being transferred on food. Tollefson WDT: page 2, lines 32-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

941. Resistant food borne pathogens that develop in response to antimicrobial drug use in food animals can be transmitted to humans through consumption of the contaminated food, among other routes. Tollefson WDT: page 2, lines 36-39

Bayer/AHI Response: Bayer/AHI do not in general dispute the fact that resistant food borne pathogens that develop in response to antimicrobial drug use in food animals can be transmitted to humans through consumption of the contaminated food, among other routes. Bayer/AHI dispute the extent to which this happens in fluoroquinolone-resistant *Campylobacter* from poultry because chicken is not a major source of campylobacteriosis B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30, and neither is turkey A-201 P.13 L.6-7; A-204 P.15 L.11-15.

942. If the resistant bacteria cause an illness in a consumer who needs treatment, medical therapy may be delayed, compromised or ineffective if the pathogenic bacteria are resistant to the drug used for treatment. Tollefson WDT: page 2, lines 40-43

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to medical therapy being compromised or ineffective for fluoroquinolone-resistant *Campylobacter* infections because the clinical significance of *Campylobacter* isolates deemed to be "resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

943. Several bacteria species are known to carry multidrug resistance genes that may confer resistance to a number of antimicrobials. Tollefson WDT: page 3, lines 1-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to the issues for this hearing (fluoroquinolone resistance and *Campylobacter*). There is no indication that having fluoroquinolone resistance confers any other resistance and because there is no indication that the genetic material conferring fluoroquinolone resistance can be transferred from bacterial species. The horizontal transfer of genes conferring fluoroquinolone resistance in *Campylobacter* has not been demonstrated. [Joint Stipulation 40].

944. For foodborne pathogens, especially for those such as *Salmonella* and *Campylobacter* that are rarely transferred from person to person in developed countries, the most likely source of antibiotic resistance is use of antimicrobials in food-producing animals. Tollefson WDT: page 3, lines 8-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF ignores the likely possibility that foodborne pathogens such as *Campylobacter* can become resistant from human use of fluoroquinolones, become present in the environment and be transferred to humans (and poultry) from the environment. This PFOF is therefore refuted by the fact that human use of a fluoroquinolone, including use for treatment of campylobacteriosis, can lead to the emergence of

fluoroquinolone-resistant *Campylobacter* in the treated individual. Joint Stipulation 8; B-127 P.1; G-589 P.4, 6; G-707 P.11. Sewage treatment plants discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of resistant bacteria, including fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9. *Campylobacter* can be isolated from many species of wild animals including, field mice, foxes, rabbits, badgers, and wild birds including passiformes and columiformes. B-1908 P.9 L.18-29; G-1459 P.3 L.21-23; B-263. *Campylobacter* is found in the environment, including in water and at beaches. G-1459 P.3 L.21-23; B-1910 P.4 L.4-6; G-75. *Campylobacter*, including fluoroquinolone-resistant *Campylobacter* are frequently isolated in surface and ground waters, including drinking water supplies. B-1910 P.4 L.9-10.

945. Antimicrobial agents can promote the emergence of resistant bacteria among both target pathogens and normal bacterial flora. Tollefson WDT: page 3, lines 12-14

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF as a general proposition. This finding of fact is so general and nonspecific, however, that it has little or no applicability to the specific issues in this hearing.

946. The normal bacterial flora in many species of animals include foodborne pathogens such as *Campylobacter*. *Campylobacter* can cause severe foodborne illness in humans even though they are non-pathogenic in animals such as poultry. Scientific evidence supporting these statements comes from a number of sources, including outbreak investigations, laboratory surveillance, molecular subtyping, and studies on infectious dose and carriage rates. Tollefson WDT: page 3, lines 17-30; Exhibit G-285; Exhibit G-702; Exhibit B-252

Bayer/AHI Response: Bayer/AHI object to this PFOF because it is a compound set of proposed facts. Bayer/AHI do not dispute the first sentence. Bayer/AHI dispute the second and third sentences to the extent that "severe" is undefined and overstates the nature of campylobacteriosis, a disease that in the majority of cases is so mild that patients do not seek medical care. The evidence shows that only 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. G-1485 P.7 L.1-3; G-580 P.7, 8. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4.

947. *Campylobacter* has been cited as the most common known cause of foodborne illness in the United States. Tollefson WDT: page 3, lines 36-37; G-615

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to the United States, which is the relevant location for the issues of this hearing. As relates to the United States, this PFOF is refuted by B-1042 in which CDC reports that the incidence of *Salmonella* infections was greater than *Campylobacter* infections.

948. Foodborne diseases have a major public health impact in the United States. A recent reliable publication estimates that foodborne infections cause 5,000 deaths and 76 million foodborne illnesses annually in the United States. Tollefson WDT: page 3, lines 32-35; G-410.

Bayer/AHI Response: Bayer/AHI object to this PFOF because it does not accurately reflect the current public health impact of foodborne disease in the United States. This PFOF characterizes as "recent" G-410 (Mead, et. al 1999) which on its face used data from 1996 and 1997 to estimate the incidence of foodborne illness. (G-410 P.3). It is undisputed that from 1996 to 2001 foodborne disease rates in the United States have fallen significantly. By way of specific relevant example, in the United States, the incidence of *Campylobacter* infections as measured through the Foodborne Disease Active Surveillance Network (FoodNet) decreased by 27% between 1996 and 2001. G-1452 P.5 L.21-23, Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28.

949. Development of resistance in foodborne pathogens complicates the medical and public health concern surrounding foodborne disease as important treatment options are compromised or lost. Tollefson WDT: page 3, lines 38-42; G-28; B-252

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates to the issues for this hearing (fluoroquinolone resistance and *Campylobacter*). For *Campylobacter* the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

950. In 1995, the FDA approved sarafloxacin for control of mortality caused by *E. coli* in chickens and turkeys. In 1996, enrofloxacin was also approved for these indications and for control of turkey mortality associated with *Pasteurella multocida* (fowl cholera) infections. Tollefson WDT: page 3, line 46 through page 4, line 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

951. Sarafloxacin and enrofloxacin are fluoroquinolone antimicrobials that are administered in the drinking water for birds. Other fluoroquinolones, including Bayer Corporation's ciprofloxacin, are important in the treatment of several serious diseases in humans. Tollefson WDT: page 3, line 46 through page 4, line 7

Bayer/AHI Response: Bayer/AHI object to this PFOF because it is a compound set of 2 proposed facts that are unrelated to each other. Moreover, the PFOF is inaccurate because sarafloxacin is no longer on the market. Additionally, as proposed, the PFOF does not describe the limitations on the use of enrofloxacin as approved nor does it define the nature of human disease for which the human drug ciprofloxacin is used. Bayer/AHI do not object to 2 separate proposed findings of fact addressing these concerns as follows: 951(a). Enrofloxacin is a

fluoroquinolone antimicrobial that is administered to sick chickens and turkeys by prescription only, for therapeutic purposes only, in the drinking water for birds. 951(b). Fluoroquinolones, including Bayer Corporation's ciprofloxacin, are important in the treatment of infectious diseases in humans.

952. The approval of the fluoroquinolones for use in animals intended as food raised serious public health concerns because of the potential risk of transfer of resistant bacteria from animals to humans. Tollefson WDT: page 4, lines 7-12

Bayer/AHI Response: Bayer/AHI object to this PFOF to the extent that, as written, it is out of historical context. It is clear from Dr. Tollefson's testimony that this passage is discussing the preapproval time frame, when the approval of fluoroquinolones for use in food animals was being considered by CVM. Therefore, Bayer/AHI do not object to a more accurate PFOF stating: Prior to the approval of the fluoroquinolones for use in animals intended as food, serious public health concerns were raised about the potential risk of transfer of resistant bacteria from animals to humans.

953. Cross-resistance occurs throughout the drug class of fluoroquinolones; thus, resistance to one fluoroquinolone compromises the effectiveness of all fluoroquinolone drugs whether used in animals or humans. Tollefson WDT: page 4, lines 12-16

Bayer/AHI Response: Bayer/AHI object to this PFOF because the conclusion stated in the second part of the PFOF does not necessarily follow the premise stated in the first part of the PFOF. Bayer/AHI do not dispute that cross-resistance occurs throughout the drug class of fluoroquinolones. Bayer/AHI do not agree that "resistance to one fluoroquinolone compromises the effectiveness of all fluoroquinolone drugs whether used in animals or humans" because the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint, indicating loss of clinical effectiveness, has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

954. FDA's joint Veterinary Medicine and Anti-Infective Drugs Advisory Committee was united in advising the agency that, if the products were to be approved, several restrictions should be placed on the use of the drugs in order to attempt to minimize the public health risks related to the development of resistant bacteria in animals. These restrictions included approval of fluoroquinolones only for therapeutic use by veterinary prescription, prohibition of extra-label use, and establishment of a nationally representative surveillance system to monitor resistance trends among both human and animal enteric bacteria. Tollefson WDT: page 4, lines 18-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

955. Shortly before FDA approved sarafloxacin in August 1995, Dr. Tollefson was asked to develop an antimicrobial resistance monitoring system consistent with the advisory

committee's recommendation. Dr. Frederick Angulo of CDC, Dr. Paula Fedorka-Cray of USDA, and Dr. Tollefson were the primary scientists involved in designing, developing and implementing an appropriate monitoring system. That system became operational in January 1996 and is known as the National Antimicrobial Resistance Monitoring System or NARMS. Tollefson WDT: page 4, lines 38-47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

956. The goals and objectives of NARMS are to: provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in enteric organisms from the human and animal populations; provide information to veterinarians, physicians and public health authorities so that timely action can be taken to protect public health; prolong the life span of approved drugs by promoting the prudent use of antimicrobials; identify areas for more detailed investigation; and guide research on antimicrobial resistance. Tollefson WDT: page 5, lines 29-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

957. NARMS consists of three testing sites, or arms: 1) human (DHHS/CDC), 2) animal (USDA Agricultural Research Service, Food Safety Inspection Service, and Animal Plant Health Inspection Service) and 3) retail meats (DHHS/FDA/CVM). Tollefson WDT: page 6, lines 18 to 24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

958. *Campylobacter* isolates from poultry were not added to the animal arm of NARMS until 1998. Tollefson WDT: page 9, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

959. The animal NARMS surveillance program reported the following levels of resistance to fluoroquinolones in the chicken carcass isolates of *Campylobacter jejuni*: 9.4% for 1998; 9.3% for 1999; 10.4% for 2000; and, for 2001, 17.6% by the "conventional" method and 20.3% by the "optimized" method. Tollefson WDT: page 12, lines 2-7; G-119; G-205; G-206; G-207; G-760; G-1363

Bayer/AHI Response: Bayer/AHI do not dispute that the animal arm of NARMS reported the levels of resistance to fluoroquinolones in the chicken carcass isolates of *Campylobacter jejuni* described in PFOF 959. Bayer/AHI dispute that the levels of resistance to fluoroquinolones in the chicken carcass isolates of *Campylobacter jejuni* reported by the animal arm of NARMS are an accurate representation of national poultry resistance levels. This is the result of problems or changes in sampling sources and schemes, problems or changes in isolation methods, and problems or changes in resistance testing methods. G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8.

960. The animal arm of NARMS received only a subset of all the *Campylobacter* isolates from poultry, which resulted in an underestimate of fluoroquinolone resistance because some of the isolates that were perceived as not *Campylobacter jejuni/coli* because they were not susceptible to nalidixic acid were in fact resistant *Campylobacter jejuni/coli*, meaning they were resistant to both nalidixic acid and fluoroquinolones. Tollefson WDT: page 9, lines 31-46

Bayer/AHI Response: Bayer/AHI agree that the problems described in this PFOF were among many problems with the animal arm of NARMS from 1996 to 2001 which render inaccurate and unreliable the reported levels of fluoroquinolone resistance from *Campylobacter* isolates. See also G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8.

961. In 2001, retail meat testing was added to NARMS. Tollefson WDT: page 12, line 9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

962. Retail food represents the point of exposure that is closest to the consumer and, when combined with data from slaughter plant samples, provides a more representative picture of the prevalence of resistant pathogens in products derived from food-producing animals. Tollefson WDT: page 12, lines 9-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF as relates specifically to poultry and fluoroquinolone-resistant *Campylobacter*. Evidence in the record refutes both that retail poultry eaten by consumers at home is a major source of campylobacteriosis (B-1901 P.19, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24) and that "data from slaughter plant samples, provides a more representative picture of the prevalence of resistant pathogens in products derived from food-producing animals" (G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8).

963. The poultry fluoroquinolone drugs were approved only for therapeutic use, by veterinary prescription. After approval, one of the first actions the Center took to minimize the public health risks for these drugs was to prohibit all extra-label uses of fluoroquinolones in food producing animals. This order, which became effective in August 1997 (21 CFR 530.4), also provided the Center with the authority necessary to enforce the prohibition. Violation of the prohibition could result in seizure of the drug and, in the case of repetitive or egregious situations, injunction or prosecution against the persons performing the prohibited act. Tollefson WDT: page 14, lines 13-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

964. FDA established the National Antimicrobial Resistance Monitoring System 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. Evaluating the consequences of fluoroquinolone use in poultry was one of the specific purposes for which NARMS was created. Tollefson WDT: page 14, lines 26-35

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

965. After approval of sarafloxacin in 1995 and enrofloxacin for poultry use in 1996, NARMS enabled CVM to detect fluoroquinolone resistance not only among the target pathogen, *E. coli*, but also among the human foodborne pathogen, *Campylobacter*. Tollefson WDT: page 14, lines 45-47 and page 15, lines 1-2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Although a goal of the NARMS system may have been to detect fluoroquinolone resistance in *Campylobacter* from poultry, it is not true that the animal arm of NARMS as actually implemented enabled CVM to do so accurately. This is because of problems or changes in sampling sources and schemes, problems or changes in isolation methods, and problems or changes in resistance testing methods. G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14,. P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8.

966. Information from other CVM compliance and surveillance programs, such as monitoring the extra-label use prohibition and the tissue residue program, provided evidence that the fluoroquinolones were not being widely misused in food-producing animals. Tollefson WDT: page 15, lines 2-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

967. By late 1999 – early 2000, all evidence available led CVM to conclude that the *E. coli* and *Campylobacter* organisms developed resistance to fluoroquinolones from the use of the fluoroquinolone drugs in chickens and turkeys even under the approved, labeled conditions of use. Tollefson WDT: page 15, lines 7-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. To the extent that the evidence referred to in this PFOF is NARMS data, the conclusion stated by this PFOF is not based on accurate data. This is because animal NARMS data is inaccurate due to problems or changes in sampling sources and schemes, problems or changes in isolation methods, and problems or changes in resistance testing methods. In addition, since NARMS was not established until after approval and marketing of fluoroquinolones for use in poultry, no valid baseline exists for measuring changes in resistance related to use. G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8.

968. The reason that there were few community-acquired fluoroquinolone-resistant *Campylobacter* infections in humans until 1996 is that there is little human-to-human transmission of these infections in the United States because generally the numbers of organisms present are low and fecal-oral transmission is required. Tollefson WDT: page 15, lines 24-32

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF ignores the likely possibility that foodborne pathogens such as *Campylobacter* can become resistant from human use of fluoroquinolones, can become present in the environment and can be transferred to humans (and poultry) from the environment. This PFOF is therefore refuted by the fact that human use of a fluoroquinolone, including use for treatment of campylobacteriosis, can lead to the emergence of fluoroquinolone-resistant *Campylobacter* in the treated individual. Joint Stipulation 8; B-127 P.1; G-589 P.4, 6; G-707 P.11. Sewage treatment plants discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of resistant bacteria, including fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9. *Campylobacter* can be isolated from many species of wild animals including, field mice, foxes, rabbits, badgers, and wild birds including passiformes and columiformes. B-1908 P.9 L.18-29; G-1459 P.3 L.21-23; B-263. *Campylobacter* is found in the environment, including in water and at beaches. G-1459 P.3 L.21-23; B-1910 P.4 L.4-6; G-75. *Campylobacter*, including fluoroquinolone-resistant *Campylobacter* are frequently isolated in surface and ground waters, including drinking water supplies. B-1910 P.4 L.9-10.

969. The agency contracted with a quantitative risk assessment expert to develop a quantitative risk assessment model to assess the human health impact of infections caused by fluoroquinolone-resistant *Campylobacter* organisms transmitted to humans through contaminated poultry. A mathematical model was derived to determine the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens. Tollefson WDT: page 15, line 34 through page 16, line 25

Bayer/AHI Response: Bayer/AHI object to this PFOF because it compounds multiple proposed facts. Bayer/AHI do not dispute that CVM/FDA contracted with a person to develop a risk assessment model. The resulting CVM/Vose risk assessment is neither quantitative nor a risk assessment as that term is generally accepted by risk assessment professionals. This PFOF is refuted by B-1901 P.11, P.16-19, P.25, P.67 and B-1904 P.8 L.5 - P.10 L.18 (excluding P.9 L.3-6, and P.9 L.10 - P.10 L.2), P.16 L.19 - P.17 L.2, P.25 L.9-10. Moreover, the CVM/Vose model does not demonstrate the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens. This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6.

970. The potential hazard to humans from the use of fluoroquinolones in poultry is not limited to infections caused by consumption of, or contact with, chickens contaminated with resistant *Campylobacter* but extends to cross-contaminated food that is generally eaten raw, such as

vegetables, that are contaminated in the consumer's kitchen by chickens contaminated with resistant *Campylobacter*. Tollefson WDT: page 16, lines 10-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by the fact that contact with and consumption of chicken in the home is protective (negatively correlated to campylobacteriosis). Evidence in the record refutes that retail poultry eaten by consumers at home is a major source of campylobacteriosis (B-1901 P.19, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24). This PFOF is also refuted by evidence 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. B-1901 P.29 (citing G-1644).

971. What the CVM *Campylobacter* risk assessment shows is that not only was there a quantifiable impact on human health from fluoroquinolone-resistant *Campylobacter* infections in humans acquired from chicken, but that the risk was substantial. Tollefson WDT: page 16, lines 30-34

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The CVM risk assessment does not determine a human health impact. This PFOF is further refuted by evidence showing that the CVM risk assessment model overestimates the true fraction of fluoroquinolone-resistant *Campylobacter* in chickens that come from fluoroquinolone use. B-1901 P.79. The CVM/Vose model does not demonstrate the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens. This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6. This PFOF is a mischaracterization of what the CVM *Campylobacter* risk assessment shows. The risk assessment does not show that there is any risk at all, or any "quantifiable impact on human health from fluoroquinolone-resistant *Campylobacter* infections in humans acquired from chicken", let alone a substantial one [Cox, B-1901, PP. 15, 40, 57, 58].

972. To put the CVM *Campylobacter* risk assessment in perspective, the risk assessment calculated risks relative to various decreasing subsets of the U.S. population, beginning with all citizens, and then all citizens with campylobacteriosis, and so on. Those people who actually had campylobacteriosis, were ill enough to see a physician, and considered ill enough by the physician to be prescribed an antibiotic represent the people who are most seriously at risk from the failure of fluoroquinolone therapy. Tollefson WDT: page 16, lines 34-43

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The CVM/Vose risk assessment is neither quantitative nor a risk assessment as that term is generally accepted by risk assessment professionals. This PFOF is refuted by B-1901 P.11, P.16-19, P.25, P.67 and B-1904 P.8 L.5 - P.10 L.18 (excluding P.9 L.3-6, and P.9 L.10 - P.10 L.2), P.16 L.19 - P.17 L.2, P.25 L.9-10. Moreover, the CVM/Vose model does not demonstrate the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens. This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6. Moreover, it has not been demonstrated that these people "are most seriously at risk

from the failure of fluoroquinolone therapy", since no such risk has been found to exist (i.e., the hazard identification portion of CVM's risk assessment did not identify any such risk) [Cox, B-1901, PP. 15, 40, 57, 58].

973. The CVM *Campylobacter* risk assessment showed that for 1999, the estimated mean number of people in the United States infected with fluoroquinolone-resistant *Campylobacter* from consuming or handling chicken, who saw a physician for their illness, and who subsequently received a fluoroquinolone as therapy is approximately 10,000 per year. This impact is a mean estimate, a value near the center of all feasible values for the expected number of people impacted. The 95th percentile estimate is just over 15,000 people impacted per year. Those 10,000 to 15,000 people were likely to have received ineffective or less effective therapy for their infections, resulting in adverse health effects. Tollefson WDT: page 15, line 34 through page 17, line 9; G-953

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The CVM/Vose risk assessment is neither quantitative nor a risk assessment as that term is generally accepted by risk assessment professionals. This PFOF is refuted by B-1901 P.11, P.16-19, P.25, P.67 and B-1904 P.8 L.5 - P.10 L.18 (excluding P.9 L.3-6, and P.9 L.10 - P.10 L.2), P.16 L.19 - P.17 L.2, P.25 L.9-10. Moreover, the CVM/Vose model does not demonstrate the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens nor does it demonstrate any "adverse health effects". This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6.

This PFOF is not a fact but a pure speculation combined with a policy decision to arbitrarily (i.e., independently of relevant facts or data) attribute a certain number of cases to enrofloxacin use in chickens. The assertion that "Those 10,000 to 15,000 people were likely to have received ineffective or less effective therapy for their infections, resulting in adverse health effects" is unjustified speculation, as no diminution in the effectiveness of therapy has been found [B-1901 P.30; G-1679 P.5, 6, 54, 56, 57; B-1900, B-1902.]. It is not a fact that "The CVM *Campylobacter* risk assessment showed that for 1999, the estimated mean number of people in the United States infected with fluoroquinolone-resistant *Campylobacter* from consuming or handling chicken, who saw a physician for their illness, and who subsequently received a fluoroquinolone as therapy is approximately 10,000 per year." It did not "show" this at all. Rather, the CVM risk assessment made a policy decision to attribute this number of cases to "consuming or handling chicken". The 10,000 number is in effect a policy input to the model, not a factual output or finding, as CVM portrays it here and elsewhere [B-1901, P. 60-62]. Thus, it is inaccurate to represent this number as a finding of fact. (The relevant facts, which show a significant reduction in consumer risk from "consuming or handling chicken", were not even mentioned in CVM's model, presumably because CVM's policy decision to attribute all domestically acquired, non-treatment resistant campylobacteriosis cases to chicken regardless of their true causes [Bartholomew, G-1454 P.9 L.28, 29] superseded such factual inputs.) Policy decisions about how many cases will be attributed to a specific source, independent of the data, should not be presented as findings of fact or as findings "shown" by the model, but rather should be listed as what they are: policy decisions.

974. The CVM *Campylobacter* risk assessment modeled the general U.S. population, but it is likely that the impact of a fluoroquinolone-resistant *Campylobacter* infection is greater to some segments of the U.S. populations. Several population groups have increased susceptibility to foodborne infections, such as persons with lowered immunity due to HIV/AIDS and those on medications for cancer treatment or for organ transplantation, as well as pregnant women and their fetuses, young children, and the elderly. Tollefson WDT: page 17, lines 14-31

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The CVM/Vose risk assessment is neither quantitative nor a risk assessment as that term is generally accepted by risk assessment professionals. This PFOF is refuted by B-1901 P.11, P.16-19, P.25, P.67 and B-1904 P.8 L.5 - P.10 L.18 (excluding P.9 L.3-6, and P.9 L.10 – P.10 L.2), P.16 L.19 – P.17 L.2, P.25 L.9-10. Moreover, the CVM/Vose model does not demonstrate the relationship between the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone-resistant *Campylobacter* in chickens nor does it demonstrate any "impact of a resistant fluoroquinolone infection". This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6.

The CVM *Campylobacter* risk assessment used FoodNet sample data, which does not represent or model the general US population. G-1468 P.5 L.17-21; G-1452 P.4 L.2-22; A-200 P.17 L.23-24 – P.18 L.1-2; A-199 P.11 L.14 – P.13 L.24; A-199 P.44-76; A-52; B-1879. This assumes that there is some "impact of a fluoroquinolone-resistant *Campylobacter* infection" on human health. No such impact (of resistance per se) has been found, i.e., it has not been shown that AIDS patients or other groups of patients with resistant *Campylobacter* recover less quickly than similar patients infected with susceptible strains.

975. In concert with its mission to protect the safety of the food supply, it is FDA's responsibility to initiate regulatory activity long before an imminent threat to human health is evident. With respect to the hazard presented by antimicrobial-resistant foodborne pathogens, it is especially important to take action early because the nature of the problem is dynamic and cumulative. Tollefson WDT: page 19, lines 4-16

Bayer/AHI Response: Bayer/AHI object to this PFOF because it is a compound of two separate proposed findings of fact. As to the first sentence, FDA's "responsibilities" are matters of law, regardless of CVM's characterizations or interpretations herein. As to the second sentence, this PFOF is not applicable to fluoroquinolone-resistant *Campylobacter* and poultry, because the evidence in the record does not demonstrate that such a hazard exists. Bayer/AHI dispute the contention that poultry is a major source of fluoroquinolone-resistant *Campylobacter*. The evidence shows that chicken is not a major source of campylobacteriosis B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30, and neither is turkey. A-201 P.13 L.6-7; A-204 P.15 L.11-15. Also, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15

L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

From the premise that "the nature of the problem is dynamic and cumulative", it does not follow that "it is especially important to take action early". In this case, taking earlier regulatory action will probably do more to harm public health than delaying regulatory action [Cox, B-1901, p. 87].

976. Unlike a static situation such as that which exists with residues of antimicrobial drugs in the tissues of food-producing animals, the development of resistant pathogens is the result of selective pressure from antimicrobial use and thus can be expected to increase over time rather than remain stable. Tollefson WDT: page 19, lines 10-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the phrases "static situation" and "expected to increase over time" are not defined and Bayer is unable to adequately interpret this sentence. Moreover, this finding of fact is repetitive of other findings of fact where Bayer has already agreed that use of fluoroquinolones may act as a selective pressure, for example # 1577. This is not a finding of fact, but an erroneous assumption. In biomathematical models of emerging resistance, it is not true that "the development of resistant pathogens is the result of selective pressure from antimicrobial use" implies "and thus can be expected to increase over time rather than remain stable", as assumed here.

977. CVM remains concerned that the harm of fluoroquinolone-resistant *Campylobacter* will continue to increase as more people will be unable to be effectively treated with fluoroquinolones when those drugs are needed for foodborne illness. Tollefson WDT: page 19, lines 18-22

Bayer/AHI Response: Bayer/AHI can neither admit or deny this PFOF in that they cannot attest to what concerns CVM. Bayer/AHI disputes that there is any evidence to support any "harm of fluoroquinolone-resistant *Campylobacter*" because the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14). This PFOF is further refuted by B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

978. CVM considers the fluoroquinolone resistance among *Campylobacter* found on chicken and turkey carcasses from the animal arm of NARMS to be underestimated until 2001 because of the methods employed in isolating the organisms, which selected only nalidixic acid-susceptible organisms. Tollefson WDT: page 19, lines 22-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

979. The retail meat studies undertaken by CVM show a greater prevalence of fluoroquinolone resistance among *Campylobacter* isolates, using methods that did not restrict the bacterial

populations to nalidixic acid-susceptible strains; this prevalence is similar to that found among the *Campylobacter jejuni* isolated from chicken carcasses in the animal arm of NARMS during 2001. Tollefson WDT: page 19, lines 28-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The prevalence of resistance among the *Campylobacter jejuni* isolated from chicken carcasses in the animal arm of NARMS during 2001 is inaccurate due to problems or changes in sampling sources and schemes, problems or changes in isolation methods, and problems or changes in resistance testing methods. G-1478 P.9-11, P.19 L.22-27; B-1913 P.45 Attachment 1 ¶ 8; A-200 P.4 L.1-3, P.5 L.18-21, P.5 L.23 – P.6 L.1, P.6 L.3-5, P.6 L.13-15, P.6 L.22-23, P.7 L.19-22, P.8 L.11-13, P.8 L.20-21, P.9 L.12-14, P.13 L.13-18 (citing G-644), P.12 L.7-9; A-199 P.5-6, P.7-8.

980. As a public health official, veterinarian and epidemiologist, Dr. Tollefson has examined the data demonstrating the selection of resistant strains of bacteria by fluoroquinolones, the inability to devise additional practicable and effective usage limitations for the poultry uses of fluoroquinolones, the international experience and the data from our own NARMS efforts. Taken as a whole, the evidence requires the Center for Veterinary Medicine to act to stop the poultry use of fluoroquinolones. This action will reduce the selection of fluoroquinolone-resistant *Campylobacter* and will thereby reduce the number of human cases rendered untreatable with the fluoroquinolones approved for human use. Tollefson WDT: p. 19, line 19 - p. 20, line 5

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This proposed finding of fact asserts legal conclusions and speculates on the effect of a potential withdrawal of the product. Further, evidence refutes the suggestion that fluoroquinolone-resistant *Campylobacter* results in "human cases rendered with a fluoroquinolone approved for human use". (B-20 P.2; (B-1920) P.4; (G-354) P.3; Pasternack (B-1909) P.12 L.20-22, P.13 L.1.

Curtis Travis (G- 1479)

981. Dr. Travis is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

982. Risk analysis is the process of answering a specific question regarding the risk of an existing or hypothetical hazard. There is no single process for conducting a risk assessment. The specific process followed, and the kinds of information needed, depend on the question being asked. Travis WDT: p. 2, lines 8-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that "Risk analysis is the process of answering a specific question regarding the risk of an existing or hypothetical hazard" as it is too vague. This definition includes the use of fortune-telling, astrology, or CVM's model to answer specific questions about possibly non-existent hazards without using any generally accepted scientific or causal methods. Risk analysis requires the use

of sound scientific methods [Vose WDT: P.2 L.37-41] that are more specific than this definition implies.

983. Risk analysis is best defined as the process of gathering and analyzing information to answer a specific question regarding the risk of an existing or hypothetical hazard. Travis WDT: p. 2, lines 24-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate; see Bayer response to 982.

984. The level of complexity needed to answer a question about risk depends, among other things, on the precision needed in the answer. In risk analysis, we tend to use the simplest approach possible consistent with the level of precision needed. Travis WDT: p. 2, lines 36-39

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that "the level of complexity needed to answer a question about risk depends... on the precision needed in the answer." For example, if exposure A does not cause adverse consequence B, then the risk of consequence B caused by exposure A is precisely zero. It may be simple to show this independent of the degree of precision needed in the answer.

985. The International Society of Risk Analysis defines risk analysis as "a detailed examination ...performed to understand the nature of unwanted, negative consequences to human life, health, property, or the environment; an analytical process to provide information regarding undesirable events; the process of quantification of the probabilities and expected consequences for identified risks." Travis WDT: p. 2, lines 45-46 and p. 3, lines 1-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

986. The National Research Council of the National Academy of Sciences defines risk assessment as "the characterization of the potential adverse health effects of human exposure to environmental hazards." Travis WDT: p. 3, lines 7-8, and lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

987. The National Research Council of the National Academy of Sciences defined risk assessment as the "evaluation of information on the hazardous properties of substances, on the extent of human exposure to them, and on the characterization of the resulting risk." They note "Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing and analyzing scientific knowledge and information of potentially hazardous activities or for substances that might pose risks under specified conditions." Travis WDT: p. 3, line 14, and lines 16-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

988. The National Research Council of the National Academy of Sciences outlined a four-step process for human health risk assessment, but noted that not every risk assessment need contain all four steps. The four steps are:
- Hazard Identification: The determination of whether a particular hazard is causally related to a particular effect.
- Dose-response assessment: The determination of the relationship between magnitude of exposure and probability of effect.
- Exposure Assessment: Determination of the extent of exposure to the hazard.
- Risk Characterization: The integration of the first three steps to develop qualitative and quantitative estimates of nature and the magnitude of human risk. Travis WDT: p. 3, line 24, and lines 27-44, and p. 4, lines 1-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

989. Guidance from the Office International des Epizooties (OIE) identified four components in antimicrobial resistance risk assessment:
- Release assessment
- Exposure assessment
- Consequence assessment
- Risk estimation. Travis WDT: p. 4, lines 4, 5, 16, 17, 19, 24, 29, and 37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

990. All of these methodological approaches to risk analysis can be placed into a more general framework that has three major components: (1) conceptualization of the problem (conceptual component); (2) analytical tools used in the analysis of the risk (analytical component); and (3) input parameters needed to apply to analytical tools (parameter component). Each component is described below.
- Conceptual component. The conceptual model is a conceptualization (blueprint) connecting the source of a risk with the impact being analyzed.
- Analytical Component. The analytical component specifies the computational tools (computer models, spreadsheet calculations, hand calculations) to be employed in the risk assessment and the general risk assessment methodology (deterministic, probabilistic, Bayesian) to be followed.
- Parameter Component. Estimates of risk are dependent of many input parameters. ... Parameter estimates also greatly influence the outcome of the risk assessments and can be another area of disagreement. Travis WDT: p. 4, lines 43 to 45, and page 5, lines 1 to 5, lines 15 to 18, lines 29 and 30, and lines 35 and 36

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that "all of these methodological approaches to risk analysis can be placed into a more general framework that has three major components..." For example, the proposed framework does not capture the key idea of causality expressed in the NAS framework (see CVM PFPF #991). We also disagree that, in general, "Estimates of risk are dependent on many input parameters." In many practical cases, they depend on only a few, or on one. For example, if enrofloxacin use in chickens does not cause ciprofloxacin-resistant campylobacteriosis in people, we believe that the risk of excess human illness-days of illness or complications due to failure of ciprofloxacin treatment caused

by enrofloxacin use in chickens should be acknowledged to be zero. If treatment of ciprofloxacin-resistant campylobacteriosis cases with realistic doses of ciprofloxacin is just as clinically effective as treatment of ciprofloxacin-susceptible campylobacteriosis cases, we believe that the risk of excess human illness-days due to enrofloxacin use in chickens should be acknowledged to be zero. Estimates of zero risk in these examples are not "dependent on many input parameters": a single zero in exposure or in potency to cause harm suffices. More generally, sensitivity analysis often shows that risk is dominated by one or a few input parameters.

991. The decision on whether to use a "farm-to-fork" approach or "epidemiological" approach is a part of the conceptual component of a risk assessment. Travis WDT: p. 6, lines 5-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague and as presenting a false dichotomy. The term "conceptual component" is not generally accepted or well-defined. The farm-to-fork and epidemiological approaches are not necessarily mutually exclusive. This PFOF presents a false dichotomy.

992. A "farm-to-fork" approach to antimicrobial resistance risk assessment is one in which the size of the pathogen population is modeled over all the steps in the production process: from farm, through transportation, to processor, to retailer, and finally to the consumer. It must account for all factors that increase or decrease microbial populations at each step. Travis WDT: p. 6, lines 8 to 12

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Farm-to-fork modeling does not have to "account for all factors that increase or decrease microbial populations at each step". It can use the technique of conditioning on observed (measured) quantities to obtain accurate numerical results without accounting for all such factors, which may not even be known. B-1260; [Cox and Popken, 2003; Rosenquist et al., 2002, G-1788; Travis, G-1479 P.17 ¶ 65 L.17]

993. Risk analysis is the process of gathering and organizing information to answer a specific question. The type of information needed depends on the question asked. Travis WDT: p. 6, lines 38 and 39

Bayer/AHI Response: Bayer/AHI dispute this PFOF. See response to 982.

994. A model is a conceptualization of how something works. Travis WDT: p. 6, line 43

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This is not a generally accepted definition. It excludes many predictive and descriptive models that do not conceptualize *how* something (e.g., a system) works, but only describe *what* it does, e.g., the observed or measured relations between its inputs and its outputs. For example, many regression models, including logistic regression models, are empirical and descriptive rather than causal: they do not describe how anything works, but only the association between measured values of their independent and dependent variables.

995. In the case of the *Campylobacter* risk assessment, CVM was interested in developing a regulatory tool (a model) for predicting how the level of resistant foodborne bacterial infections in humans would change as a function of changes in the level of resistant bacteria in the food animal source. The particular case of interest was that of predicting how the level of fluoroquinolone-resistant *Campylobacter* infections in humans would change if the levels of fluoroquinolone-resistant *Campylobacter* in poultry were reduced. Risk analysis uses models to make such predictions. The output of the CVM *Campylobacter* risk assessment is an estimate (along with its attendant uncertainty) of the proportion of the U.S. population with fluoroquinolone-resistant *Campylobacter* attributable to the use of fluoroquinolones in poultry, and who are likely to be treated with a fluoroquinolone. Estimates of this quantity were provided for 1998 and for 1999. Travis WDT: p. 7, lines 7 to 17

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and as being outside the scope of Dr. Travis's expertise or personal knowledge. Although CVM has sometimes claimed that it was interested in "predicting how the level of fluoroquinolone-resistant *Campylobacter* infections in humans would change if the levels of fluoroquinolone-resistant *Campylobacter* in poultry were reduced", this claim is not substantiated by their actions or by their actual model development. Instead, their risk assessment, model development, and subsequent actions have shown a strong interest in *attributing* a substantial fraction of fluoroquinolone-resistant *Campylobacter* cases to poultry, rather than in *predicting* the causal impacts on human health "if the levels of fluoroquinolone-resistant *Campylobacter* in poultry were reduced" by withdrawing approval for enrofloxacin [Cox (B-1901) P.22, P.57-64].

CVM's revealed interest in attribution, rather than prediction, of human health effects appears to be clear, in that (a) CVM has refused to analyze whether its attribution of human health effects to enrofloxacin use in chicken reflects any genuine causation. (Causation is needed for prediction, but not for attribution.); and (b) CVM has stated that they consider predictions of the future human health consequences (specifically including predictions of how the level of *Campylobacter* infections in humans would change if enrofloxacin is withdrawn to reduce levels of fluoroquinolone-resistant *Campylobacter* in poultry) to be "irrelevant and immaterial" for the purposes of this hearing. For example, CVM's Motions to Strike in this case include the following passages moving to strike Dr. Cox's testimony specifically on prediction of human health effects: "Attachment, Page 12-14 section titled Scoping: This section should be stricken because it is irrelevant and immaterial, as the issue for this hearing is whether Baytril has been shown to be safe, not the [human health] effects of its withdrawal. ... Attachment, Pages 74-76 (all): This... testimony should be stricken because it is irrelevant and misleading in that it attempts to substitute a non-issue, the future [human health] effects of withdrawal of Baytril, for the actual issue for this hearing, whether Baytril is currently shown to be safe."

Thus, we believe that CVM's actions, including this hearing, clearly reveal that their interest is in withdrawing enrofloxacin without regard for "predicting how the level of fluoroquinolone-resistant *Campylobacter* infections in humans would change" if they do so. In reality, CVM considers predictions of human health effects from their desired withdrawal to be "irrelevant and immaterial" and "a non-issue". This attitude is clearly reflected in their risk model, which is attributive rather than predictive [Cox (B-1901) P.22, P.57-64]. A true predictive model would not support their desire to withdraw approval for enrofloxacin, and hence CVM has no real

interest in predictive modeling, as indicated in their Motions to Strike. Indeed, the PFOF itself states that "The output of the CVM *Campylobacter* risk assessment is an estimate (along with its attendant uncertainty) of the proportion of the U.S. population with fluoroquinolone-resistant *Campylobacter* attributable to the use of fluoroquinolones in poultry, and who are likely to be treated with a fluoroquinolone. Estimates of this quantity were provided for 1998 and for 1999." Clearly, this output (attributions made for 1998 and 1999) do *not* correspond to "predicting how the level of fluoroquinolone-resistant *Campylobacter* infections in humans would change" in future. CVM's emphasis is on retrospective attribution, not prediction.

To this day, CVM has not quantified or predicted "how the level of fluoroquinolone-resistant *Campylobacter* infections in humans would change if the levels of fluoroquinolone-resistant *Campylobacter* in poultry were reduced" and has not developed or adopted any causal or predictive model capable of addressing this question [Cox, B-1901, p. 24]. We further disagree that "The output of the CVM *Campylobacter* risk assessment is an estimate (along with its attendant uncertainty) of the proportion of the U.S. population with fluoroquinolone-resistant *Campylobacter* attributable to the use of fluoroquinolones in poultry, and who are likely to be treated with a fluoroquinolone." We deny that what CVM has produced can be interpreted reasonably as such an estimate [Cox (B-1901) P.5 L.11-13].

996. Another way to look at a model is that it is simply a relationship between a set of input variables and one or more output variables. Travis WDT: p. 7, lines 27 and 28

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Many useful models do not have separate input variables and output variables. (Equilibrium models such as the ideal gas law PV = nRT, for example, impose constraints on the joint values of variables without requiring that "a set of input variables and one or more output variables" be identified.) Moreover, not all relationships between a set of input variables and one or more output variables constitute models.

997. All models are approximations of nature. Travis WDT: p. 7, line 40

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Many decision models and other prescriptive models, specifically including those used in risk management decision-making and risk attribution, are not approximations of nature, but instead include policy judgments and normative prescriptions. We believe that CVM's risk assessment model is of this type [Cox, B-1901, p. 20, "Instead of using a traditional risk characterization derived from objective data analysis, CVM uses "attributable fraction" calculations and policy judgments to attribute an unrealistically high proportion of human CP illnesses to chicken consumption"] and is thus *not* an approximation of nature. We believe that some spreadsheet models, including CVM's, embody hidden policy decisions, ad hoc assumptions and mathematical errors and fail to include the relevant causal information needed to constitute "approximations of nature". (Cox, B-1901, p. 24).

998. A predictive model is one that can be used to predict the behavior of a system under conditions different than those used to conceptualize the model. In risk analysis, we are usually concerned with two types of predictions: prediction of equilibrium behavior between

known data points (interpolation) or prediction of future behavior starting from known data points (extrapolation). Travis WDT: p. 8, lines 9 to 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Risk analysis predictions (for antimicrobial resistance, as well as in many other areas) typically deal with attribution or prediction starting from *uncertain* data points than with interpolation between or extrapolation from *known* data points, as claimed in this PFOF. Moreover, in risk analysis for antimicrobial resistance, we are usually interested in transient behaviors (e.g., emergence of a resistance epidemic or endemic) than with equilibrium behaviors.

999. The CVM model of *Campylobacter* is a predictive model. It can be used to predict the level of fluoroquinolone-resistant *Campylobacter* in humans given the level of fluoroquinolone-resistance *Campylobacter* in poultry. Travis WDT: p. 8, lines 20 to 22

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that "The CVM model of *Campylobacter* is a predictive model" [Cox, B-1901, p. 24]. We object to the CVM model of *Campylobacter* in part because it is *not* a predictive model [Haas (B-1904) P.16 L.19 through P.17 L.2]. We also disagree that "It can be used to predict the level of fluoroquinolone-resistant *Campylobacter* in humans given the level of fluoroquinolone-resistance *Campylobacter* in poultry", as the model is attributive rather than predictive [Cox, B-1901, p. 24; see also our response to CVM PFOF #995.]

1000. Models cannot be used to predict conditions that they were not designed to predict. The CVM *Campylobacter* model is not a "farm-to-fork" model. Thus, it cannot be used to predict how improvements in hygiene practices during the farm-to-fork trip will reduce microbial loads on chicken at the point of consumption. This does not mean that the CVM *Campylobacter* model is not predictive. The CVM model was not designed to predict microbial loads on chicken at the point of consumption. The CVM model is predictive of the conditions it was designed to predict: how changes in levels of fluoroquinolone-resistance *Campylobacter* in chicken result in changes in fluoroquinolone-resistance levels of *Campylobacter* in humans. Travis WDT: p. 8, lines 24-32

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that "The CVM model is predictive of the conditions it was designed to predict: how changes in levels of fluoroquinolone-resistance *Campylobacter* in chicken result in changes in fluoroquinolone-resistance levels of *Campylobacter* in humans." For example, we do not believe that the CVM model can even predict how changing the level of fluoroquinolone-resistance *Campylobacter* in chicken by multiplying each such *Campylobacter* 100-fold (replacing each resistant CFU with 100 resistant CFUs) would change fluoroquinolone-resistance levels of *Campylobacter* in humans. We believe it has no predictive power whatsoever [Cox, B-1901, p. 24; Bayer response to CVM PFOF #995; Haas (B-1904) P.16 L.19 through P.17 L.2].

1001. Models can be deterministic or probabilistic (stochastic is a term used interchangeably with probabilistic). In the deterministic case, one assumes that model input parameters are known exactly and when these parameters are inserted into the model, a single, exact estimate of the output parameter is obtained. In the probabilistic case, one assumes that the

input parameters are not known exactly, but instead one knows a probability distribution around the input value. Travis WDT: p. 8, lines 36 and 37, lines 38 to 41, and lines 42 to 44

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree first that "stochastic is a term used interchangeably with probabilistic". (For example, the probabilistic estimates in CVM's model reflect epistemic uncertainties that are not stochastic uncertainties. It makes sense to use "probabilistic" to describe epistemic uncertainties, as in "I formed a probabilistic estimate for the value of the billionth digit of pi based on the frequencies in the first ten million digits". It would not make sense to replace "probabilistic" with "stochastic" in this case, or in describing the sources of uncertainty in CVM's model.) We disagree that "In the deterministic case, one assumes that model input parameters are known exactly and when these parameters are inserted into the model, a single, exact estimate of the output parameter is obtained." Sensitivity and uncertainty analyses of deterministic models are well-developed disciplines that repudiate this claim and that are specifically relevant to risk analysis for enrofloxacin and *Campylobacter* (B-1260; Cox and Popken 2003). We also disagree that "In the probabilistic case, one assumes that the input parameters are not known exactly". In many probability models (e.g., for tossing a fair coin), the input parameters ($p = 0.5$) are known exactly. We believe that the distinction embodies a false dichotomy, as there are many deterministic models for random and chaotic behaviors.

1002. If one propagates the probability distribution for x through the model, one obtains a probability distribution the output variable y. Travis WDT: p. 9, lines 1 to 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Propagating a probability distribution through a model does *not* necessarily yield a probability distribution for the output variable. For example, propagating standard normal distributions for independent random inputs X and W through the simple model $Y = X/W$ fails to produce a probability distribution for the output variable Y. As a perhaps simpler example, propagating a probability distribution (such as the standard uniform distribution) for x through the model $y = E(1/x)$, where E denotes expectation, need not yield a probability distribution for the output variable y. These and many other examples repudiate the claim in PFOF #1002.

1003. The CVM used a probabilistic approach to estimate the risk of fluoroquinolone-resistant *Campylobacter* infections in humans. Travis WDT: p. 9, lines 13 and 14

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. Although we agree that CVM may have tried to do this, we disagree that they succeeded. [Haas (B-1904) P.16 L.19 through P.17 L.2]. (For example, what is CVM's estimate of the probability that the risk of fluoroquinolone-resistant *Campylobacter* infections in humans from enrofloxacin use is zero? It is not clear from their model, although it would be clear from a true probabilistic approach.)

1004. One commonly accepted way of propagating a probability distribution through a model is called Monte Carlo simulation. CVM used a Monte Carlo simulation approach to propagate parameter variability through their model for fluoroquinolone-resistant *Campylobacter* in humans. Travis WDT: p. 9, lines 24 to 27

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. We disagree that the specific Monte Carlo simulation approach used by CVM to propagate parameter variability through their model, sometimes called forward sampling, is "one commonly accepted way of propagating a probability distribution through a model" (or even a correct and appropriate way) for cases such as this one, where *measurements are available for output quantities* (e.g., campylobacteriosis case rates) as well as for input quantities. Other forms of Monte Carlo uncertainty analysis, such as Gibbs Sampling or MCMC sampling, are then required. B-1020, Chapters 3 and 4. CVM's "Monte Carlo simulation approach to propagate parameter variability through their model for fluoroquinolone-resistant *Campylobacter* in humans" is not "commonly accepted", but rather is technically incorrect and inappropriate.

1005. A probabilistic output distribution indicates the most likely output value along with the range of other possible output values, thereby illustrating the degree of uncertainty in the final result. Travis WDT: p. 9, lines 38 to 40

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. A probabilistic output distribution does *not* necessarily indicate the most likely output value. For example, the most likely output value (whether interpreted as a maximum-likelihood estimate (MLE) or maximum a posteriori probability (MAP) value) may not exist. (*Example:* Suppose that the likelihood of an output value for Y is proportional to the value of Y over the interval $0 \leq Y < 1$. What is the. largest value less than 1? This question has no answer.) Moreover, many probabilistic output distributions do *not* "illustrate the degree of uncertainty in the final result", as they fail to incorporate model uncertainties and/or use inappropriate (e.g., continuous rather than discrete or mixed) input probability distributions. CVM's model illustrates all of these errors [Cox (B-1901) P.10, 23]. For example, it fails to put a positive probability density on the output value of zero risk for enrofloxacin-caused human health harm, yet this discrete value should have a positive discrete probability mass assigned to it. By using Beta distributions and other continuous distributions that assume a zero probability for the value zero, rather than putting a positive discrete probability mass on zero, the CVM model fails to "indicate the most likely output value along with the range of other possible output values, thereby illustrating the degree of uncertainty in the final result".

1006. There are two views on calculating the probability associated with the occurrence of an event in nature. The frequency view holds that a unique probability can be associated with any event. According to this view, absolute estimates of probabilities can be determined by repeated sampling of nature. The probability of an event is the limiting relative frequency of the occurrence of an event in an infinite sequence of identical independent trials. Travis WDT: p. 9, lines 44 to 46, and p. 10, lines 1 to 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. There are many more than "two views on calculating the probability associated with the occurrence of an event in nature". (Well-known views include the Principle of Insufficient Reason, constrained maximum entropy calculations of probabilities, minimum description length, maximum likelihood, frequentist, fiducial, etc.) It is also not true that "The frequency view holds that a unique probability can be associated with any event." For example, all events that do not have limiting

frequencies in infinite sequences of trials do not have unique associated probabilities. This includes "events" such as "enrofloxacin use in chickens does not increase ciprofloxacin resistance rates in human patients".

1007. The subjective view holds that there is no absolute probability associated with an event. Bayes' Theorem provides a way to update our views as new information arrives, so that we retain a consistent view of the world. Travis WDT: p. 10, lines 5 and 6, and lines 8 to 10

Bayer/AHI Response: Bayer/AHI dispute the first sentence of this PFOF as inaccurate, but agree with the second. The subjectivist view allows for the possibility that there may be absolute (objective probabilities associated with some events. However, we do agree that "Bayes' Theorem provides a way to update our views as new information arrives, so that we retain a consistent view of the world. Travis WDT: p. 10, lines 5 and 6, and lines 8 to 10."

1008. A Bayesian approach starts with the probability distribution, called the *prior* distribution, for the parameter of interest based on information available prior to collection of data specific to the situation. Travis WDT: p. 10, lines 28 to 30

Bayer/AHI Response: Bayesian approaches are also possible with unknown and uncertain priors.

1009. Bayes' Rule is applied to combine the prior distribution and the likelihood distribution to obtain a *posterior* distribution for parameter and situation of interest. Travis WDT: p. 10, lines 36 and 37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1010. The principle reason models are used in risk analysis is that risk analysis is usually concerned with predicting consequences of events that have not occurred. Travis WDT: page 11, lines 17 and 18

Bayer/AHI Response: Models are also used in risk analysis to attribute risk to causes.

1011. Simply put, models are needed in risk assessment in situations where direct measurements are not available. Travis WDT: p. 11, lines 20 and 21.

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Models are usually used where (some) direct measurements are available. In the absence of validation data, models in risk assessment are typically not needed or useful.

1012. Risk analysis is usually concerned with events that have not occurred. Travis WDT: p. 11, lines 28 and 29

Bayer/AHI Response: Models are also used in risk analysis to attribute risk to causes. CVM's model is used this way.

1013. Scenario Uncertainty is the incorrect conceptualization of past, present, or future conditions. Travis WDT: p. 11, lines 38 and 39

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. "Scenario uncertainty" usually refers to uncertainty about which of several possible scenarios will occur, even if there is no error in conceptualization. (Validity of conceptualization is sometimes addressed under the heading of "Construct validity".)

1014. Model Uncertainty is the inability of mathematical models to completely describe complex situations. Travis WDT: p. 11, lines 41 and 42

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Model uncertainty usually refers to uncertainty about which of several possible models is correct (or most nearly correct) [Cox, B-1901, p. 15]. It can exist even when there is no "inability of mathematical models to completely describe complex situations"

1015. Parameter Uncertainty. The parameters used in a risk assessment can be grouped into two categories. The first set consists of non-case specific parameters, which include chemical properties like solubility or toxicity, and exposure parameters like food ingestion rates. The second category includes parameters that are case specific. Travis WDT: p. 12, lines 4 to 8

Bayer/AHI Response: Bayer/AHI dispute this PFOF as vague. The terms "non-case-specific" and "case-specific" are undefined here. In common usage, both toxicity parameters and food ingestion rates may be case-specific (i.e., particular to an individual case). We are not sure what is meant here.

1016. In the case of the CVM *Campylobacter* risk assessment, the major uncertainties come from parameter uncertainties. Different modelers may use different parameter values, yielding different results. For example, Cox and CVM use different parameter values for the fraction of *Campylobacter* cases attributable to chicken consumption and the proportion of *Campylobacter* infections from chicken that are resistant to fluoroquinolones. Travis WDT: p. 12, lines 10-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. For the CVM *Campylobacter* risk assessment, model uncertainties are far more important than the parameter uncertainties [Cox (B-1901) P.23]. For example, CVM's failure to include any protective effect of chicken consumption in its risk model represents a model form uncertainty ($y = Kx$ cannot express a negative relation between x and y if both are positive variables) rather than a parameter uncertainty (what is the best value of the parameter K within this incorrect model form).

1017. A model is a representation of how something works. A model is valid if it gives a correct representation of the system (under a specified set of conditions). That is, a model is valid if it can correctly predict the behavior of the system under different conditions. The process of determining if a model is valid is called model validation. This usually involving comparing model simulations (predictions) with actual measurements indicating how the

system should perform. In practice, model validation is rarely done, primarily because insufficient data (measurements) exist with which to validate the model. Travis WDT: p. 12, lines 19 to 25

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. First, we disagree that, necessarily or usually "A model is a representation of how something works." (See response to CVM PFOF #994.) Specifically, risk attribution models reflect policy judgments rather than representing how something works [Cox, B-1901, pp. 60-62]. We disagree that "A model is valid if it gives a correct representation of the system (under a specified set of conditions)." For example, the model "y = 2x" gives the same value of y as the model "y = x*x" under the specified conditions that x = 0 or x = 2. But this does not imply that both models are valid, even if both are correct representations of a system (under the specified set of conditions). We disagree that "In practice, model validation is rarely done, primarily because insufficient data (measurements) exist with which to validate the model." In both principle and practice, model validation is a standard part of modeling and methods such as model cross-validation have been developed to allow for validation even when data are scarce. B-1020, Chapter 3.

1018. Risk assessors usually rely on the logical structure of the model to convince them that it is a reasonable representation of a system. Travis WDT: p. 12, lines 28 and 29

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. This is poor practice and is specifically discouraged in many modeling texts. What seems "reasonable" is often incorrect, making formal validation techniques, such as model cross-validation, essential and a widely recognized part of modeling. B-1020, Chapter 3.

1019. To evaluate the human health impact of antimicrobial use in animals, CVM developed a quantitative risk assessment model. The risk assessment was intended to estimate the risk to human health from antibiotic resistant food borne pathogens associated with the domestic use of antimicrobials in food producing animals. Specifically, a mathematical model was derived 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. Travis WDT: p. 12, lines 35-42

Bayer/AHI Response: Bayer/AHI object to this PFOF because it compounds multiple proposed facts and it is inaccurate. Bayer/AHI dispute that the CVM/Vose model is "a quantitative risk assessment model" as that term is generally accepted by risk assessment professionals. This PFOF is refuted by B-1901 P.11, P.16-19, P.25, P.67 and B-1904 P.8 L.5 - P.10 L.18 (excluding P.9 L.3-6, and P.9 L.10 - P.10 L.2), P.16 L.19 - P.17 L.2, P.25 L.9-10. Moreover, the CVM/Vose model does not "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". This PFOF is further refuted by B-1901 P.19, P.39, P.67 and B-1904 P.22 L.10-18, P.26 L-5-6.

1020. The CVM *Campylobacter* Risk Assessment takes an epidemiologic approach to estimating the risk of fluoroquinolone-resistant illnesses in humans. It starts with the human

epidemiologic data on the rate of campylobacteriosis in humans and then works backwards to estimate the fraction of this total illness burden that is fluoroquinolone-resistant and due to chicken consumption. Travis WDT: p. 12, lines 44 to 46, and p. 13, lines 1 to 4

Bayer/AHI Response: Bayer/AHI object to this PFOF because it compounds multiple proposed facts and it is inaccurate and misleading. It is misleading because it misrepresents CVM's decisions about how many FQ-r CP cases to blame on enrofloxacin use in chickens as being driven by "epidemiologic data on the rate of campylobacteriosis in humans". In fact, attribution of the fraction that is "due to chicken consumption", in the sense that CVM has defined this term, requires causal analysis and modeling that was never done [Cox, B-1901, pp, 60-62]. Instead, CVM has made an essentially *ad hoc* political decision about how much (100%) of domestically-acquired non-treatment related resistance it would blame on enrofloxacin use in chickens [Bartholomew, G-1454, p. 9, lines 28 and 29]. This should not be characterized as being estimated by "working backward" from human epidemiological data (or any other data). We believe that "the fraction of this total illness burden that is fluoroquinolone-resistant and due to chicken consumption" is not based on human data at all, but on *ad hoc* decisions that are contradicted by relevant human data [Cox (B-1901) P.27]

1021. The incremental human health impact of resistant food borne disease can be determined without assessing all the factors influencing the cause of the food borne illness itself. Travis WDT: page 13, lines 27 to 29.

Bayer/AHI Response: Bayer/AHI object to this PFOF as incorrect. Without identifying and assessing the "factors influencing the cause of the food borne illness itself", it may be impossible to determine "the incremental human health impact of resistant food borne disease". In the current case, for example, if it were clear that the other (non-resistance related) factors influencing food-borne campylobacteriosis accounted for 100% of all cases, then the estimated "incremental human health impact of resistant food borne disease" would presumably fall to zero.

1022. Cox developed a risk assessment model of microbial hazards in food, using *Campylobacter jejuni* as an example. Travis WDT: p. 13, lines 33 and 34

Bayer/AHI Response: Bayer/AHI object to this PFOF as inaccurate. The final Cox risk assessment model for *Campylobacter* is specifically developed for *Campylobacter* and chicken.

1023. Cox's model is based on a discrete-event simulation (DES) model of the microbial load reaching consumers via ingested chicken. Microbial load is quantified in terms of colony-forming units (CFUs). The DES model simulates the probabilistic amplification and reduction on microbial load at successive states from farm to table. Ingested microbial load enters a non-linear dose-response model that predicts resulting probabilities of infection and illness. Travis WDT: p. 13, lines 39 to 44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1024. Cox takes a "farm-to-fork" approach. A "farm-to-fork" microbial risk assessment tracks the level of bacterial contamination in food products at each step in the process from the farm to the table. These steps include slaughtering, processing, transportation, storage, retail and food handling prior to consumption. Such an assessment attempts to predict (model) the actual number of colony-forming units of *Campylobacter* at each step in the trip from farm-to-fork. Such an assessment must consider sources of contamination at each step and subsequent microbial growth and reduction events between stages. Travis WDT: p. 14, lines 1 to 7

Bayer/AHI Response: Bayer/AHI agree that Cox uses an approach often referred to as "farm-to-fork". We disagree that "Such an assessment must consider sources of contamination at each step" when enough data are available so that *measurements* of actual microbial loads can be used without explicitly considering or modeling the sources of contamination at each step [Cox, B-1901, p. 13].

1025. The major components of the Cox model are:
- A "farm-to-fork" microbial loading model that produces a probability distribution of the load of *Campylobacter jejuni* (measured as the number of colony-forming units, CFU, of *Campylobacter jejuni*) on individual chickens at the point of consumption.
- A nonlinear dose-response model that predicts the probability of illness resulting from consumption of chicken contaminated with a given number of CFU of *Campylobacter jejuni*. This component of the model has been extended to predict probability of infection and illness for different age groups. Travis WDT: p. 14, lines 14 to 24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1026. Cox describes the microbial loading component of his model as being able to predict how different processes within the farm-to-table supply-chain affect the microbial load. The model considers the effects of:
- The initial microbial load of chickens leaving the farm (by season),
- The effects of transport from farm to processing plant,
- The effects of the processing plant itself, including cross-contamination, and
- The effects of storage and preparation practices prior to consumption. Travis WDT: p. 14, lines 26 to 33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1027. To be able to predict the impact of fluoroquinolone-resistant *Campylobacter* in poultry meat on human health using Cox's model, it is necessary to know the dose-response function relating *Campylobacter* consumption with the probability of illness as an intermediary step. Cox assumes a Beta Poisson model fit to the Black et al. data to define the dose-response function. In assuming a Beta Poisson with the specified parameters Cox assumes that an ingested dose of less the 500 colony forming units (CFU) has a zero probability of producing illness in humans. Travis WDT: p. 14, lines 35-41

Bayer/AHI Response: Bayer/AHI object to this PFOF as compounding multiple proposed facts and being inaccurate and misleading. We disagree that "it is necessary to know the dose-response function relating *Campylobacter* consumption with the probability of illness as an intermediary step". Any useful approximation to this dose-response model, combined with uncertainty/sensitivity analyses will suffice. As stated by Dr. Cox, "In reality, the key conclusions of the Cox-Popken risk assessment... are very robust to uncertainties in the assumed dose-response relation, provided that it captures the patterns observed in the data... *The assumption of zero response probability below 500 CFU is inessential:* non-threshold s-shaped dose-response curves would yield essentially the same results" [Cox, B-1901 P.14, emphasis in original] (b) Cox does not "assume a Beta Poisson model fit to the Black et al. data to define the dose-response function", but only assumes that this model provides a useful initial approximation to the true but unknown dose-response functions for individuals. (c) Cox does not require that "an ingested dose of less the 500 colony forming units (CFU) has a zero probability of producing illness in humans." [Cox, B-1901 P.14].

1028. Cox takes a farm-to-fork approach to predicting the prevalence of campylobacteriosis in the human population. However, he does not estimate (predict) the fraction of fluoroquinolone-resistant *Campylobacter* at each step on the trip from farm to human exposure to illness. Travis WDT: p. 14, lines 45 and 46 and p. 15, lines 1 and 2

Bayer/AHI Response: The Cox model treats the fraction of fluoroquinolone-resistant *Campylobacter* at each step as a constant proportion of all *Campylobacter* CFUs at that step.

1029. To estimate the prevalence of fluoroquinolone-resistant *Campylobacter* in humans, Cox assumes that the fraction of *Campylobacter* cases in humans that is fluoroquinolone-resistant is 0.6809 times the fraction of *Campylobacter* isolates in chicken that is fluoroquinolone-resistant. Travis WDT: p. 15, lines 9 to 12

Bayer/AHI Response: Bayer/AHI object to this PFOF as inaccurate. See footnotes to Table 8 of B-1260.

1030. Cox uses a dose-response model to predict the probability that a person will develop a *Campylobacter jejuni* infection or illness following consumption of chicken contaminated with a fixed number of *Campylobacter jejuni* CFU. The human dose-response model used by Cox was developed by Teunis et a., based on empirical testing data from Black et al. Travis WDT: p. 15, lines 16 to 20

Bayer/AHI Response: Bayer/AHI object to this PFOF as inaccurate. The human dose-response model used by Cox was an extension of the Teunis et al. model to include some demographic attributes (Travis WDT: p. 14, lines 14 to 24)

1031. At the lowest doses used in the Black et al study (800 CFU), 50% of subjects had positive stool cultures and 10% developed diarrhea or fever. The strain used, A3249, was the weaker of the two strains used in this study, thus other strains of *Campylobacter* may be more virulent at low doses. Travis WDT: p. 15, lines 30-34

Bayer/AHI Response: Bayer/AHI object to this PFOF as speculative. We believe it is also outside of Dr. Travis's area of expertise. The conclusion that "other strains of *Campylobacter* may be more virulent at low doses" is speculation, not fact.

1032. Black et al concluded that even low does of *C. jejuni* may produce infection and illness in humans. Travis WDT: p. 16, lines 29 and 30

Bayer/AHI Response: Bayer/AHI object to this PFOF as vague. "Low doses" is an ambiguous qualitative phrase. Black et al. showed that most subjects had no clinical adverse symptoms at 800 CFU (Travis WDT: p. 15, lines 30-34).

1033. Teunis et al. found that the Beta Poisson model appears to be well suited to describe the majority of known results from human feeding studies. They also concluded that this does not mean that no better models could be constructed. Travis WDT: p. 15, line 38, and lines 43 to 45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1034. There is a great deal of uncertainty in dose-response for *Campylobacter* at low doses. Travis WDT: p. 16, lines 11 and 12

Bayer/AHI Response: Bayer/AHI object to this PFOF as vague. "A great deal of uncertainty" is an ambiguous qualitative phrase, as is "low doses". What seems certain is that average doses of *Campylobacter* received via chicken cause little or no risk of campylobacteriosis in humans. [Cox, B-1901, p. 22]

1035. To overcome the problem of not knowing the correct parameter values to use in the "farm-to-fork" model, Cox calibrates the model. Travis WDT: p. 16, lines 17 and 18

Bayer/AHI Response: Bayer/AHI object to this PFOF as inaccurate. The purpose of calibration is to support contingent risk analysis after the correct parameter values (approximately zero risk at realistic exposure levels, within the power of epidemiological data to resolve) have already been determined (B-1260; Cox and Popken, 2003).

1036. Calibration consists of finding values for the model parameters so that if the model starts with the assumed initial level of *Campylobacter* infection (CFUs) on chickens at the farm, it is able to predict the assumed current prevalence of campylobacteriosis. Travis WDT: p. 16, lines 25 to 27

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as inaccurate. Calibration in this case refers specifically to predicting the assumed prevalence of campylobacteriosis *attributed to chickens* – a policy decision. Thus, it reflects a policy input to the model. (If data-driven values were used instead, the risk attributed to enrofloxacin would fall to zero; Cox, B-1901, pp 33, 40.)

1037. It is difficult, if not impossible, to identify all the various factors that can influence the presence and growth of bacterial during the trip from farm-to-fork. Travis WDT: p. 17, lines 8 and 9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1038. Thus, it is highly likely that in developing a "farm-to-fork" model, important factors will be overlooked and omitted from the model. Travis WDT: p. 17, lines 16 and 17

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is refuted in [Cox, B-1901 P.13]. The Cox farm-to-fork model includes important factors by conditioning on measured values of causal predecessors. Conditioning on measured values, rather than seeking to model or simulate unknown factors, allows for accurate numerical results without modeling what is not measured [Cox, B-1901 P.13, "The result is that many details and important factors may be omitted from the model (as mentioned by Dr. Travis, G-1479 P.17 ¶ 65 L.17) *without impairing the ability of the model to produce accurate results.* This is the answer to Dr. Travis's concern, i.e., it is not necessary to identify all factors or to model all details (impossible in any model) to obtain accurate results."]

1039. There currently does not exist sufficient knowledge of parameter values to parameterize the model used by Cox. Travis WDT: p. 17, lines 23 to 25

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is refuted in B-1901 P.13, "Similarly, Dr. Travis's concern (*ibid*, lines 24 and 25 and paragraphs 66 and 67) that "there currently does not exist sufficient knowledge of parameter values to parameterize the model" is addressed in B-1020 (the final version of the model) by identifying all required parameter values from available data". The model has been fully parameterized using available data (B-1020; B-1260). Rather than trying to model what is not known, the model used conditioning on measured values of causal predecessors to allow for accurate numerical results without modeling what is not measured.

1040. The difficulty in applying the Cox model is that Cox does not know all the parameter values that should be used in each component of the microbial loading model. Travis WDT: p. 17, lines 28-30

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is refuted in B-1901 P.13. The model has been fully parameterized using published parameter values based on available data. Uncertainties about parameter values and risk estimates were assessed without difficulty using uncertainty and sensitivity analysis methods documented in (B-1020; B-1260).

1041. It is generally agreed that currently there does not exist sufficient data to develop a predictive "farm-to-fork" model for any one of the common food borne pathogens and that the current use of such a model is limited to identifying intervention points in the farm-to-fork process where action might help reduce the overall level of bacterial contamination in food products at the consumer consumption level. Travis WDT: p. 17, lines 32 to 36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It is refuted in [Cox, B-1901, p. 13]. The Cox model is a predictive farm-to-fork model that has been fully parameterized using published parameter values based on available peer-reviewed data (B-1020; B-1260). The Rosenquist et al. model (2002, G-1788) has also been developed as a predictive model. It is *not* "generally agreed that currently there does not exist sufficient data to develop a predictive 'farm-to-fork' model for any one of the common food borne pathogens". This point of view has been advanced by David Vose and some others who seek to substitute their own proposed methods for traditional quantitative risk assessment, but it does not represent a consensus view.

1042. The Cox implementation of the Teunis et al. model makes two assumptions:
- An ingested dose of *Campylobacter jejuni* less than 500 CFU has a zero probability of producing illness in humans.
- A Beta Poisson model provides an adequate fit to the Black et al. data. Travis WDT: p. 17, lines 40 to 45

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as compounding multiple proposed facts and being inaccurate and misleading. Cox does not "assume a Beta Poisson model provides an adequate fit to the Black et al. data", but only assumes that this model provides a useful initial approximation to the true but unknown dose-response functions for individuals.. Cox also does not require that "an ingested dose of less the 500 colony forming units (CFU) has a zero probability of producing illness in humans." B-1901 P.14. As stated in B-1260, neither of these assumptions is required to make reasonably accurate predictions "provided that the assumed aggregate [dose-response] relationship is roughly accurate." Ingested doses less than 500 CFU need not have zero probability of producing illnesses and the Beta Poisson model fit to the Black et al, data need not satisfy any specific definitions of "adequate fit" provided that its main qualitative features (listed in the section on "Approximate modeling of pareameter variability and its effects" in Cox and Poken, 2002) hold.

1043. In his model, Cox states, that the minimum infective dose for *Campylobacter jejuni* in the Black et al. study was 800 CFU. Other research has shown that the minimum dosage may be as low as 500 CFU. The Cox statement is somewhat misleading and may be misunderstood. It could be mistaken to mean that doses below 800 CFU were ineffective in the Black et al study. In fact, 800 CFU was the lowest dose used in the Black et al study and this dose level produced a 50% infection rate and a 10% illness rate. Thus, the 800 CFU dose level in the Black et al. study was not a dose level below which there is a zero probability of producing an illness. The Black et al. study actually predicts that one CFU of *Campylobacter jejuni* has a positive probability of causing infection and illness. Travis WDT: p. 18, lines 3-14, G-284

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Cox explicitly references the fact that "Other research has shown that the minimum dosage may be as low as 500 CFU" and does not state, imply, or assume that "the 800 CFU dose level in the Black et al. study [was] a dose level below which there is a zero probability of producing an illness". B-1901 P.14. Thus, CVM's PFOF that "The Cox statement is somewhat

misleading and may be misunderstood. It could be mistaken to mean that doses below 800 CFU were ineffective in the Black et al study" is based on a speculative supposition that requires the hypothetical reader not to read what was clearly written.

1044. Holcomb et al. compared six microbial dose-response models, including exponential and Beta Poisson models considered in the Teunis et al study, for their ability to fit four microbial dose-response data sets from human feeding studies. Travis WDT: p. 18, lines 22 to 25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1045. Holcomb et al. concluded that when applied to the Black et al. *Campylobacter jejuni* data set, 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 doses were less than 1.0 CFU, meaning that a dose of 1.0 CFU infects more than one percent of the population. Travis WDT: p. 18, lines 29 to 33

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. We disagree that "However, three of the predicted ID doses were less than 1.0 CFU" can be interpreted as "meaning that a dose of 1.0 CFU infects more than one percent of the population." Instead, this example only points out the well-known dangers of using specific parametric models to extrapolate outside the range of the data. B-1020, Chapter 3.

1046. The basic limitations of incorporating a dose-response function into Cox's *Campylobacter* risk assessment are:
- There is uncertainty in the appropriate shape of the dose-response function for *Campylobacter* infection
- The shape of the dose-response for *Campylobacter* infection may not be the same as the shape of the dose-response for *Campylobacter* illness
- It is not clear, and it is not likely, that an ingested dose of *Campylobacter jejuni* less than 500 CFU has a zero probability of producing illness in humans. Travis WDT: p. 18, lines 35 to 45

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We disagree that the proposition "There is uncertainty in the appropriate shape of the dose-response function for *Campylobacter* infection" is "a basic limitation of incorporating a dose-response function" into a risk assessment. B-1901 P.14. The uncertainty is there whether or not a dose-response function is incorporated into a risk assessment, and a risk assessment that ignores it is in no sense less limited than one that explicitly incorporates and addresses it. We also disagree that there is much relevant "uncertainty in the appropriate shape of the dose-response function for *Campylobacter* infection". It is clear that the appropriate shape involves disproportionately small risks at low doses (below a few hundred CFUs), rising to an approximate plateau as the dose increases to hundreds or to thousands of CFUs, under the conditions of the Black et al. feeding study. We further disagree that the fact that "The shape of the dose-response for *Campylobacter* infection may not be the same as the shape of the dose-response for *Campylobacter* illness" is "a basic limitation of incorporating a dose-response function into Cox's *Campylobacter* risk assessment." This possibility has already been incorporated in the dose-response model (which has separate components for infection and illness, see Travis WDT:

p. 13, lines 39 to 44), and hence is not "a basic limitation". We further disagree that the proposition that "It is not clear, and it is not likely, that an ingested dose of *Campylobacter jejuni* less than 500 CFU has a zero probability of producing illness in humans" is "a basic limitation of incorporating a dose-response function into Cox's *Campylobacter* risk assessment." Indeed, as clearly stated in B-1020 and B-1260 (Cox and Popken, 2003), this assumption is not required for the model's main results, as these are not strongly sensitive to the exact assumptions made about the dose-response model. B-1901 P.14.

1047. CVM estimates 153,580 cases of fluoroquinolone-resistant *Campylobacter* cases resulting from chicken consumption, while Cox estimates the number to be 38,419 cases. The difference between these two estimates can be traced to differences in the following parameter choices:

- Fraction of *Campylobacter* cases Attributable to Chicken Consumption
  - CVM uses 57.4%, based on two case-control studies.
  - Cox uses 60%, based on the same two case-control studies.
- Proportion *of Campylobacter* Infections From Chicken That are Resistant to Fluoroquinolone
  - CVM uses 19.6% in 1999, based on subtracting the proportion of fluoroquinolone-resistant *Campylobacter* isolates from NARMs for which the resistance might have been derived through foreign travel or through having received a fluoroquinolone prior to stool culture. The proportion to be subtracted was determined from the CDC's *Campylobacter* Case Control study.
  - Cox uses 6.4%, based on two CDC FoodNet *Campylobacter* Case Control Studies.
- Children Under the Age of One (27.5% of cases)
  - CVM removed children from its calculations by multiplying the number expected to receive an antibiotic by the fraction expected to receive a fluoroquinolone since children are not expected to be prescribed this class of drugs.
  - Cox removed children from its calculations by removing the number of U.S. citizens below the age of 2 from the starting U.S. population size in his model. Travis WDT: p. 19, lines 4-35

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as compounding multiple proposed facts and being inaccurate and misleading. Cox estimates the most likely number of cases of fluoroquinolone-resistant *Campylobacter* cases resulting from chicken consumption to be zero, not 38,419. B-1901 P.22, P.40, P.57-64; B-1260; Cox and Popken, 2003]. Also, the 6.4% and 19.6% numbers are based on the same data, but Cox corrects an error in applying Bayes Rule made by CVM. B-1901 P.70.

1048. The difference between the Cox and CVM estimate of the number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken consumption does not result from Cox's use of a more complex model. Travis WDT: p. 19, lines 39 to 41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1049. Both Cox and CVM use the same method for estimating the number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken consumption. Travis WDT: p. 20, lines 1 to 3

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. Cox uses a different method. B-1901 P.57-64.

1050. CVM estimates 153,580 cases of fluoroquinolone-resistant *Campylobacter* cases resulting from chicken consumption while Cox estimates the number to be 38,419 cases. Travis WDT: p 19, lines 7 and 8

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Cox estimates the most likely number of cases of fluoroquinolone-resistant *Campylobacter* cases resulting from chicken consumption to be zero, not 38,419 [Cox (B-1901) P.22, P.40, P.57-64; B-1260; Cox and Popken, 2003]. This PFOF refers to a hypothetical calculation made by Dr. Cox that was explicitly made *contingent* on CVM assumptions that Cox identified as incorrect and misleading, and seeks to present this hypothetical calculation as Cox's estimate.

1051. For the fraction of cases attributable to chicken consumption, CVM uses 57.4%, based on two case-control studies. Cox uses 60%, based on the two case-control studies. Travis WDT: p. 19, lines 13 and 14

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Cox estimates the number to be closer to zero [Cox (B-1901) P.22, P.57-64; B-1260; Cox and Popken, 2003]. This PFOF refers to a hypothetical calculation made by Dr. Cox that was explicitly made *contingent* on CVM assumptions that Cox identified as incorrect and misleading, and seeks to present this hypothetical calculation as Cox's estimate.

1052. For the proportion of *Campylobacter* infections from chickens that are resistant to fluoroquinolones, CVM uses 19.6% in 1999, Cox uses 6.4%, based on two CDC FoodNet *Campylobacter* Case Control Studies. Travis WDT: p. 19, line 18 and lines 25 and 26

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Cox estimates the number to be closer to zero [Cox (B-1901) P.22, P.57-64; B-1260; Cox and Popken, 2003]. This PFOF refers to a hypothetical calculation made by Dr. Cox that was explicitly made *contingent* on CVM assumptions that Cox identified as incorrect and misleading, and seeks to present this hypothetical calculation as Cox's estimate. Also, the 6.4% and 19.6% numbers are based on the same data, but Cox corrects an error in applying Bayes Rule made by CVM. B-1901 P.70.

1053. The Cox and CVM estimates differ solely because of differences in the parameter values. Travis WDT: p. 20, lines 4 and 5

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. Cox also uses a different model form and a different underlying causal model (B-1020, Chapter 4; B-1252) to conclude that the risk is closer to zero. B-1901 P.22.

David Vose (G-1480)

1054. Dr. Vose is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Mr. Vose's CV indicates that he has no relevant training or advanced degrees or credentials in health risk analysis, epidemiology, advanced statistics, or other relevant disciplines. He is a self-declared expert with acknowledged experience and expertise in the use of Monte Carlo simulation in spreadsheets. This does not qualify him to address most of the topics on which he offers testimony.

1055. Risk assessment is a decision-support tool. Vose WDT: p. 2, line 20

Bayer/AHI Response: The full context of this quote is as follows (G-1480 P.2 ¶ 5 L. 20-23): "Risk assessment is a decision-support tool. That means that risk analyses are designed to provide managers who face making decisions in uncertain circumstances with a means to better understand... the effects, both positive and negative, and costs of actions that they might choose to take." We agree with this description of what risk assessment should be, but not that it is a description of what CVM's risk assessment is. The decision or action that the CVM decision-makers propose is a withdrawal of the approval for enrofloxacin. Following Vose's own testimony here, the CM risk assessment should "provide managers... with a means to better understand the [human health] effects, both positive and negative" (overwhelmingly negative, by our calculations), of this action that they might choose to take. But the CVM risk assessment does not do this. Any inference from CVM's PFOF #1055 that CVM's risk assessment is a decision-support tool would be mistaken. Instead, as stated by Vose, G-1480 P.5 ¶ 16, "In the case of CVM, the question asked was whether the use of antimicrobials under their authority is introducing a significant human health burden and, if so, whether any action they could take would significantly reduce that burden." The answer given by CVM ("Yes" to both) is based on an assumption that most resistant campylobacteriosis cases are attributable to chickens. But the human health effects ("both positive and negative") of decisions are not assessed anywhere in the CVM risk assessment. Only a health burden that CVM attributes to past enrofloxacin use in chickens is estimated. This is not the same as assessing the health effects of a decision to withdraw approval for enrofloxacin — a future event not modeled in the CVM risk assessment model. Thus, we agree that risk assessment should be a decision-support tool, but do not agree that it is such a tool as it has been developed by CVM in this context.

1056. Risk analysis applies methods of analysis to matters of risk. Its aim is to increase understanding of the substantive qualities, seriousness, likelihood, and conditions of a hazard or risk and of the options for managing it. Vose WDT: p. 2, lines 32-35

Bayer/AHI Response: The intended meaning of this PFOF is not clear to us. (What is meant by "the likelihood of... options for managing it", for example?) We believe that the aim of health risk analysis is to identify how the probable frequency and severity of adverse health outcomes will change if different risk management actions are taken.

1057. Risk analysis uses observations about what we know to make predictions about what we don't know. Risk analysis is a fundamentally science-based process that strives to reflect the

realities of Nature in order to provide useful information for decisions about management risks. Risk analysis seeks to inform, not to dictate, the complex and difficult choices among possible measures to mitigate risks. Risk analysis enriches fair and transparent deliberative decision-making processes in a democratic society. Vose WDT: p. 2, lines 37-41

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We disagree that the CVM risk analysis "uses observations about what we know to make predictions about what we don't know". Instead, it uses estimated attributable fractions (which are not "observations about what we know", but rather reflect policy judgments and assumptions) to make retrospective attributions of resistant campylobacteriosis cases to enrofloxacin use in chickens. B-1901 P.18, citing B-1252; P.64-70. This does not match the description in PFOF #1057. We also disagree that risk analysis necessarily or always "strives to reflect the realities of Nature", and we specifically deny that it does so in the CVM risk model. For example, it ignores the protective effects of chicken handling and consumption against risk of campylobacteriosis; ignores human ciprofloxacin contamination of streams and other water supplies (and instead attributes resistance from such sources to enrofloxacin use in chickens); uses models and assumptions that conspicuously do not fit the available data; and embeds policy judgments about attribution and causation that contradict "the realities of Nature" as reflected in available data [Cox (B-1901) P.15; citing B-1252] . We also disagree that risk analysis, as practiced by CVM in the context of this hearing, "enriches fair and transparent deliberative decision-making processes in a democratic society."

1058. Risk analysis seeks to integrate knowledge about the fundamental physical, biological, social, cultural, and economic processes that determine human, environmental, and technological responses to a diverse set of circumstances. Because decisions about risks are usually needed when knowledge is incomplete, risk analysts rely on informed judgment and on models reflecting plausible interpretations of the realities of Nature. Vose WDT: p. 2, lines 42-46

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We do not agree that risk analysts necessarily "rely on informed judgment". For example, we believe that CVM risk analysts have instead relied primarily on a*d hoc* decisions about risk attribution (of resistance in human campylobacteriosis cases to enrofloxacin use in chickens) that demonstrably contradict available information (showing that there is no significant relation between the two), rather than being informed by it. We also do not agree that CVM's risk analysts have relied on "models reflecting plausible interpretations of the realities of Nature", as their modeling ignores the protective effects of chicken handling and consumption against risk of campylobacteriosis; ignores human ciprofloxacin contamination of streams and other water supplies (and instead attributes resistance from such sources to enrofloxacin use in chickens); uses models and assumptions that conspicuously do not fit the available data; and embeds policy judgments about attribution and causation that contradict "the realities of Nature" as reflected in available data [Cox (B-1901) P.15; citing B-1252]. Thus, we do not believe that CVM's proposed FOF #1058 is accurate, at least in the context of CVM's risk analysis.

1059. 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. Vose WDT: p. 3, lines 19-22

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and vague. The definitions of "appropriate to the decision", "appropriate input", and "significant concerns" are not given, so we do not know what this PFOF is asserting. We agree that items (1)-(4) in CVM's proposed FOF #1059 are necessary for "a risk characterization to fulfill its purpose". Rather, we believe that what is necessary and sufficient for a risk characterization to fulfill its purpose is that it "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" (Cox, 2001). We believe that widely accepted definitions of "risk characterization" do not entail items (1)-(4) in CVM's proposed FOF #1059, but instead correspond more closely to the Joint FAO/WHO Expert Consultation's definition of risk characterization as the "integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties) (http://www.foodsafety.gov/~dms/lmriskgl.html).

1060. 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. Risk characterization is a prelude to decision making and depends on a iterative, analytic-deliberative process. Vose WDT: p. 3, lines 28-31

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and vague. This vague language does not correspond to what we understand to by the term "risk characterization". It seems that this proposed definition could apply to many power point presentations, white papers, op ed pieces, and other documents that we would not agree meet the definition of "risk characterization." See the Bayer/AHI response to CVM PFOF #1059.

1061. Both the Society for Risk Analysis and the National Research Council conclude that risk assessments need to address decision questions, and that the form of that risk assessment will be driven by the decision-makers needs. The risk assessment produced by CVM does exactly that. Vose WDT: p. 3, lines 33-35

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It mischaracterizes what the CVM risk assessment does. Instead of "doing exactly that", the CVM-Vose risk assessment fails to address the key decision question: "What will be the human health effects, positive and negative, of a withdrawal of approval for enrofloxacin?" Specifically, it does not address the effects of such a withdrawal on increasing human cases of campylobacteriosis and salmonellosis. Thus, it leaves a significant concern unaddressed, violating the NRC principles cited on p. 3, line 20 of Dr. Vose's testimony.

1062. The Georgetown University risk assessment discussed in Anderson et al (2001) was not a farm-to-fork model, but began its risk assessment with retail meat, and only modeled consumer handling and a dose-response relationship, rather than looking at farm, slaughter and processing practices where the key food safety controls are. Vose WDT: p. 4, lines 4-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1063. The food safety risk assessment community is beginning to recognize that farm-to-fork risk assessments have not produced what was hoped, and that more decision-question focused assessments are necessary, using more efficient alternative modeling approaches. Vose WDT: p. 4, lines 37-40

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It is essentially an unsubstantiated and incorrect opinion being presented as a fact. In reality, competent risk assessors in this area are have found that many farm-to-fork risk assessments *have* "produced what was hoped" by promising and delivering to decision-makers useful estimates of the effects of decisions on microbial load distributions and the effects of load distributions on dose-response relations and illness rates (Cox and Popken, 2003; Rosenquist et al., 2002, G-1788.). There is no general or emerging agreement in the "food safety risk assessment community... that farm-to-fork risk assessments have not produced what was hoped". While Vose appears to be on a mission to persuade clients that new methods, invented by Vose himself, are needed, we believe that more traditional methods (including well-conducted farm-to-fork modeling) already incorporate the "more decision-question focused assessments,... using more efficient alternative modeling approaches" that CVM PFOF #1063 calls for. The alternative approach suggested by CVM/Vose is less decision-focused and less efficient and produces meaningless numbers [Cox (B-1901) P.16].

1064. An antimicrobial risk assessment is similar in principle to a microbial risk assessment, the principle difference being the hazard (a risk analysis term defined by CODEX in food safety as influenced by foodborne agents as 'a biological, chemical or physical agent in or property of food that may have an adverse health effect'): in a microbial food safety risk assessment, the hazard is a bacterium or other human pathogen, whilst in an antimicrobial food safety risk assessment it is a resistant determinant. Vose WDT: p. 4, lines 45-48, and p. 5, lines 1-2

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and seeking to create a false dichotomy. A well-conducted microbial food safety risk assessment can include resistant as well as susceptible bacteria [Cox, B1901, p. 12] and can thus subsume what Vose terms an "antimicrobial food safety risk".

1065. The risk management question asked by CVM was whether the use of antimicrobials under their authority is introducing a significant human health burden and, if so, whether any action they could taken would significantly reduce that burden. Vose WDT: p. 5, lines 41-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1066. The CVM conducted a draft risk assessment to determine the human health impact of the use of an antimicrobial drug in food producing animals. The CVM also produced versions of the risk assessment model that could be run and modified by anyone with access to Microsoft Excel, a commonly used spreadsheet program. The CVM risk assessment was released and made available on the CVM Internet homepage, including the downloadable versions of the risk assessment model. There followed 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 weaknesses of the draft assessment. Vose WDT: p. 6, lines 25-33

Bayer/AHI Response: Bayer/AHI disagrees that CVM completed a "risk assessment". It failed to complete a risk assessment by failing to identify a hazard, failing to join human exposure assessment information with a dose-response analysis, and failing to carry out the steps required for a risk assessment [Cox, B-1901, pp. 19, 24, 25]. It calls its collection of *ad hoc* assumptions, incorrect formulas, and erroneous parameter values a "risk assessment", apparently under the assumption that linking these elements into a spreadsheet model and calling the outputs risk estimates is all that is required for risk assessment. But risk assessment requires much more, and CVM has not completed one [Cox, B-1901, pp. 19, 24, 25].

1067. CVM chose a predictive model approach that would provide it with meaningful and useful input in a timely fashion to help determine whether to allow continued use of fluoroquinolone in poultry. The approach was supported by reliable data, and was designed to help enable industry to manage its use of fluoroquinolone so that the human health impact did not become unacceptable. CVM also made exceptional efforts to incorporate stakeholders' views and data. Vose WDT: p. 6, lines 38-43

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We disagree that "CVM chose a predictive model" [Cox, B-1901, p. 24]. For example, its model is heavily based on retrospective attribution using attributable fractions estimated from past data rather than for future conditions [Cox (B-1901) P.22, P.57-64]. We disagree that the model approach "would provide... meaningful and useful input", as we believe its results are meaningless (in a rigorous technical sense as well informally) and cannot be used to improve decisions [Cox (B-1901) P. 25]. We disagree that "The approach was supported by reliable data", as it is blatantly contradicted by available reliable data and uses extremely unreliable, non-representative, and outdated data for its key estimation of attributable fractions [Cox (B-1901) P.50; Feldman (B-1902) P.34 L.12-21]. We deny that "CVM also made exceptional efforts to incorporate stakeholders' views and data" as it repeatedly ignored the specific comments and recommendations repeatedly offered by industry and by members of its own expert panels, including Dr. Cox. This PFOF mischaracterizes what happened. CVM refused to incorporate the data from Friedman et al. on the protective effects of chicken consumption and the zero or negative value of the attributable fraction. They did not incorporate or respond to Bayer/AHI recommendations that they use appropriate objective causal analysis methods, correct the mistakes they made in applying Bayes' Rule, correct for confounders such as restaurant dining and contaminated water consumption, use recent and relevant data sets (e.g., CDC case-control data) to quantify risks (or the absence of risk), or seek to validate their model by appropriate statistical analysis and/or simulation.

1068. The CVM risk assessment estimates the amount of domestically-produced poultry meat after slaughtering that contains fluoroquinolone-resistant *Campylobacter*. It also estimates the number of people who get ill from consuming that fluoroquinolone-resistant *Campylobacter* contaminated meat. Both estimates are based almost entirely on U.S. federally collected data, the Centers for Disease Control (CDC) for the human data and the

United States Department of Agriculture (USDA) for the poultry meat data. Vose WDT: p. 6, lines 47-48 and p. 7, lines 1-4

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We disagree that "It also estimates the number of people who get ill from consuming that fluoroquinolone-resistant *Campylobacter* contaminated meat". It estimates the number of people who get ill *and* consume that fluoroquinolone-resistant *Campylobacter* contaminated meat, not "the number of people who get ill *from consuming* that fluoroquinolone-resistant *Campylobacter* contaminated meat." The distinction matters since "from consuming" suggests a causal relation that is not justified. (Illnesses may have occurred anyway from the susceptible *Campylobacter* in the meat even if the resistant strains had been removed.) We further disagree that "Both estimates are based almost entirely on U.S. federally collected data, the Centers for Disease Control (CDC) for the human data and the United States Department of Agriculture (USDA) for the poultry meat data." To the contrary, as testified by Dr. Bartholomew (CVM PFOF #140), "Two case-control studies from the literature were used for input values for determining the proportion of all campylobacteriosis cases attributable to chicken (Harris et al. 1986; Deming et al. 1987)." This crucial factor drives the whole rest of the risk assessment, as estimated risk would be zero if this estimated attributable fraction were 0. It is not "based almost entirely on U.S. federally collected data," but instead is based entirely on two small, obsolete, non-representative studies, one in a student population [Cox (B-1901) P.38, P.57-64]

1069. In the CVM *Campylobacter* risk assessment model, *K* is 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. Vose WDT: p. 7, lines 25-28

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and vague. First, probabilities apply to *events*, not pathways. The term "aggregate probability" is undefined. *K* also does *not* consider "all possible pathways via which people get exposed". For example, it does not include the pathway from hospital waste to drinking water to people (and perhaps chickens), or from the environment to sea gulls to intermediate vectors to people and chickens. It does not consider paths that lead to both people and chickens. It does not consider pathways from people to chickens and back. The "conditional probability distribution of how many bacteria would be received in the exposure" is *not* considered in the model or used in calculating K. Neither is the dose-response probability function. Instead, K is just a ratio of two aggregate quantities, neither of which reflects these two ingredients. For these reasons, Vose's claims that K "implicitly" includes dose-response and microbial load information are also incorrect [Haas (B-1904) P.15 footnote 5].

1070. The draft Danish farm-to-fork risk assessment "Risk Assessment on *Campylobacter jejuni* in Chicken Products" demonstrates exactly the same behavior as we have assumed, i.e. if the prevalence of contaminated product at the end of the slaughter plants increases by some factor, the incidence of human illness will, on average, also increase by this factor. Vose WDT: p. 7, lines 34-35, and lines 37-40

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. The Danish farm-to-fork risk assessment (published as Rosenquist et al., 2002, Exhibit G-1788, pp. 10-1)1 shows precisely the opposite of what Vose claims here. It notes that a change if the prevalence of contaminated product at the end of the slaughter plants changes by a factor of 10%, the incidence of human illness will, on average, change by a factor of 30-. Obviously, in this case, the change in human health risk (30-fold) is *not* directly proportional to the prevalence of contamination (1.1-fold), as Vose asserts in CVM's PFOF #1070.

1071. The CVM modeling approach is mathematically simple, with few assumptions, but which nevertheless addressed the decision question and provided the ability to predict future levels of human health impact resulting from changes in the level of consumption, prevalence of contaminated meats, etc. Vose WDT: p. 8, lines 7-10

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. See responses to CVM's PFOFs #1055, #1057, and #1067. The CVM modeling approach is not mathematically simple. (For example, it seeks to use Bayesian conjugate priors but does so incorrectly; see Cox and Popken, 2003) It is not a predictive model. It provides no ability to predict future levels of human health impact *resulting from* anything, as it is not based on causal modeling and confuses reduced-form with structural equations [Haas (B-1904) P.16 L.19 through P.17 L.2],

1072. CVM did not use a farm to fork model. A farm-to-fork risk assessment tracks the bacterial on the food-producing animal, usually from the time it leaves the farm, through to the final food product being consumed and the effect of the consumption of the bacteria. A farm-to-fork model requires modeling an almost infinitely complex system, regarding all important components of the farm-to-fork continuum with respect to the attenuation, growth, redistribution and cross-contamination of the bacteria in question. Vose WDT: p. 8, lines 14-20

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misinformed. We disagree that "A farm-to-fork model requires modeling an almost infinitely complex system, regarding all important components of the farm-to-fork continuum with respect to the attenuation, growth, redistribution and cross-contamination of the bacteria in question." In fact, in most farm-to-fork models, the complexity of the modeled system is quite low (comparable to or simpler than PBPK models and many other models used in risk assessment). CVM's PFOF #1072 reveals a basic lack of understanding of farm-to-fork modeling. In reality, successful farm-to-fork models decompose the system being modeled into modules that are described and validated using available data (Cox, 2001). The result is that many details and important factors may be omitted from the model (as mentioned by Dr. Travis, G-1479 P.17 ¶ 65 L.17) without impairing the ability of the model to produce accurate results. It is *not* necessary to identify all factors or to model all details or "all important components of the farm-to-fork continuum with respect to the attenuation, growth, redistribution and cross-contamination of the bacteria in question" to obtain accurate results. Successfully completed farm-to-fork models (e.g., Cox and Popken, 2001; Rosenquist et al., 2002) show that Vose's claims are mistaken.

1073. An expert group of highly regarded risk assessors working on the Joint FAO/WHO Activities on Risk Assessment of Microbiological Hazards in Food, produced the report 'Hazard identification, hazard characterization and exposure assessment of *Campylobacter* spp. in broiler chickens' ... This report discusses at length the data available to quantify a dose-response relationship and noted:

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and incomplete. This proposed FOF ends with an incomplete sentence, rather than with a fact. The characterization of the authors of the report as "An expert group of highly regarded risk assessors" is unsubstantiated and inaccurate: the FAO/WHO group's main expertise was primarily in microbiology and veterinary medicine related to food-borne pathogens, rather than in risk assessment per se. The FAO/WHO invited review and comments from additional experts trained in risk assessment and related disciplines to complement the expertise of the author group.

1074. There is insufficient information in the epidemiological literature, that we have been able to review, to allow a dose-response relationship to be derived using this type of data. There is one human feeding trial study that has been conducted Black et al. (1988). This study used healthy young adult volunteers from the Baltimore community. The challenge dose was administered in milk, and the volunteers fasted for 90 minutes before and after ingesting the organism. This study involved the use of two strains of *C. jejuni* (A3249 and 81-176). Vose WDT: p. 9, lines 14-25

Bayer/AHI Response: Bayer/AHI agree that the FAO/WHO report found that "this type of data" (i.e., information in the epidemiological literature, such as that relied on by Vose for his "implicit" dose-response relationship, K) is insufficient to allow a valid or useful dose-response relationship to be derived. However, we note that this quote is taken out of context and that the FAO/WHO report in fact did use non-epidemiological data from human feeding studies to develop Beta-Poisson and related dose-response relations for *Campylobacter*, much as in B-1260 and Rosenquist et al. (2002) models. The full context of the quote in CVM's proposed FOF #1074 is as follows:

"The dose-response analysis translates the number of organisms to which an individual is exposed, into an estimate of the individual's probability of infection. In developing a relationship for the quantitative dose-response analysis there are two types of data that can be used if they are available: 1) epidemiological, outbreak data, and 2) feeding trials with human subjects. ... **There is insufficient information in the epidemiological literature**, that we have been able to review, to allow a dose-response relationship to be derived using this type of data. **There is one human feeding trial study** that has been conducted Black *et al.* (1988). This study used healthy young adult volunteers from the Baltimore community. The challenge dose was administered in milk, and the volunteers fasted for 90 minutes before and after ingesting the organism. This study involved the use of two strains of *C. jejuni* (A3249 and 81-176). Strain A3249 was isolated from a 16-year old boy with a sporadic infection after an outbreak at a camp in Connecticut. Strain 81-176 was isolated from an ill nine-year old girl in an outbreak in Minnesota. The results of the feeding trial study are presented in Table 4.1 and in Figure 4.1 and 4.2.... Several investigators have examined the available data and proposed non-threshold models for a number of pathogens

(Haas, 1983, Teunis *et al.*, 1996). **The sufficiency of these models to describe the data and more importantly the acceptance of the theory underpinning the models has resulted in non-threshold dose-response models being the currently accepted models for describing the dose-response relationship.** The primary non-threshold, single-hit models currently used in microbial risk assessment are the exponential and beta-poisson dose-response models. .. Some of the human feeding trial data of Black *et al.* (1988) has been fit to dose-response models. The dose-response data for infection for strain A3249 have been fit to the dose-response models presented using maximum likelihood techniques. The beta poisson model has been reported to provide a statistically significant fit to the data with parameters alpha = 0.145 and beta = 7.59 (Medema *et al.*, 1996; Teunis *et al.* 1996)."

This full context makes clear that the quote selected in CVM's proposed FOF #1074 is *not* part of a passage suggesting that dose-response models should not be used or that current data are not adequate to support dose-response modeling, as the selective quoting by CVM might appear to suggest. Rather, it is specifically directed at warning that epidemiological data of the type used by CVM/Vose is *not* adequate for the purposes they used it for (implicit dose-response modeling), while the more traditional dose-response modeling based on data from human feeding studies *is* adequate and appropriate for dose-response modeling – and indeed has been used for this purpose by the very FAO/WHO report that CVM cites.

1075. Later the expert group working of the Joint FAO/WHO report state: 'The human feeding trial data does not indicate a clear dose-response relationship for the conditional probability of illness following infection." Vose WDT: p. 9, lines 29-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1076. CVM did not use a farm to fork risk analysis because:

- A farm-to-fork analysis would require significant assumptions that could not be supported by data. The much simpler analysis performed by the CVM nonetheless had to deal with data gaps and thus required making a number of assumptions described in the report. A farm-to-fork analysis would have suffered far more from gaps in data;
- A farm-to-fork would be costly and difficult to maintain and update because any changes in husbandry, transportation, processing, and human behavior could require new studies and data gathering activity;
- A farm-to-fork requires a dose-response (D-R) model, for which available data on *Campylobacter* were poor, based on feeding trials (known to be poor predictions of real world risk) and for which there is no generally agreed upon analysis;

In the CVM modeling approach chosen, yearly updated K and p values can track change, as they relate to this risk question, of the consumer risk/lb contaminated meat. In other words, if industry found methods to reduce the human health impact during processing, storage, consumer handling, retail, etc. this could have been taken into account without the need of large data collection studies. Vose WDT: p. 10, lines 24-40

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being a conjunction of inaccurate, misinformed, misleading, and unsubstantiated opinions rather than a statement of fact. These unsupported opinions and personal interpretations are contradicted by (among

others) the facts that experimental dose-response data in humans are readily available; that data from these feeding studies are *not* known to be poor predictors of real-world risk (which also occurs through ingestion); that several peer-reviewed published dose-response models for *Campylobacter* have already been developed that are based solidly on data without suffering from the data gaps and required assumptions mentioned in this PFOF; and that it is generally agreed that the analysis by the Beta-Poisson model provides an appropriate analysis of the feeding trial data (e.g., Travis testimony, G-1479, p. 16, lines 7-9; FAO/WHO report cited in CVM PFOFs #1073-1075.)

1077. The WHO expert panel concluded, in their efforts to produce a *Campylobacter* spp. in broiler chickens farm-to-fork risk assessment:
"Given the value of knowing the relative importance of consumer behavior variables in food safety (cooking temperature profiles and cross-contamination processes), the ultimate risk characterization (in both the absolute and comparative senses) will be highly dependent upon several 'ungrounded' assumptions. It is possible that a carefully directed research effort could elucidate some of these issues. In the near term, however, risk characterization as it relates to consumer risk factors of cooking and cross-contamination will continue to be largely a matter of mathematical combinations of unvalidated assumptions. These may be useful for conceptualizing the risk factors in support of food safety decisions, but are not likely to be sufficient to stand-along as providing reliable numerical estimates of risk." Vose WDT: p. 10, lines 42-49, and p. 11, lines 1-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1078. The CVM investigated alternative approaches to modeling the risk issue, but concluded that the paucity and ambiguity of available data made taking other modeling approaches impractical. Their conclusions have subsequently been borne out by the WHO expert panel. Vose WDT: p. 11, lines 5-8

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. The WHO panel's comments referred only to its own model and so do not substantiate or bear out a broader claim that "the paucity and ambiguity of available data made taking other modeling approaches impractical". (Indeed, members of the WHO expert consultation also considered and rejected Vose-CVM's approach to modeling as obviously wrong and irrelevant to scientifically accurate or useful work, rather than "bearing out" CVM's conclusions.) That other modeling approaches are practical, despite Vose/CVM's claims to the contrary, is demonstrated in the published, peer-reviewed models by Cox and Rosenquist et al. Had The "the paucity and ambiguity of available data" that CVM refers to stem solely from their refusal to use the plentiful data from CDC (described in testimony of Dr. Angulo) and other sources [Cox (B-1901) P.50, 56].

1079. The risk assessment implicitly includes pathogen load in the factor *K*. Vose WDT: p. 11, lines 16-17

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. It misinterprets K, which does not include pathogen load in any way (implicit or explicit) [B-1901, p. 19] K is a ratio of two aggregate quantities (number of cases and pounds of

meat). It has the same value, given these two aggregate input quantities, no matter how pathogen load changes. For example, if pathogen load has no epidemiologically detectable effect on number of cases or pounds of meat consumed, as we believe is realistic, then K will remain the same even if all pathogen loads are reduced 10-fold. Thus, K will not change at all even if pathogen load changes greatly, contrary to the claim that the risk assessment "implicitly includes" pathogen load [Haas (B-1904) P.15 footnote 5; Haas (B-1904) P.15 L.11 – P.16 L.2]

By Mr. Vose's own testimony (P.11 ¶ 42 L.28, 29), if K truly included pathogen load, *K should not be a constant,* but instead should depend on the distribution of microbial loads, which is variable. Since risk management decisions such as a ban on enrofloxacin are expected to change microbial loads, they should change K, so that the current estimate of K does not predict the risks from actions that change microbial loads. Treating K as a constant ignores this. According to Vose's own testimony (*ibid*), K should have different values for different pounds of contaminated meats, depending on the microbial loads that they carry. But treating K as a constant ignores this distribution. For all these reasons, we disagree that "The risk assessment implicitly includes pathogen load in the factor *K*."

1080. *K* is effectively the probability that a pound of contaminated meat at slaughter plant will produce a case of campylobacteriosis in humans. If one were to break up that probability into smaller steps, one could do so as follows:

- The probability the contaminated meat contains X bacteria;
- The probability that after processing, storage, etc the bacteria contains Y bacteria given it started off with X bacteria;
- The probability that exposure to the Y bacteria then causes an illness.

Integrating these probabilities for all values of X, all values of Y, and all dose-response relationships for the individuals in the U.S., one arrives at *K*. The integration over all X in the inclusion of the bacterial load at the slaughter plant. The integration to Y is taking into account the distribution of bacteria at the point of consumption. Vose WDT: p. 11, lines 19-31

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and incomplete as well as misleading. First, this proposed FOF interprets *K* causally, which is unjustified and mistaken. (Cox B-1901, p. 20 especially the discussion of the distinction between "structural" (causal) and "reduced-form" (statistical) equations, which CVM has confused in its PFOF #1080.) No causal analysis has been done and no valid causal interpretation of K is possible [Haas (B-1904) P.19 L.12 through P.20 L.6; Cox, 2001, Chapter 4] Second, the assertion "The integration over all X in the inclusion of the bacterial load at the slaughter plant" appears to be a sentence fragment. Third, the description "Integrating these probabilities for all values of X, all values of Y, and all dose-response relationships for the individuals in the U.S., one arrives at *K*" is inaccurate and misleading: this is not at all how *K* was arrived at in CVM's work. We believe that arriving at it this way gives a value of zero (correct answer) rather than the positive value that CVM has arrived at by taking the ratio of two positive numbers based on causally irrelevant aggregate statistics [Haas (B-1904) P.15 footnote 5]. The assumption that the procedure outlined in PFOF #1080 would arrive at the same value of *K* as CVM's is unjustified and unsubstantiated.

1081. One possible method of correction for year-to-year differences in the bacterial contamination load was discussed in Section 1 of the CVM *Campylobacter* risk assessment report under the heading: *Accounting for changes in the bacterial load of contaminated carcasses*. Vose WDT: p. 11, lines 44-46

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. The method that CVM proposed is in fact inappropriate and *ad hoc* and technically flawed. It does not truly account for changes in the bacterial loads [Cox (B-1901) P.55, P.83-87; Cox, 2001, p. 127]

1082. Simple corrections to the model to account for future changes in medical practice, patient behavior, and resistant *Campylobacter* prevalence in poultry, and for changes in the number of U.S. citizens were also discussed in the same section, highlighting the adaptive nature of the CVM model. Vose WDT: p. 11, lines 45-49 and p. 12, lines 1-2.

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being an inaccurate characterization. The CVM model is *not* adaptive according to standard definitions. Rather, the section mentioned in CVM's PFOFs #1081 and #1082 seem to say "We think we could have corrected our analysis by fixing some of its mistakes (especially, our failure to treat microbial loads) and we think we could correct it in future by making some changes, especially to use relevant future inputs instead of irrelevant past ones, but we chose not to do it correctly now. If we correct the analysis in future, we expect its answers will change." This is not "highlighting the adaptive nature of the CVM model", but arguing (without apparent justification) that its flaws are not so bad that they might not some day be fixed. We disagree, since the suggested fixes seem wholly inadequate [Cox (B-1901) P.25].

1083. The method proposed in the report to correct for bacterial load was to make an approximation that the number of bacteria on a contaminated carcass was log-exponentially distributed (i.e. the log of the number of bacteria is exponentially distributed). Then a fractional reduction of bacterial load would be mathematically equivalent to a reduction in the prevalence of contaminated carcasses, with the remaining carcasses having the same load distribution as the original. The method is fairly crude but by continuous updating of the parameter K only very sudden changes from one year to the next of the bacterial load distribution (for example, with the introduction of irradiation of carcasses) would need to be addressed in this manner. Other correction methods could, of course, also be explored. Vose WDT: p. 12, lines 4-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1084. Although CVM's model does not attempt to explicitly incorporate modeling of pathogen load, the effect of pathogen load is nonetheless implicitly incorporated into the model. Vose WDT: p. 12, lines 35-37

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. See response to CVM PFOF #1079.

1085. The model assumes that the distribution of pathogen load remains fairly constant between successive years, but possible corrections are available if this were to change dramatically. Vose WDT: p. 12, lines 40-42

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and misleading. The assertion that "possible corrections are available if this were to change dramatically" is unsubstantiated and incorrect. The correction methods that CVM has suggested as being possible in Section 1 are ad *hoc*, inappropriate, and technically flawed [Cox (B-1901) P.55, P.83-87; Cox, 2001, p. 127].

1086. An *explicit* dose-response step need only be included in a microbial or antimicrobial risk assessment if its inclusion materially improves the quality of the decision that would be made from it. Vose WDT: p. 13, lines 2-4

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and unsubstantiated opinion rather than fact. An explicit dose-response step is needed to get correct answers, whether or not the answers are used to change decisions [Haas (B-1904) P.10 L.13-15].

1087. It was unnecessary for the purpose of the CVM risk assessment to explicitly include a dose-response component. In fact, given the very poor current understanding of what that dose-response relationship might be between *Campylobacter* and the human illness, it was of considerable value in improving the robustness of the analysis to be able to find an alternative risk assessment approach that did not oblige defining this dose-response relationship. Vose WDT: p. 13, lines 47-48 and p. 14, lines 1-5

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and as being unsubstantiated opinion rather than fact. The assertion "It was unnecessary for the purpose of the CVM risk assessment to explicitly include a dose-response component" is an unsupported opinion. It was indeed necessary "to explicitly include a dose-response component" to produce correct and meaningful results – CVM just did not do so [Haas (B-1904) P.10 L.13-15]. The assertion "It was of considerable value in improving the robustness of the analysis to be able to find an alternative risk assessment approach" is also an unsupported opinion, not a fact. Indeed, the failure to take into account relevant dose-response information made the analysis *less robust,* not more, by making its conclusions depend totally on an assumption (proportional relation between exposure and response) that turns out to be incorrect [Haas (B-1904) P.19 L.12 through P.20 L.6].

1088. A key assumption in the CVM model is that fluoroquinolone use in poultry results in reduced susceptibility of *Campylobacter* in the poultry to fluoroquinolones, and that humans are exposed to these bacteria and become ill. Vose WDT: p. 14, lines 8-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1089. There are a number of guidelines for attempting to validate causal relationships. The most important are 1) we can postulate why one variable (in this case, prevalence of resistance in U.S. *Campylobacter* is domestically-reared poultry, call it X) influences the size

of another variable (in this case, the number of domestically-acquired fluoroquinolone-resistant case of human campylobacteriosis, call it Y); and 2) we can observe a lagged correlation between these values (in this case, and increase in X produced a corresponding increase in Y some time later). Vose WDT: p. 14, lines 20-27

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and unsubstantiated. Although we agree that "There are a number of guidelines for attempting to validate causal relationships" (e.g., Shipley, 2000, cited in Cox (B1901), p. 29; Cox, 2001, Chapter 4), items (1) and (2) in CVM PFOF #1089 are not among them, let alone being "the most important". Vose's discussion of "a lagged correlation" between values for which "we can postulate why one variable... influences the size of another" is a personal and incorrect intuitive view of methods "for attempting to validate causal relationships". It does not correctly characterize current methods for building and validating causal models (Shipley, 2000; Cox (B1901), p. 29). In fact, lagged correlations may occur because of confounders, and thus have no relation to valid causality between two variables. Moreover, correct methods of causal analysis and validation are *not* based on "what we can postulate", as claimed in item (1) of this PFOF, but rather on what can be objectively discovered from data, e.g., using conditional independence tests [Cox, B1901, p. 29]. CVM's PFOF #1089 illustrates Vose/CVM's idiosyncratic view of how to validate causal relations. It is an incorrect view, and is inconsistent with correct techniques for causal analysis [Cox, B1901, p. 29].

1090. Anderson et al (2001), in their AHI-sponsored risk assessment, discuss the significant evidence internationally for correlation between the introduction of fluoroquinolone for use in food-producing animals and the increase in fluoroquinolone-resistant cases of campylobacteriosis. Vose WDT: p. 14, lines 40-43

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. First correlation is not an appropriate measure of association between an intervention (introduction of fluoroquinolone for use in food-producing animals) and a trend (increase in fluoroquinolone-resistant cases of campylobacteriosis). Second, "the significant evidence internationally" shows that there is no association between introduction of fluoroquinolone for use in food-producing animals and the increase in fluoroquinolone-resistant cases of campylobacteriosis (Cox, 2001), other than the spurious association inevitable when events occur in the midst of increasing time series [Cox (B-1901) P.44; Cox (B-1901) P.53]. The apparent implication on CVM's PFOF #1090 that international evidence indicates a possible causal relation between introduction of fluoroquinolone for use in food-producing animals and the increase in fluoroquinolone-resistant cases of campylobacteriosis is incorrect and unsubstantiated.

1091. The incidence of cases of campylobacteriosis is very seasonal, due in part to travelling (which we excluded from our analysis), in part probably to changes in cooking practices, food handling and eating practices, and also probably in part due to the weather allowing greater survivability of these thermophilic bacteria. ... the model does not require estimating seasonal variations because it estimates an average for the year. This is valid mathematically because a special feature of the Poisson mathematics that is used in the CVM model is that the expected number of cases for each season can be added together." Vose WDT: p. 15, lines 4-7 and lines 9-12

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. First, it is not true that traveling was "excluded from our analysis"; to the contrary, CVM's estimates of excess illness-days associated with resistance depend entirely on *not* excluding foreign travel cases [Cox (B-1901) P.22]. Second, we deny the embedded assumption that "Poisson mathematics" is appropriate. This assumption is embedded in the assertion "This is valid mathematically because a special feature of the Poisson mathematics that is used in the CVM model is that the expected number of cases for each season can be added together". The assumption is incorrect. Poisson mathematics implies that the means and variances of counts (e.g., cases) are equal. As Dr. Molbak's testimony correctly notes, there is very large (extra-Poisson) variation in the count data from different FoodNet areas [Molbak (G-1468) P.4 L.38-44; P.6, Table 1; P.8 L.17-18; P.9, Table 3]. Clearly, the simple Poisson model is *not* appropriate for these data.

1092. All food safety models contain important assumptions. Vose WDT: p. 15, line 16

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. For example, food safety models based directly on relevant data (e.g., the data showing how human risk of campylobacteriosis decreases with chicken handling and consumption) analyzed using flexible nonlinear regression models (Shipley, 2000, cited at [Cox, B1901, p. 29]. need not "contain important assumptions."

1093. CVM called for data in the Federal Register, making available the draft report and model on the Web, sponsored a public conference to discuss the draft assessment, sponsored experts from around the world to discuss the assessment in an open forum in that conference, and evaluated and responded to comments received. CVM has taken great care to collect, evaluate and list sources of data used in its risk assessment. Despite the simplicity of the modeling, the report uses 125 references, obviously not including material that was read and found irrelevant. CVM even provided data, advice and personnel time to Dr. Cox to help in his efforts to produce an alternative model. Vose WDT: p. 15, lines 27-37

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It is not true that CVM "responded to comments received" for many key comments from Bayer, AHI, other members of industry, and members of its own expert panels. They refused to respond to comments urging them to incorporate the CDC case-control data, US and international data on the protective effects of chicken handling and consumption, repeated pleas and recommendations that they use appropriate objective causal analysis, correct the mistakes they made in applying Bayes' Rule, correct for confounders, use recent and relevant data sets (e.g., CDC case-control data) to quantify risks (or the absence of risk), seek to validate their model by appropriate statistical analysis and/or simulation, etc. They do not appear to have made any effort to incorporate or respond to any of our most important recommendations. Further, we disagree that "CVM even provided data, advice and personnel time to Dr. Cox to help in his efforts to produce an alternative model." Cox and Vose met to discuss how to improve upon the CVM approach to risk assessment. We are unaware of data that FDA provided voluntarily to Dr. Cox to help in his efforts to produce an alternative model.

1094. In conclusion, all CVM assumptions have been thoroughly investigated, explained and debated with the risk management staff. The structure of CVM's model means that there are a minimal number of these assumptions which increases confidence in using the results. Vose WDT: p. 16, lines 34-36

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. It mischaracterizes what has happened. In reality, the crucial assumption that adverse health response is proportional to exposure has not been investigated. When it is investigated, it is inconsistent with the data from FoodNet and elsewhere [Cox (B-1901) P.15; citing B-1252]. Second, we disagree that "The structure of CVM's model means that there are a minimal number of these assumptions". Over a dozen assumptions are listed in CVM's report, and this number could be greatly reduced by using fewer assumptions and more relevant data. Third, we disagree that making a small number of assumptions "increases confidence in using the results", especially since all the main assumptions that have been made by CVM (e.g., that human health risk is proportional to chicken consumed, that K is the same for all people, that all domestic non-treatment related resistance comes from chickens, that chickens are a dominant contributor to human campylobacteriosis rates, etc.) are incorrect Haas (B-1904) P.23 L.10-11. We disagree that using even a small number of incorrect assumptions "increases confidence in using the results" when the results are determined directly by the mistakes in the assumptions, as in this case (*ibid*).

1095. The Society for Risk Analysis and the National Research Council agree that the form that a risk assessment takes should be driven by the decision-makers needs. The CVM model did this, whereas a farm-to-fork would not have. Vose WDT: p. 16, lines 40-42

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. We specifically disagree that "The CVM model did this, whereas a farm-to-fork would not have." Both parts of this compound assertion are incorrect, unsubstantiated opinions. For example, the CVM model does not quantify the effects on human health of any risk management decisions. The farm-to-fork models of B-1260; Cox and Popken (2003) do. Vose's bashing of the farm-to-form approach reflects his personal opinion, not fact.

1096. Antimicrobial risk assessment needs to address more complicated issues than microbial risk assessment, and requires a flexible modeling approach. Vose WDT: p. 16, lines 43-44

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate and introducing a false dichotomy. A well-conducted microbial food safety risk assessment can include resistant as well as susceptible bacteria [Cox, B1901, p. 12] and can thus subsume what Vose terms an "antimicrobial food safety risk".

1097. The CVM model was predictive and provided CVM management with meaningful and useful decision-support in a timely fashion. Vose WDT: p. 16, lines 45-46

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. See response to CVM PFOF #1067.

1098. The CVM model was designed to help industry manage their use of fluoroquinolones in the least restrictive way possible to protect the human health. Vose WDT: p. 16, lines 47-48

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate. The CVM model does not even address the impacts of changes in use of enrofloxacin on protecting human health [Cox (B-1901) P.49] and therefore is *not* "designed to help industry manage their use of fluoroquinolones in the least restrictive way possible to protect the human health". More specifically, the model does not quantify whether or by how much increasing the use of enrofloxacin would increase protection of human health. It provides no predictively useful information (Haas (B-1904) P.23 L.10-11) to "help industry manage their use of fluoroquinolones in the least restrictive way possible to protect the human health". Instead, the CVM model arbitrarily allocates all blame for ciprofloxacin-contaminated streams and other sources of domestic resistance to enrofloxacin use in chickens (Bartholomew, WDT G-1454, p. 9, lines 28 and 29). ; [Patterson (B-1910) P.4 L.8-12; Newell (B-1908) P.40 L.20-22; Feldman (B-1902) P.35 L.1 – P.36 L.11]). CVM has designed and used the model not to find "the least restrictive way possible to protect the human health" but to propose the most restrictive and least effective possible risk management approach (withdrawal of enrofloxacin) for promoting human health of all that have been evaluated. B-1260; (Cox and Popken, 2003).

1099. The CVM model requires the minimum of assumptions, and was supported by largely federally collected data. Vose WDT: p. 17, lines 1-2

Bayer/AHI Response: Bayer/AHI disagree with this compound PFOF as being inaccurate. The CVM model requires many unnecessary and incorrect assumptions (e.g., that human health risk is proportional to chicken consumed, that K is the same for all people, that all domestic non-treatment related resistance comes from chickens, that chickens are a dominant contributor to human campylobacteriosis rates, etc.) because it refuses to use relevant data instead [Cox (B-1901) P.50, 56]. It is refuted, rather than supported, by Federally collected data such as the CDC case-control study (*ibid*).

1100. The CVM investigated alternative approaches, and cooperated with Dr. Cox to help develop his models, but concluded that the CVM approach provided the greatest decision-support. Vose WDT: p. 17, lines 3-5

Bayer/AHI Response: Bayer/AHI disagree with this compound PFOF as being inaccurate. CVM did not cooperate with Dr. Cox to help develop his models.

1101. The CVM went to great lengths to invite debate about their approach and collect useful information. Vose WDT: p. 17, lines 6-7

Bayer/AHI Response: Bayer/AHI disagree with this compound PFOF as being an inaccurate and unsubstantiated opinion rather than a fact. In our experience, it seems that CVM sought to suppress and limit debate and critical discussion at their public meetings, packed the agenda with known supporters, and in many cases ignored and tried to cut off critical comments and recommendations. They did not "go to great lengths to collect useful information" about relevant data and methods of analysis, but instead repeatedly refused to use many recommended

data sources and analytic methods that did not support their conclusions. For example, CVM refused to incorporate the data from CDC and other studies (in 2000, 2001, 2002, and even now) on the protective effects of chicken consumption and the zero or negative value of the attributable fraction [Cox (B-1901) P.22, P.57-64]. They did not incorporate or respond to repeated recommendations that they use appropriate objective causal analysis methods, correct the mistakes they made in applying Bayes' Rule, correct for confounders such as restaurant dining, use recent and relevant data sets (e.g., CDC case-control data) to quantify risks (or the absence of risk), or seek to validate their model by appropriate statistical analysis and/or simulation.

1102. The CVM modeling approach was able to avoid direct modeling of bacterial load and dose-response relationships for which data are sparse and theories are currently tenuous. This was consistent with NRC/NAS guidelines. Vose WDT: p. 17, lines 8-12

Bayer/AHI Response: Bayer/AHI disagree with this compound PFOF as being inaccurate. Data on bacterial loads are not sparse (e.g., B-1260; Cox and Popken, 2003). NRC/NAS guidelines call for using relevant exposure (i.e., bacterial load) and dose-response information when it is available, as it is in this case, rather than avoiding it [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] Thus, we disagree that "This was consistent with NRC/NAS guidelines."

Robert D. Walker (G-1481)

1103. Dr. Walker is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

1104. In vitro antimicrobial susceptibility testing is performed by exposing a known concentration of a pure bacterial culture, in the appropriate growth phase, to increasing concentrations of antimicrobial agents. Walker WDT: p. 3, lines 1-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1105. The results of in vitro antimicrobial susceptibility testing may be reported qualitatively (*susceptible, intermediate or resistant*) or quantitatively, via a numerical value representing the minimum concentration of the drug that is required to inhibit the growth of the pathogen. Walker WDT: p.3, lines 3-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1106. The quantitative value of in vitro antimicrobial susceptibility testing is referred to as the minimal inhibitory concentration (MIC). Walker WDT: p. 3, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1107. The MIC values are expressed in micrograms per milliliter or milligrams per liter. Walker WDT: p. 3, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1108. MIC refers to the lowest concentration of an antimicrobial agent that it takes to inhibit the growth of a bacterium. Walker WDT: p. 3, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1109. Standardized susceptibility testing methods use one of three methods. These are agar dilution, the "Gold Standard" of susceptibility testing, broth dilution, and agar diffusion. Walker WDT: p. 3, lines 15-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1110. Agar dilution tests are performed by incorporating the antimicrobial agent to be tested into the appropriate agar medium using serial two-fold dilution and applying the bacterial inoculum to the surface of the agar plate, usually by using a multi-pin replicating apparatus. Walker WDT: p. 3, lines 17-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1111. The endpoint for agar dilution tests, the MIC, is determined by the unaided visual inspection of the agar surface. Walker WDT: p. 3, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1112. The results of agar dilution tests may be reported qualitatively, if appropriate interpretive criteria has been determined for the bacterium/drug combination that was tested and/or quantitatively. Walker WDT: p. 3, lines 22-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1113. *Broth dilution* may be performed using macro (volumes greater than one mL) or micro (usually volumes of 100 µL or less). Walker WDT: p. 3, lines 26-27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1114. With *broth dilution*, a standardized suspension of bacteria is tested against two-fold serial dilutions of an antimicrobial agent in a standardized liquid medium. Walker WDT: p. 3, lines 27-29

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1115. The endpoint for the broth dilution is also the MIC. Walker WDT: p. 3, lines 29-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1116. Broth dilution results may be reported as qualitative and/or quantitative. Walker WDT: p. 3, lines 32-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1117. The *disk diffusion* testing method generates an endpoint based on the diffusion of an antimicrobial agent from a solid carrier *(e.g.,* paper disk) into a solid culture medium that has had the surface seeded with a known bacterial inoculum. Walker WDT: p. 3, lines 35-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1118. The diffusion of the antimicrobial agent into the culture medium produces an antimicrobial gradient. Walker WDT: p. 3, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1119. In the disk diffusion method, when the concentration of the antimicrobial is sufficient to inhibit the growth of the bacterium growing on the surface of the agar, a zone of inhibition is formed. Walker WDT: p. 3, lines 39-41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1120. In the disk diffusion method, the boundary of this zone of inhibition correlates with the MIC for that particular bacterium/antimicrobial combination. Walker WDT: p. 3, lines 41-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1121. In the disk diffusion method, the larger the zone of inhibition, the smaller the concentration of antimicrobial required to inhibit the organism's growth. Walker WDT: p. 3, lines 43-44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1122. The Etest represents a diffusion testing method that can generate quantitative results. Walker WDT: p. 4, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1123. With Etest, a predefined concentration gradient of an antimicrobial drug is impregnated into one side of a plastic strip which is approximately 5 mm wide and 60 mm long. The gradient covers a continuous concentration range which corresponds to 15 two-fold dilutions in a conventional MIC method. This plastic strip is placed on a seeded agar surface similar to

the method in which the disks are placed for the disk diffusion test. Walker WDT: p. 4, lines 2-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1124. When an Etest strip is applied to an inoculated agar plate, there is an immediate release of the antimicrobial from the plastic carrier surface into the agar matrix. A continuous and exponential gradient of antimicrobial concentrations is created directly underneath the Etest strip. After incubation, a symmetrical inhibition ellipse centered along the strip is observed on the agar plate. Walker WDT: p. 4, lines 7-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1125. In the Etest method, the MIC value for the bacterium/drug combination is read from the scale on the strip in terms of μg/mL where the ellipse edge intersects the strip. Walker WDT: p. 4, lines 12-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1126. One of the advantages of the Etest is that because it comprises a continuous gradient, MIC values between two-fold dilutions can be obtained. Walker WDT: p. 4, lines 14-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The E-test is in essence a disc diffusion test and carries disadvantages compared to the approved method of agar dilution. Silley, B 1913, P 16 15-22. In addition, broth dilution and agar dilution testing methods easily generate intermediate MICs of 3, 5, 6, 12 if required; the antibiotic concentrations added to the media are simply altered to give a different dilution series.

1127. Broth dilution and agar dilution testing methods may generate MICs such as 2, 4 or 8 μg/mL (doubling dilutions), where the Etest can generate these same MIC values plus 3, 5, 6 and 12 μg/mL. Walker WDT: p. 4, lines 16-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The E-test is in essence a disc diffusion test and has been shown not to be as accurate as the microdilution broth test when comparing to the approved method of agar dilution. Silley, B 1913, P 11, L 10-16, P16 L 17-22 In addition, broth dilution and agar dilution testing methods easily generate intermediate MICs of 3, 5, 6, 12 if required; the antibiotic concentrations added to the media are simply altered to give a different dilution series.

1128. Regardless of the testing method, susceptibility results are generated as numerical values. These values may be expressed as the MIC of a bacterium/drug combination (e.g. 0.5 μg/mL) or the size of the zone of inhibition (e.g., 33 mm). Walker WDT: p. 4, lines 23-25

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1129. The interpretative criteria used for bacterium/antimicrobial agent interactions are susceptible, intermediate and resistant. Walker WDT: p. 4, lines 31-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1130. "Susceptible" implies that there is a high likelihood of a favorable clinical outcome when the drug is administered at its label dose. Walker WDT: p.4, lines 33-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The statement is incomplete. "Susceptible" needs to be defined and it is only clinical susceptibility, determined by the use of interpretive criteria, i.e., clinical breakpoints, that is directly predictive of the clinical outcome of an antimicrobial treatment. B-1913 P. 45-53.

1131. "Intermediate" is a "buffer zone" to minimize the impact of small, uncontrolled technical factors. Walker WDT: p. 4, lines 35-36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1132. Intermediate is also used for antimicrobial agents that can inhibit bacterial pathogens causing disease in body sites where the drug may be concentrated. Walker WDT: p.4, lines 36-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1133. "Resistant" implies that the concentration of the drug required to inhibit the growth of the pathogen is such that there would not be a favorable clinical outcome. Walker WDT: p.4, lines 38-40

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The statement is incomplete. "Resistant" needs to be defined and it is only clinical resistance, determined by the use of interpretive criteria, i.e., clinical breakpoints, that is directly predictive of the clinical outcome of an antimicrobial treatment. B-1913 P.45-53.

1134. The MIC, or zone diameter size, used to determine if a bacterium is susceptible, intermediate or resistant is called the breakpoint. In other words, the breakpoint is a dividing point at which a distinction is made within a population. Walker WDT: p. 4, lines 40-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1135. In reference to bacteria and antimicrobial agents, the breakpoint is the concentration, expressed as a MIC or the size of the zone of inhibition, that distinguishes between a susceptible, intermediate or resistant bacteria. Walker WDT: page 5, lines 1-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1136. NCCLS has published two documents, the M23-A2 and the M37-A2, which describe guidelines that a drug sponsor needs to follow to establish interpretive criteria acceptable to the NCCLS. Walker WDT: page 5, lines 21-24; G-1795 and G-1797

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1137. The pharmacology of antimicrobial chemotherapy can be divided into two principal components; pharmacokinetics (PK) and pharmacodynamics (PD). Walker WDT: page 6, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1138. Pharmacokinetics refers to the absorption, distribution and elimination of drugs in the body. Walker WDT: page 6, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1139. Pharmacodynamics includes the relationship between antimicrobial concentration, either in serum or at the site of infection or both, and the pharmacological and toxicological effects of the antimicrobial drug. Walker WDT: page 6, lines 11-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1140. With respect to antimicrobial drugs, the essential factor is the relationship between concentration of the antimicrobial drug and the antimicrobial effect against the bacterium. Walker WDT: page 6, lines 14-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1141. The maximum concentration of drug attained in serum after a dose is referred to as the Cmax. Walker WDT: page 6, lines 16-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1142. The product of detectable drug concentration relative to time is described by the area under the curve (AUC). In other words, AUC is the area under the graphed serum-drug-concentration vs. time curve following administration of an antimicrobial agent. Walker WDT: page 6, lines 17-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1143. Regarding the PK-PD parameters for fluoroquinolones, the AUC:MIC ratio generally has the strongest correlation with successful outcome in animal and human infections. Walker WDT: p. 6, lines 22-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1144. There are no NCCLS interpretive criteria for any antimicrobial agent for the in vitro antimicrobial susceptibility testing of *Campylobacter*. Walker WDT: p. 6, lines 34-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1145. There is a NCCLS approved standardized testing method and quality control ranges for five antimicrobial agents (Ciprofloxacin, doxycycline, erythromycin, gentamicin, and meropenem). Walker WDT: p. 6, lines 36-38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1146. 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. Walker WDT: p. 6, lines 42-44

Bayer/AHI Response: Bayer/AHI dispute this PFOF. These breakpoints are not relevant as they are microbiological breakpoints and have not been established according to the criteria for clinical breakpoints. In addition the disc diffusion was used in the establishment of these breakpoints, which is a method not advocated for *Campylobacter* by Dr. Walker in his WDT. Ref nr 15 in WDT by Dr Walker G-1481.

1147. The proposed resistance breakpoints for *Campylobacter* by the Comite de L'Antibiogramme de la Societe Francaise de Microbiologie are >2 µg/mL for ciprofloxacin and >4 µg/mL for erythromycin. Walker WDT: p. 6, line 44 and p. 7 lines 1-2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. These breakpoints are not relevant as they are microbiological breakpoints and have not been established according to the criteria for setting clinical breakpoints. In addition the disc diffusion method was used in the establishment of these breakpoints which is a method not advocated for *Campylobacter* by Dr. Walker in his WDT. Ref nr 1 in WDT by Dr. Walker G-1481.

1148. The Danish surveillance system lowered its resistance breakpoint for ciprofloxacin to 1 µg/mL in 2001, based on the distribution of MIC values in the population of *Campylobacter* analyzed in their surveillance laboratories. Walker WDT: p. 7, lines 3-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This is not relevant as a breakpoint based on the *in vitro* distribution of MICs since it is a microbiological breakpoint and does not predict clinical efficacy. In addition the statement is false as DANMAP 2001 P 31 (G-1606) reads "In 2001 the breakpoint for ciprofloxacin was adjusted from >1 to >2."

1149. Many scientific reports use the NCCLS interpretive criteria generated for *Enterobacteriaceae* to determine susceptibility and resistance to ciprofloxacin for *Campylobacter* (4 µg/mL). Walker WDT: p. 7, lines 8-10

Bayer/AHI Response: Bayer/AHI agree that many scientific reports use the NCCLS interpretive criteria generated for *Enterobacteriaceae* to determine susceptibility and resistance to ciprofloxacin for *Campylobacter* (4 mcg/mL), however they do not agree that this is appropriate since these breakpoints do not accurately predict clinical efficacy. Newell DWT, P.14 L.1-2, Burkhart DWT, P.4 L.22-24, P.10 L.1-2.

1150. 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). Walker WDT: p. 7, lines 17-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is not relevant and is misleading. Gastrointestinal tract concentrations are much greater than serum concentrations rendering serum concentrations useless in predicting clinical efficacy for enteric infections. Silley WDT: P. 13, L.12-13, 17-19.

1151. 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. Walker WDT: p. 7, lines 32-35

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As in PFOF 1150, this is not relevant as it refers to serum concentrations and a vast majority of the *Campylobacter jejuni* and *coli* infections are localized in the gut, where the achieved ciprofloxacin concentrations are much higher, and which would support substantially higher clinical breakpoints than those presently used. Silley B 1903, P13 L 8-11).

1152. The overall agreement of MICs between the Etest and agar dilution methods was 61.9%. Walker WDT: p. 9, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1153. Ciprofloxacin MIC agreement between the Etest and agar dilution methods was 85.2%. Walker WDT: p. 9, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1154. Using a ciprofloxacin-resistant breakpoint of either 1.0 or 4.0 µg/mL, Etest under-reported the number of ciprofloxacin-resistant strains. Walker WDT: p. 9, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF to the extent this PFOF refers to in vitro resistance.

1155. Surveillance programs or diagnostic laboratories using the Etest for measuring ciprofloxacin susceptibility in *Campylobacter* are likely to underestimate the true prevalence of fluoroquinolone-resistant strains. Walker WDT: p. 9, lines 14-16

Bayer/AHI Response: Denied. This statement is inaccurate as most data is based on sensitive strains. Baker (1992) showed that the E-test resulted in marginally lower MICs for ciprofloxacin (geometric mean MIC 0.07 μg/ml) compared to broth dilution and agar dilution (geometric mean MIC values 0.08 and 0.13μg/ml respectively), however as in most of these studies the comparisons were carried out with largely sensitive strains. It is therefore worth commenting that Baker (1992) also showed that for tetracycline where there was a greater spread in susceptibility of the test strains that whilst the E-test averaged one $\log_2$ dilution lower for susceptible strains it was fourfold higher for resistant strains. It remains to be seen whether this would hold for ciprofloxacin. This point was similarly made by Ge *et al,* (2002) although the apparent lack of a full data set made it difficult to establish whether the statement, "the E-test tended to yield much higher resistant MICs than those measured by agar dilution at the resistant end of the MIC ranges" was true for ciprofloxacin. These workers did show that E-test MICs were always one to two dilutions lower than those obtained via agar dilution at the susceptible end of the MIC ranges. (Silley B-1903 P.43-44)

1156. MICs obtained using Etest were generally lower than those by agar dilution regardless of the antimicrobial tested. Walker WDT: p. 9, lines 18-19

Bayer/AHI Response: Denied. This is not accurate In the comments from Ge et al (2003), belonging to Dr Walkers group, it was suggested that one of the reasons why the E-test may result in lower MICs for *Campylobacter* spp. for certain antimicrobials is that it has not been standardized and validated for *Campylobacter* as has the agar dilution method. The authors also commented that whilst it is a simple method, reading of the plates can be subjective and variable. One of the technical problems that arose during the reported study was poor growth of some *Campylobacter* isolates on E-test plates causing difficulty in interpreting E-test results. (Silley B-1903 P.43-44)

1157. The College of American Pathologists (CAP), the American Association of Veterinary Laboratory Diagnosticians (AAVLD) and the United States Food and Drug Administration (FDA) have all accepted the NCCLS as the standards setting body for antimicrobial susceptibility testing. Walker WDT: p. 9, lines 31-35

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1158. Based on the absorption, distribution and elimination pattern of ciprofloxacin in humans, a bacterial pathogen (including *Campylobacter*) with an MIC >1.0 μg/mL to ciprofloxacin would most likely not respond to therapy and thus should be considered resistant. Walker WDT: p. 10, lines 11-14

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This statement is based on the assumption that it is the serum concentration that is responsible for activity against *Campylobacter.* The vast majority of *Campylobacter* infections are enteric and it is thus the concentrations in the gastrointestinal tract which will determine the response to treatment and thereby, the clinical breakpoint. Applying the arguments by Dr. Walker, considering the high ciprofloxacin concentrations in the gastrointestinal tract, will result in a substantially higher breakpoint for clinical resistance. B-1913 Silley P.20 L.2-14.

Nicholas Weber (G-1482)

1159. Dr. Weber is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

1160. A residue means any compound present in edible tissues of the target animal which results from the use of the sponsored compound, including the sponsored compound, its metabolites, and any other substances formed in or on food because of the sponsored compound's use. Weber WDT: p. 1, line 48 – p. 2, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1161. A withdrawal period is the interval between the time of the latest administration of the new animal drug and the time the animal can be safely slaughtered for food. Weber WDT: p. 2, lines 16-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1162. If proper withdrawal times are followed, the use of drugs other than Baytril in poultry (e.g., sulfonamides) will not result in unsafe drug residues. Weber WDT: p. 6, lines 10-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it contains inaccurate information about sulfonamide. Evidence in the record demonstrates that usage of sulfas has been very limited in recent years because of serious concerns for sulfa residues in poultry meat and poultry products. Sulfa drugs typically have long withdrawal periods. Since respiratory disease in broilers usually occurs in the late stages of the production cycle, it is difficult to use a sulfa drug for treatment in broilers without risking product residues. This problem is potentially enhanced in areas of the country that have acidic drinking water. Sulfa drugs are typically less soluble in acidic water and can precipitate in water lines. Sulfa residues in water lines can potentially cause residues in poultry tissues even when the treatment is withdrawn at the proper time. Since poultry companies are focused on product quality, the potential for sulfa residues in poultry products is considered to be too high of a risk and consequently many companies voluntarily abstain from the use of sulfa drugs. B-1903 P.8 L.10 through P.9 L.2; A-202 P.26 L.10-22.

1163. The basic ring structure of nalidixic acid is very closely related to that of a quinolone. Weber WDT: p. 7, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1164. Enrofloxacin is a fluoroquinolone antibiotic. Weber WDT: p. 7, line 16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1165. Ciprofloxacin is a fluoroquinolone that has bactericidal properties similar to other members of the fluoroquinolone family including enrofloxacin. Weber WDT: p. 7, lines 27-28

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1166. Ciprofloxacin is a drug widely used in human medicine. Weber WDT: p. 7, line 28 – p. 8, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1167. Ciprofloxacin is a metabolite of enrofloxacin. Weber WDT: p. 8, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1168. Nalidixic acid, enrofloxacin, and ciprofloxacin all have very similar core structures. Weber WDT: p. 8, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1169. Nalidixic acid, enrofloxacin, and ciprofloxacin often inhibit a specific receptor molecule called a topoisomerase. Weber WDT: p. 8, lines 5-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1170. When bacteria develop resistance by a slight chemical alteration in their topoisomerase genes, the bacteria often show cross-resistance to compounds of very similar chemical structure. Weber WDT: p. 8, lines 9-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1171. Bacteria resistant to enrofloxacin are also often resistant to ciprofloxacin and nalidixic acid as well as other fluoroquinolones. Weber WDT: p. 8, lines 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Henrik Wegener (G-1483)

1172. Dr. Wegener is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

1173. Thermophilic *Campylobacter*, notably *Campylobacter jejuni* and *Campylobacter coli*, are normal inhabitants of the gastrointestinal tract of most warm-blooded animals including the major food-animals cattle, swine and poultry. Wegener WDT: page 2, lines 43-46

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1174. *Campylobacter* does not usually cause disease in the food animals. *Campylobacter* bacteria colonize the animals' intestines together with hundreds of other species of harmless bacteria. Wegener WDT: page 4, lines 2-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1175. While poultry and cattle predominantly are colonized by *Campylobacter jejuni*, swine are predominantly colonized by *Campylobacter coli*. *Campylobacter jejuni* causes the majority of human infections in all countries investigated. Wegener WDT: page 4, lines 8-10

Bayer/AHI Response: Bayer/AHI object to this PFOF as compound. Bayer/AHI do not dispute the second sentence if it means "Among *Campylobacter* species, *Campylobacter jejuni* causes the majority of human infections in all countries investigated". Bayer/AHI dispute that "poultry ... predominantly are colonized by *Campylobacter jejuni*" since evidence in the record demonstrates that turkeys are predominantly colonized by *C. coli*. A-201 P.12 L.17-23 and P.13. L.3-9; G-727; B-1908 P.4 L.7-8; A-210 P.12 L.16 – P.13 L.3; B-1917 P.20 L.1-5.

1176. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. Food animals reared in continuous production systems such as cattle and swine probably acquire the infection from the parent animals by faecal-oral transmission. Broiler chicken and other poultry, where there is no contact between the parent bird and the progeny, acquire the infection from the environment. Wegener WDT: page 4, lines 14-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1177. The animal gastrointestinal tract is probably the only significant place where *Campylobacter* grow and multiply in the farm to fork chain. Wegener WDT: page 4, lines 18-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and misleading. Chickens and chicken products are exposed to multiple potential sources of *Campylobacter* as they make the transitions from farm to fork, including wild birds, soil and water from the environment, human bacteria, contamination by food-handlers, etc. Several of these may be "significant places where *Campylobacter* grow and multiply in the farm to fork chain". Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all

animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Predominant routes of fluoroquinolone resistant *Campylobacter* infection in humans are other than associated with poultry. B-1910 P.7 L.20-22. It is clear that there exist important sources of *Campylobacter* infection other than food animals. *See also*, Joint Stipulation 32. The animal gastrointestinal tract is *not* the only significant place where *Campylobacter* grow and multiply in the farm to fork chain.

1178. Faeces can, and will, contaminate the animal carcass during slaughter and, consequently, *Campylobacter* is smeared onto the surface of the meat during processing of the fresh meat products. Wegener WDT: page 4, lines 25-27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1179. During the process called evisceration, where the intestines and other internal organs are removed from the killed animal, some degree of faecal contamination is inevitable no mater how stringent hygiene measures are applied. Although, from the moment the animal is slaughtered and the intestines removed, the *Campylobacter* present on that carcass do not multiply further, they may be passed onto other food products by cross-contamination. Wegener WDT: page 5, lines 1-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1180. One process during the slaughter of broilers that is considered a potential "hot spot" for *Campylobacter* contamination is the defeathering process, where feathers are removed from the killed bird by rotating rubber fingers rubbing the surface of the carcass. Wegener WDT: page 5, lines 11-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1181. Prior to defeathering, the birds are immersed in hot water (50-52 degrees C. soft scald; 56-58 degrees C. hard scald) to loosen the feathers. Varying proportions of the *Campylobacter* present on the surface of the bird may be killed during scalding depending primarily on the water temperature and time submersed. Wegener WDT: page 5, lines 14-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1182. Poultry evisceration is carried out by a mechanical claw, a process that inevitably causes some degree of faecal contamination. Wegener WDT: page 5, lines 19-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1183. Broiler carcasses destined for freezing are usually chilled in a cold-water bath (a "spin-chiller"). During this process, *Campylobacter* transmits from contaminated to non-contaminated carcasses ("cross contamination"). Wegener WDT: page 5, lines 22-24

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1184. Several anatomical features in broiler chickens can serve as insulating "pockets" for *Campylobacter*, supporting enhanced survival during freezing and thawing. Wegener WDT: page 5, lines 27-28

Bayer/AHI Response: Bayer/AHI object to this PFOF as being out of context. The cited testimony goes on to say that "Nevertheless, a chicken product that has been frozen and thawed harbors less viable *Campylobacter* than the equivalent fresh product." G-1483 P.5 L.26-30. There is evidence in the record demonstrating that freezing kills *Campylobacter*, which is thermophilic. Freezing and thawing of meat kills a proportion of the viable *Campylobacter* in the meat. G-1483 P.5 L.26-27; Joint Stipulation 24. A chicken-product that has been frozen and thawed harbors less viable *Campylobacter* than the equivalent fresh product. G-1483 P.5 L.29-30. Freezing of poultry reduces the number of live *Campylobacter* in the products. G-1483 P.5 L.31. Under the normal conditions of food storage, freezing chicken products may reduce the population of *Campylobacter*. Joint Stipulation 31. Freezing chicken (and turkey) products may reduce the population of *Campylobacter*. Joint Stipulation 24. Poultry meat undergoing any heat treatment or freezing during processing will harbor less *Campylobacter* than meat produced without such treatment. G-1483 P.8 L.2-3.

1185. Water is not a natural reservoir for *Campylobacter*. Wegener WDT: page 9, lines 1-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Water is indeed one of the most common reservoirs for *Campylobacters*. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12.

1186. In poultry, notably chicken, several anatomical features support the survival of *Campylobacter* during cooking. Wegener WDT: page 9, lines 29-30

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Thoroughly cooking chicken will eliminate *Campylobacter*. Like nearly all other bacteria *Campylobacter* is sensitive to cooking, and it is assumed that an adequately cooked chicken will harbor no viable *Campylobacter*. G-1483 P.9 L.21-23. *Campylobacter* is sensitive to high temperatures and will be eliminated when poultry is properly cooked. G-1459 P.5 L.26-28; G-1483 P.9. 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. VM Response to Bayer's Interrogatory 26.

1187. Contaminated meat products can serve as sources of contamination of other food products anywhere along the line of processing and distribution. Wegener WDT: page 9, lines 38-39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1188. Complete avoidance of cross-contamination, both in the professional processing plant and in the private kitchen, is virtually impossible. Wegener WDT: page 10, lines 3-9

Bayer/AHI Response: Bayer/AHI object to this PFOF as being too general and categorical in using the phrases "complete avoidance" and "virtually impossible". Bayer/AHI dispute this PFOF as inaccurate to the extent that it means, implies or suggests that all detectable increased risk of campylobacteriosis (from cross-contamination as well as other sources) cannot easily be eliminated in private kitchens. Recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, Bayer/AHI note that there is evidence in the record that consumers are increasingly aware of the need to improve food handling practices to reduce the frequency of cross-contamination. A-204 P.10-12.

1189. Cross-contamination to products that are consumed without heating, such as ready to eat meat products, vegetables and salads, probably takes place frequently in the consumers' kitchen, as indicated by studies tracing the spread of drip fluid from chicken to the kitchen environment, kitchen utensils, and food products during preparation of a meal. Wegener WDT: page 10, lines 15-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF as speculative and inaccurate, illogical or containing a false premise. "Probably takes place frequently in the consumers' kitchen" is speculative. "As indicated by studies tracing the spread of drip fluid from chicken to the kitchen environment" is inaccurate, illogical and/or contains a false premise (namely, the premise that drip fluid from chicken is a source of "cross-contamination", assuming that this means "cross-contamination by *Campylobacter* that can increase the risk of campylobacteriosis.") This is illogical or inaccurate insofar as it entails a false assumption "drip

fluid from chicken" is a source of contamination leading to increased risk. Recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, Bayer/AHI note that there is evidence in the record that consumers are increasingly aware of the need to improve food handling practices to reduce the frequency of cross-contamination. A-204 P.10-12.

1190. Chicken products contain *Campylobacter* much more frequently and in much higher numbers that products of beef and pork because the processing of chicken favors the survival of *Campylobacter* whereas the processing of beef and pork includes steps that effectively reduce the *Campylobacter* load in the products. Wegener WDT: page 10, lines 23-26

Bayer/AHI Response: Bayer/AHI disputes this PFOF as inaccurate and unsubstantiated. No data are presented to support the opinion that "Chicken products contain *Campylobacter* much more frequently and in much higher numbers that products of beef and pork" at the point of consumption. Often times "processing of chicken" includes steps such as cooking, freezing, irradiation or other processes that kill *Campylobacter*. Like nearly all other bacteria, *Campylobacter* is sensitive to cooking, and an adequately cooked chicken will harbor no viable *Campylobacter*. G-1483 P.9 L.21-23; G-1459 P.5 L.26-28. 181. Freezing and thawing of meat kills a proportion of the viable *Campylobacter* in the meat. G-1483 P.5 L.26-27; Joint Stipulation 24. A chicken-product that has been frozen and thawed harbors less viable *Campylobacter* than the equivalent fresh product. G-1483 P.5 L.29-30. Freezing of poultry reduces the number of live *Campylobacter* in the products. G-1483 P.5 L.31. Under the normal conditions of food storage, freezing chicken products may reduce the population of *Campylobacter*. Joint Stipulation 31. Freezing chicken (and turkey) products may reduce the population of *Campylobacter*. Joint Stipulation 24. Poultry meat undergoing any heat treatment or freezing during processing will harbor less *Campylobacter* than meat produced without such treatment. G-1483 P.8 L.2-3. Meat that is dried, cured, salted, smoked, irradiated or exposed to other preservation methods, will harbor less *Campylobacter* compared to the unpreserved product. G-1483 P.5 L.4-6.

1191. While optimal kitchen hygiene and cooking probably can reduce the risk of *Campylobacter* infection from food, this risk cannot be eliminated. Investigations of professional food handlers as well as ordinary consumers' practices in the kitchen document that the majority are either unable or unwilling to adhere to the necessary strict hygiene practices. Wegener WDT: page 10, lines 32-36

Bayer/AHI Response: Bayer/AHI dispute this PFOF as unsubstantiated speculation and as inaccurate. Evidence in the record demonstrates that U.S. consumers are increasingly aware of the need to improve food-handling practices to reduce the frequency of cross-contamination. A-204 P.10-12. Risk of campylobacteriosis has been declining steadily in the US since the

introduction of Baytril and HACCP measures, and no fundamental limits have been found on how much of the risk of *Campylobacter* infection from food can be eliminated. Moreover, this PFOF embodies the false premise that "ordinary consumers' practices in the kitchen" must "adhere to the necessary strict hygiene practices" to eliminate "the risk of *Campylobacter* infection from food". But recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home, as well as preparation of other food at home, is associated with a statistically significant *reduction* in risk of campylobacteriosis, indicating that home-cooked food is *not* a risk factor for campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24.

1192. The putative sources of human *Campylobacter* infections are direct animal contacts, food, water, environment, and human contacts. While all sources undoubtedly contribute to the total number of human infections, a single source probably predominates over all others in industrialized countries. Poultry, notably broiler chicken, is the most important source of foodborne campylobacteriosis in the industrialized world. Wegener WDT: page 10, line 38 through page 11, line 21; page 13, line 6 through page 15, line 7 and lines 34-36

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Bayer/AHI agree that sources of human *Campylobacter* infections are direct animal contacts, food, water, the environment, and human contacts. Bayer/AHI disagree with the remainder of this PFOF as inaccurate and unsubstantiated. Recent epidemiological and genetic data agree in showing that chicken is at most a very minor contributor to foodborne campylobacteriosis in the US (B-1252) and other industrialized countries. For example, a recent prospective case-control study from Quebec (Michaud et al., 2002, Exhibit G-1681) identifies poultry as the "principal suspected source of infection" in only about 10% of cases, comparable to drinking tap water at home (9%). Genetic data (Nadeau et al., 2002, Exhibit G-1684) suggest that only about 20% of human CP isolates (5 of 24) were genetically related to genotypes found in chickens. Recent studies from the UK and elsewhere confirm that poultry is at most a minor contributor to campylobacteriosis in industrialized countries.

1193. A number of independent and methodologically different studies from multiple different countries support the conclusion that, poultry, notably broiler chicken, is the most important source of foodborne campylobacteriosis in the industrialized world. While each study in itself may have limitations, the sum of studies only leaves one conclusion possible 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 WDT: page 10, line 38 through page 11, line 21; page 13, line 6 through page 15, line 7 and lines 34-36; G-1777; G-185; G-602; G-1686; G-182; G-307; G-1718; G-334; G-474; G-299; B-412

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Evidence in the record disputes the conclusion that poultry is the most important source of foodborne campylobacteriosis in the industrialized world, or even a major source. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19;

B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record refutes the suggestion that poultry is the most important source of foodborne campylobacteriosis in the industrialized world.

1194. The detection of *Campylobacter* in broilers and broiler products shows that broilers are a potential source of infection; indeed there are no examples where human pathogenic bacteria can be consistently detected in a fresh meat product and where this particular product cannot be linked to human disease. Wegener WDT: page 11, lines 10-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. The assertion "The detection of *Campylobacter* in broilers and broiler products shows that broilers are a potential source of infection" is incorrect on its face: presence in these products does not even imply potential presence after processing (e.g., freezing or irradiation) or preparation (e.g., after thorough cooking). Nor does "detection of *Campylobacter* in broilers and broiler products" imply that sufficient numbers are present to constitute "a potential source of infection" in humans. (The "one-hit" hypothesis has not been established as true for *Campylobacter*.) While chicken can be a potential source, so are non-poultry meats, at about the same risk. In the 1998-1999 FoodNet *Campylobacter* case-control study on risk factors, the population attributable fraction for eating chicken in a restaurant was 24 percent (95% CI: 17%, 30%); the risk for non-poultry meat in a restaurant was 21 percent (95% CI: 13%, 30%). G-1452 P.10 L.36-41; G-1452, Attachment 3. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is any more of a "potential" source than, for example, non-poultry meats. The assertion that "there are no examples where human pathogenic bacteria can be consistently detected in a fresh meat product and where this particular product cannot be linked to human disease" is unsubstantiated and the meaning of "linked" is not given. While anything can perhaps be "linked" to anything

else using sufficiently weak links, we disagree that "there are no examples where human pathogenic bacteria can be consistently detected in a fresh meat product and where this particular product cannot cause human disease after appropriate processing". Chicken products provide an example.

1195. There exists a close correlation between the prevalence of *Campylobacter* in broiler chicken and chicken products and human disease incidence, both when comparing absolute prevalence between otherwise comparable countries such as Denmark and Norway and when evaluating seasonal variations within a given country. Figure 4, "Seasonality of *Campylobacter* in humans and broilers in Denmark", 1998-2001, inserted in Dr. Wegener's testimony shows the trend in human campylobacteriosis and the trend in *Campylobacter* in broiler flocks in Denmark. Wegener WDT: page 11, lines 14-21; G-1777

Bayer/AHI Response: Bayer/AHI dispute this PFOF as misleading and incomplete. It is incomplete specifically by failing to point out that the "close correlation" is such that changes in prevalence of human disease tend to *precede* changes in prevalence of *Campylobacter* in broiler chicken. B-1901 P.28-29. Bayer/AHI does not dispute that there exists a seasonal peak of human campylobacteriosis in all countries with longitudinal surveillance data. G-1908 P.3 L.22-23, P.25 L.23 – P.26 L.1. There is a strong seasonal pattern in the number of *Campylobacter* cases in the United States with cases peaking in June or July. G-1452 Attachment 1 P.55; B-15; G-615; G-1679 P.23; B-1902 P.11 L.6-7, citing B-215. The seasonal pattern of *Campylobacter* infection is observed in all countries in the temperate climate zones, both in the northern and the southern hemisphere. The seasonal peak occurs in both humans and poultry. The mechanism behind this seasonal pattern remains obscure. G-1483 P.3 L.19-21; B-1908 P.26 L.1-11. However, evidence in the record refutes this PFOF because 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. B-1908 P.26 L.12-14. In fact there is evidence that 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. B-1908 P.26 L.14-16, B-1901, P.28-29. In the alternative, there may be a common source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20, B-1901, P. 28-29.

1196. The seasonal variation observed in broiler poultry flocks can also be found in the derived food products. Furthermore, the incidence in domestically acquired infections displays the same pattern as the poultry curve. This finding is common to a number of **nations** irrespective of which hemisphere. Wegener WDT: page 12, lines 1-4

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. It is untrue that "the incidence in domestically acquired infections displays the same pattern as the poultry curve"; in fact, the former tend to precede the latter. B-1901 P.28-29. Bayer/AHI does not dispute that there exists a seasonal peak of human campylobacteriosis in all countries with longitudinal surveillance data. G-1908 P.3 L.22-23, P.25 L.23 – P.26 L.1. There is a strong seasonal pattern in the number of *Campylobacter* cases in the United States with cases peaking in June or July. G-1452 Attachment 1 P.55; B-15; G-615; G-1679 P.23; B-1902 P.11 L.6-7, citing B-215. The seasonal pattern of *Campylobacter* infection is observed in all countries in the temperate climate zones, both in the northern and the southern hemisphere. The seasonal peak occurs in both

humans and poultry. The mechanism behind this seasonal pattern remains obscure. G-1483 P.3 L.19-21; B-1908 P.26 L.1-11. However, evidence in the record refutes this PFOF because 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. B-1908 P.26 L.12-14. In fact there is evidence that 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. B-1908 P.26 L.14-16. In the alternative, there may be a common source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20; B-1901, P. 28-29.

1197. There are few examples of documented *Campylobacter* outbreaks. Wegener WDT: page 12, line 6

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. There are repeated, well documented outbreaks of *Campylobacter* infections in humans. G-589; Olsen et. al. etc. Dr. Wegener's own publication with Drs. Friedman, Neimann, and Tauxe (2000) discusses over 100 outbreaks reported in the US alone (Table 4 of Friedman CR, Neimann J, Wegener HC, Tauxe RV. Epidemiology of *Campylobacter Jejuni* infections in the United States and Other Industrialized Nations. In Nachamkin I and Blaser MJ, *Campylobacter*, 2nd Ed. ASM Press, Washington, D.C., 2000. 121-138.)

1198. If *Campylobacter* occurred frequently in water or milk, which is shared by many persons at the same time, outbreaks would occur much more frequently. Wegener WDT: page 12, lines 9-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Water has been established as a major source of campylobacteriosis in both outbreaks and in sporadic cases and accounts for over half of *all* outbreak-associated cases reported in the US according to Dr. Wegener's own paper (Table 4 of Friedman CR, Neimann J, Wegener HC, Tauxe RV. Epidemiology of *Campylobacter Jejuni* infections in the United States and Other Industrialized Nations. In Nachamkin I and Blaser MJ, *Campylobacter*, 2nd Ed. ASM Press, Washington, D.C., 2000. 121-138.). B-1910 P.27 L.8-9. According to this same source, milk-associated outbreaks are more than 10 times more frequent than chicken-associated outbreaks.

1199. By far the majority of human *Campylobacter* infections are registered as sporadic infections; that is, they cannot be linked to any other patient by a common source of the infection and appear to be isolated events with no common source of the infection. Wegener WDT: page 12, lines 18-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF, although outbreaks do occur and water has been established as a major source of campylobacteriosis in both outbreaks and in sporadic cases. B-1910 P.27 L.8-9.

1200. In a questionnaire-based investigation, it is extremely difficult to identify risk factors if they are very common. For example, most people eat chicken at least once a week.

Therefore, asking cases as well as controls if they ate chicken in the week before the disease onset (or the week before receipt of the questionnaire, for the controls) is likely to lead to a similar result, i.e., both groups had chicken at least once. This outcome would fail to identify chicken as a risk factor even if it was one. Wegener WDT: page 12, lines 21-39

Bayer/AHI Response: Bayer/AHI agree that in a questionnaire-based investigation, it is extremely difficult to identify risk factors if they are very common. Bayer/AHI object to the remainder of this PFOF as being vague, irrelevant, speculative, and misleading. Statistical methods provide for the much more precise quantitative calculation of statistical power for detecting risk factors with effects of different sizes. Such calculations are provided in B-1901, cf. P.34, which states that "The graphs show that the CDC data have enough power to detect even relatively small effects (if they exist) with high probability." The speculative conjecture in the PFOF that "asking cases as well as controls if they ate chicken in the week before the disease onset (or the week before receipt of the questionnaire, for the controls) is likely to lead to a similar result" is demonstrably untrue in data sets including the CDC case-control data set [*ibid*] and the Effler et al. data set (G-185). The speculation that both cases and controls "will lead to a similar result" is refuted by the data. Moreover, many surveys, including the CDC case-control study survey, do not ask only "if they ate chicken in the week before the disease onset (or the week before receipt of the questionnaire, for the controls)", but *how many times* they ate chicken. Thus, the concern expressed in this PFOF is purely hypothetical.

1201. The findings of twelve independent studies from three different continents and nine different countries strongly indicate that chicken is a source of human *Campylobacter* infection and indeed a frequent source in most industrialized countries. Table 4 inserted in Dr. Wegener's testimony is a survey of 16 published case-control studies. Wegener WDT: page 14 (Table 4 "Risk Factors for *Campylobacter* infections identified in case control studies from 1979-1998"); page 15, lines 4-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. First, the studies are not "independent", insofar as the cite each others' conclusions and use each other's conclusions to establish expectations and to suggest interpretations for ambiguous data. Second, to the extent that they make the same methodological errors (e.g., failing to control for the same confounders, failing to distinguish between "eating chicken" and eating chicken in a restaurant", failing to consider non-chicken risk factors etc.), their conclusions are not "independent". Third, we dispute both the conclusion that "chicken is a source of human *Campylobacter* infection and indeed a frequent source in most industrialized countries" and also the assertions that the twelve studies "indicate" this (as opposed to venturing speculations and opinions about it). Evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-

1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis.

1202. Epidemiological studies provide strong scientific support that poultry, notably chicken, is an important risk factor for human campylobacteriosis. Wegener WDT: page 15, lines 31-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Indeed, epidemiological studies provide strong scientific support that poultry, notably chicken, is *not* an important (or, in many cases, even epidemiologically detectable) risk factor for human campylobacteriosis (e.g., B-1252). This PFOF ignores the most recent, robust epidemiological data from the U.S. that refute the contention that poultry is an important risk factor for human campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is an important risk factor for human campylobacteriosis.

1203. Multiple epidemiological studies, which have compared patients to healthy controls by means of interviewing, have shown that consumption of poultry, notably chicken, is a risk factor for *Campylobacter* infection. Wegener WDT: page 15, lines 34-36

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Indeed, multiple epidemiological studies and data sets which have compared patients to healthy controls by means of interviewing have shown that consumption of poultry, notably chicken, is *not* an important risk factor for human campylobacteriosis (e.g., B-1252). Studies that report an association between consumption of poultry, notably chicken, and *Campylobacter* infection have not "shown that consumption of poultry" increases risk of *Campylobacter* infection (a causal relation), but at most have shown statistical associations, which exist because some confounders (such as foreign travel or restaurant dining) affect both (B-1252). This PFOF ignores the most recent, robust epidemiological case/control data from the U.S. that dispute the contention that poultry is a major risk factor for *Campylobacter* infection. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1

P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major risk factor for *Campylobacter* infection.

1204. Effler's case-control study found that eating chicken prepared by a commercial food establishment was a statistically independent predictor of illness caused by *Campylobacter* (adjusted OR, 1.8; p=0.03). Effler's study was conducted in Hawaii during a five-month period in 1998 and enrolled 211 cases and 211 controls matched on age and telephone exchange. Wegener WDT: page 14; G-185

Bayer/AHI Response: Bayer/AHI objects to this PFOF as incomplete and potentially misleading, in that "eating chicken prepared by a commercial food establishment" is a predictor of campylobacteriosis because of being "prepared by a commercial food establishment", not because it is chicken. Other meats "prepared by a commercial food establishment" are equally risky, while the same meats (specifically including chicken) prepared at home are not. B-1901, Figure 1, P.34; B-1252. Indeed, in Effler's own data, eating chicken prepared at home was a significantly negative (protective) factor associated with a nearly 50% reduction in risk of campylobacteriosis. B-1252. The assertion that "eating chicken prepared by a commercial food establishment was a statistically independent predictor of illness caused by *Campylobacter*" obscures the fact that "eating chicken" per se is "a statistically independent predictor" of significantly *reduced* "illness caused by *Campylobacter*". It is only when this protective factor is put in the hazardous environment of "a commercial food establishment" that some of the risks associated with that environment are incurred, thus creating an association between eating chicken (or anything else) in that environment and risk of campylobacteriosis. The PFOF is misleading insofar as it suggests that chicken consumption per se, rather than eating in a commercial food establishment, is a risk factor for campylobacteriosis.

1205. Studahl's case-control study found a statistically significant association between eating chicken and having a *Campylobacter* infection (OR 2.29, 95% CI: 1.29, 4.23). Studahl's study was conducted in Sweden during the twelve-month period in 1995 and enrolled 101 cases and 198 controls matched on age, sex, and district of residence. Wegener WDT: page 14; G-602

Bayer/AHI Response: Bayer/AHI object to this PFOF. First, the wording is misleading in that "a statistically significant association between eating chicken and having a *Campylobacter* infection" is expected in *any* study that does not properly control for strong confounders creating such a statistical association between them (e.g., restaurant dining, foreign travel), even if there is no true (causal) relation and no such statistical association between them when the analysis

removes the effects of (e.g., stratifies on) the relevant confounders. Thus, the phrase "found a statistically significant association" is ambiguous (an association may be "statistically significant" for some modeling assumptions and not others) and it is inherently misleading insofar as such spurious [non-causal] associations are not "found" but are "created" by choice of analytic methods and statistical modeling techniques. B-1020. Only true (causal) relations can be "found", in the sense that they cannot be eliminated by more accurate and complete analysis. But the associations described in the PFOF are not causal.

Second, Bayer/AHI dispute that the Studahl findings in Sweden are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1206. Neal's case-control study found that eating chicken was independently associated with *Campylobacter* gastroenteritis and that this association was statistically significant (OR 1.4, 95% CI: 1.1, 1.8). Neal's study was conducted in the United Kingdom during a 14-month period between 1994-1995 and enrolled 313 cases and 512 controls matched on sex and age group. Wegener WDT: page 14; G-1686

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, the wording is misleading in that "a statistically significant" association between eating chicken and campylobacteriosis is expected in *any* study that does not properly control for strong confounders creating such an association between them (e.g., restaurant dining, foreign travel), even if there is no true (causal) relation and no such statistical association between them when the analysis removes the effects of (e.g., stratifies on) the relevant confounders. Thus, saying that the study "found" a "statistically significant" association is ambiguous (the association may be "statistically significant" for some modeling assumptions and not others). This wording is also inherently misleading insofar as such spurious [non-causal] associations are not "found" but are *created* by choice of analytic methods and statistical modeling techniques. B-1020. Only true (causal) relations can be "found", in the sense that they cannot be eliminated by more accurate and complete analysis. But the associations described in the PFOF are not causal.

Second, Bayer/AHI dispute that the Neal findings in the UK are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1207. Eberhart-Phillips' case-control study found that risk of campylobacteriosis was strongly associated with recent consumption of raw or undercooked chicken (matched OR 4.52, 95% CI: 2.88, 7.10) and that there was also an increased risk associated with chicken eaten in restaurants (matched OR 3.84, 95% CI: 2.52, 5.88). Eberhart-Phillips' study was conducted in New Zealand during a nine-month period between 1994-1995 and enrolled 621 cases and 621 controls matched on sex, age group, and home telephone prefix. Wegener WDT: page 14; G-182

Bayer/AHI Response: Bayer/AHI object to this PFOF. First, the wording is misleading in that "a statistically significant" association between eating chicken and campylobacteriosis is expected in *any* study that does not properly control for strong confounders creating such an association between them (e.g., restaurant dining, foreign travel), even if there is no true (causal) relation and no such statistical association between them when the analysis removes the effects of (e.g., stratifies on) the relevant confounders. Thus, saying that the study "found" a "statistically significant" association is ambiguous (the association may be "statistically significant" for some modeling assumptions and not others). This wording is also inherently misleading insofar as such spurious [non-causal] associations are not "found" but are *created* by choice of analytic methods and statistical modeling techniques. B-1020. Only true (causal) relations can be "found", in the sense that they cannot be eliminated by more accurate and complete analysis. But the associations described in the PFOF are not causal.

Second, Bayer/AHI dispute that the Eberhart-Phillips findings in New Zealand are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data

demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1208. Ikram's case-control study found that eating poultry at a friend's house (OR 3.18; CI: 1.0, 10.73; p=0.03), eating poultry at a barbecue (OR 3.00; CI: 0.99, 9.34; p.=0.03), or eating undercooked chicken (OR 4.94; CI: 1.03, 23.62; p=0.05) were risk factors for acquiring a *Campylobacter* infection. Ikram's study was conducted in New Zealand during a two-month period in 1992-1993 and enrolled 100 cases and 100 controls matched on sex and age. Wegener WDT: page 14; G-182; G-307

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, we object that the wording is misleading in that "a statistically significant" association (or "risk factor", in the language of this PFOF) between eating chicken and campylobacteriosis is expected in *any* study that does not properly control for strong confounders creating such an association between them (e.g., restaurant dining, foreign travel), even if there is no true (causal) relation and no such statistical association between them when the analysis removes the effects of (e.g., stratifies on) the relevant confounders. Thus, saying that the study "found" these risk factors is ambiguous (the associations may be statistically significant for some modeling assumptions and not others). The wording is also inherently misleading insofar as such spurious [non-causal] associations or risk factors are not "found" but are *created* by choice of analytic methods and statistical modeling techniques. B-1020. Only true (causal) relations can be "found", in the sense that they cannot be eliminated by more accurate and complete analysis. But the associations and risk factors described in the PFOF have not been shown to be causal. For example, eating undercooked chicken may be a marker for other risky behavior (e.g., poor kitchen hygiene or cooking practices) that are true risk factors. B-1901 P.62. Thus, the PFOF is misleading insofar as it suggests a causal relation between eating poultry under various conditions and "acquiring a *Campylobacter* infection", where no such relation has been established.

Bayer/AHI also dispute that the Ikram findings in New Zealand are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-

1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1209. In Schorr's case-control study, consumption of poultry liver was shown to be an independent risk factor for *Campylobacter* enteritis (adjusted matched OR 5.7, 95% CI: 1.4, 22.8). Schorr's study was conducted in Switzerland during an eleven-month period in 1991 and enrolled 167 cases and 282 controls matched on sex. Wegener WDT: page 14; G-1718

Bayer/AHI Response: Bayer/AHI object to this PFOF. It is misleading in describing non-causal statistical associations as "risk factors" where no causal relation has been established (see responses to CVM PFOFs 1204-1208). Bayer/AHI also dispute that the Schorr findings in Switzerland are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1210. Kapperud's case-control study found that eating poultry that was brought into the house raw (frozen or refrigerated) was independently associated with *Campylobacter* illness (OR 3.20, p=0.024). Kapperud's study was conducted in Norway during an 18-month period between 1989-1990 and enrolled 52 cases and 103 controls matched by sex, age, and geographic location. Wegener WDT: page 14; G-334

Bayer/AHI Response: Bayer/AHI object to this PFOF. Bayer/AHI dispute that the Kapperud findings in Norway are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30.

Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1211. Oosterom's case-control study found that significantly more index patients with a *Campylobacter jejuni* infection had eaten chicken meat (47 v. 29, p=0.0002) particularly at barbecues (14 v. 2, p=0.0015) compared with controls. Oosterom's study was conducted in the Netherlands during four-month period in 1982 and enrolled 54 cases and 54 controls. Wegener WDT: page 14; G-474

Bayer/AHI Response: Bayer/AHI object to this PFOF. Its use of the term "significantly" is potentially misleading (see responses to CVM PFOFs 1204-1208). Bayer/AHI dispute that the Oosterom findings in the Netherlands are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, The Oosterom findings are from 1984, so are outdated. Recent evidence in the record refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1212. Among chicken-eaters in the Hopkins/Olmstead case-control study, eating undercooked chicken was identified as a risk factor for sporadic *Campylobacter jejuni* infection (unmatched OR 2.77, 95% CI 1.01, 12.7; matched OR 6.27, 95% CI 0.90, 43.84). The Hopkins/Olmstead study was conducted in Colorado during a 2.5-month period in 1981 and enrolled 40 cases and 71 controls matched on age and sex. Wegener WDT: page 14; G-299

Bayer/AHI Response: Bayer/AHI object to this PFOF. It is misleading in describing non-causal statistical associations as "risk factors" where no causal relation has been established (see

responses to CVM PFOFs 1204-1208). Bayer/AHI also dispute that the Hopkins/Olmstead findings are probative of the issues in this hearing. Evidence in the record more recent than the 1981 Hopkins/Olmstead findings refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is a statistically significant association between eating chicken and having a *Campylobacter* infection in the U.S.

1213. The Hopkins/Scott case-control study determined that handling raw chicken or preparing chicken was significantly associated with *Campylobacter jejuni* illness. This study was conducted in Colorado during a one-month period in 1982 and enrolled 10 cases and 15 controls. Wegener WDT: page 14; B-412

Bayer/AHI Response: Bayer/AHI object to this PFOF. It is potentially misleading in using the term "significantly associated" without specifying the assumptions that create this apparent association (see responses to CVM PFOFs 1204-1208). Bayer/AHI also dispute that the Hopkins/Scott findings are probative of the issues in this hearing. Evidence in the record more recent than the 1982 Hopkins/Scott findings refutes that in the U.S. there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that in the U.S., retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that handling raw chicken or preparing chicken was significantly associated with *Campylobacter jejuni* illness in the U.S.

1214. Different methods are used for typing of *Campylobacter*. The most informative methods currently used for typing of *Campylobacter* are pulsed-field gel-electrophoresis (PFGE),

amplified fragment-length polymorphisms (AFLP) and, more recently, Multilocus Sequence Typing (MLST). Wegener WDT: page 16, line 27 and lines 30-32

Bayer/AHI Response: Bayer/AHI agree to this PFOF. However, which methods are "most informative for typing of *Campylobacter*" depends on how the methods are used and what hypotheses about typing they are used to provide information about.

1215. Investigation of strains of *Campylobacter* from animals food and human patients by genetic fingerprinting and other sensitive methods for tracing sources of human infection has provided scientific support for the hypothesis that poultry, notably chicken, is a source of human fluoroquinolone-resistant *Campylobacter* infections. Furthermore, the route of transmission from the farm to the patient has been supported. Wegener WDT: page 17, line 41 through page 18, line 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate and as providing an incorrect interpretation of genetic data. The only scientific support from DNA subtyping studies is that, to varying degrees in various studies, there is a measure of population overlap in genetic similarity between human and poultry *Campylobacters* (G-1785). Such overlap data do *not* "provide scientific support for the hypothesis that poultry, notably chicken, is a source of human fluoroquinolone-resistant *Campylobacter* infections", any more than for the hypothesis that human ciprofloxacin-resistant bacteria are a source of *Campylobacter* infections in chickens, or, for the hypothesis that multiple species are exposed to common sources. In no case has the route of transmission from farm to the patient been supported. Such a report would require the linkage of epidemiologic data and molecular subtyping data. The study which comes closest to a finding of this sort is G-1775 from Taiwan, however there is no epidemiologic association between the human cases and poultry as a related source in this study and it is not known if genetically similar poultry isolates came from a farm source or a product source.

The overlap data referred to (indirectly) in this PFOF suggest the possibility that the similar human and poultry isolates were infected from the same source, such as water. Moreover, genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

1216. In Belgium, a food scare caused by detection of a harmful toxin "dioxin" in animal feed led the authorities to require withdrawal of Belgian poultry and eggs from the market. Imported poultry and other meat products remained available to the consumers. The incidence of human *Campylobacter* infections declined by 40% in the period that Belgian poultry and eggs were withdrawn from the shops. When Belgian poultry and eggs were readmitted in the market, incidence of human *Campylobacter* infections returned to the "normal" level. The Belgian investigators concluded that the decline in the number of *Campylobacter* infections in Belgium by 40% was due to the withdrawal of Belgian poultry from the market. Wegener WDT: page 18, lines 13-21; G-672

Bayer/AHI Response: Bayer/AHI object to this PFOF as compound. Bayer/AHI dispute this PFOF. The causal attribution (Belgian poultry was withdrawn from market and caused a decline in *Campylobacter* incidence) is speculation, not fact. The decline in infection during 1999 was not noticeably different from the time pattern in other years and has no apparent connection with chicken consumption. B-1901, appendix. The authors' conclusions appear to have been based entirely on fallacious *ex post* analysis [*ibid*]. This PFOF is refuted by B-1901 P.36, P.94; B-1908 P.23 L.18-21.

1217. In Iceland, a sharp increase in human *Campylobacter* infections occurred in the period from 1997 to 1999. This increase coincided with the marketing of fresh chicken products where, in the past, most chicken products have been frozen products. Chicken marketed in Iceland is almost exclusively of domestic origin. A control program was implemented by which flocks are tested for *Campylobacter* a week prior to slaughter; *Campylobacter*-positive flocks are slaughtered independently of *Campylobacter*-negative flocks, and chicken meat from positive flocks is frozen before it is marketed. Following the introduction of this control program, the incidence of domestically acquired campylobacteriosis has been reduced by approximately 70%. Wegener WDT: page 18, line 25 through page 19, line 13

Bayer/AHI Response: Bayer/AHI do not dispute that the incidence of domestically acquired campylobacteriosis has been reduced in Iceland. The causes of the decrease have not been established. However, as noted by Dr. Norm Stern for the Iceland study (cited in B-1901, "Clearly there may be other interventions (e.g. changes in consumption and consumer handling practices) or natural phenomena (e.g. chances in the environmental sources of *Campylobacter* in the period 1999-2000) which could also explain the dramatic decrease in the human health burden" (Stern et al., 2002)." This PFOF is refuted by B-1902 P.39 L.12 – P.40 L.2 and B-1901 P.52.

1218. In Norway, a *Campylobacter* action plan was initiated in 2002 based on the same principles as the plan of Iceland. A nearly 50% reduction in domestically acquired human campylobacteriosis has been observed in the first 39 weeks of 2002 compared to the same time period in 2001. Wegener WDT: page 19, lines 14-18

Bayer/AHI Response: Bayer/AHI do not dispute that in Norway a nearly 50% reduction in domestically acquired human campylobacteriosis was observed in the first 39 weeks of 2002 compared to the same time period in 2001. The causes of the decrease have not been established.

1219. The three independent intervention studies in Belgium, Iceland, and Norway document, beyond reasonable scientific doubt, that poultry, notably chicken, constitutes a major source of human campylobacteriosis in these countries. Interventions primarily or exclusively aimed at poultry have reduced the human incidence of campylobacteriosis by 40-70% in the respective countries. Wegener WDT: page 20, lines 4-8

Bayer/AHI Response: Bayer/AHI object to this PFOF as inaccurate and as being based on an unjustified causal inference. The validity of the inference leading to this conclusion has been refuted in B-1901 P.52 as follows:

> "Some of CVM's witnesses seem also not to have fully recognized the importance of ruling out threats to validity of causal inference in interrupted time series data before such data can be interpreted as evidence of causal relations (Campbell and Stanley, 1963). For example, Dr. Nachamkin (G-1478, p. 4, paragraph 12) interprets the reductions in CP rates in Iceland and Norway following changes in chicken processing as justification for an opinion that "poultry consumption is one of the most important sources for human *Campylobacter* infection" (presumably, at least in those two countries). (See also Dr. Tauxe's testimony, G-1475, p. 17, paragraph 51). However, to properly assess the impacts of these interventions, *it is necessary to adjust for the impacts of other simultaneous interventions,* such as a massive public education effort to improve kitchen hygiene. An unexamined attribution of improvements in CP rates to interventions in chicken-freezing policy may over-state the impact caused by that intervention if other simultaneous interventions were also reducing CP rates. Indeed, as noted by Dr. Norm Stern for the Iceland study, "Clearly there may be other interventions (e.g. changes in consumption and consumer handling practices) or natural phenomena (e.g. chances in the environmental sources of *Campylobacter* in the period 1999-2000) which could also explain the dramatic decrease in the human health burden" (Stern et al., 2002)."

Second, Bayer/AHI dispute that the intervention studies in Belgium, Iceland, and Norway are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that in the U.S. poultry, notably chicken, constitutes a major source of human campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644).

Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry, notably chicken, constitutes a major source of human campylobacteriosis in the U.S.

1220. When resistance emerges in *Campylobacter* in animals, resistant *Campylobacter* transmits to humans. Wegener WDT: page 20, lines 24-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF as unsubstantiated opinion and as inaccurate. (It is also overly broad, if it is intended to apply to all animals and to all species of *Campylobacter*.) Evidence in the record shows that in many instances, fluoroquinolone-resistant *Campylobacter* rates in humans occurs *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. These data support the view that resistant *Campylobacter* emerge in humans when humans start to use fluoroquinolones, not when animals start to use them. Evidence in the record also indicates that resistant *Campylobacter* transmits *from* humans to animals, rather than from animals to humans as claimed in this PFOF. B-1901 P.28, 29, 43, 45. Thus, the PFOF is not a statement of fact, but an unsubstantiated and unjustified interpretation of data.

1221. 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 all countries, 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. Wegener WDT: page 23, lines 5-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Evidence in the record shows that in many countries, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. The claimed "common association with the licensing of quinolones for food animals in all countries" is inaccurate and misleading, as there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Finally, analysis of 1996-1999 Minnesota data suggests that there was an increase in the slope of the FQ-r rate (a change point) in early 1998, years *after* the introduction

of FQ in chickens, rather than "association with the licensing of quinolones for food animals" B-1901 P.29. Thus, the PFOF is inaccurate in several ways.

1222. *Campylobacter* is among the most common causes of travelers' diarrhea in industrialized countries. Wegener WDT: page 23, lines 17-20

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but deny its relevance for this hearing, which involves domestically-acquired campylobacteriosis and does not concern travelers' diarrhea.

1223. On *Campylobacter*, the WHO consensus statement reads: "Following the introduction of fluoroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones. Fluoroquinolone-resistant *Campylobacter* has been associated with treatment failures." (World Health Organization 1997 Meeting). Wegener WDT: page 25, lines 1-6

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO consensus statement reads as stated. Bayer/AHI dispute the substance of the quoted statement as inaccurate. For example, the assertion that "Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones" is refuted by peer-reviewed publications such as Svedhem et al., 1981 (B-1851) cited in B-1901. Further in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Finally, we dispute the statement that "Fluoroquinolone-resistant *Campylobacter* has been associated with treatment failures" as inaccurate: the claimed association disappears after properly controlling for confounding (e.g., B-1901 P.31). The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views. This PFOF is also misleading since the occurrence of "treatment failures" for susceptible and resistant *Campylobacters* is similar. B-20, P.2; B-1920, P.4; Pasternack DWT, P.12, L.20-22, P.13, L.1

1224. In 1998, the World Health Organization convened another meeting addressing in particular the use of quinolones in food animals and potential impact on human health. It was a meeting of experts and stakeholder including pharmaceutical industries, and a consensus report was produced from the meeting. Dr. Wegener participated in the meeting as an invited expert and speaker. The consensus statements were agreed upon by these

experts and stakeholders, including pharmaceutical industry representation by Bayer Corporation. Wegener WDT: page 25, lines 10-17

Bayer/AHI Response: Bayer/AHI object to this PFOF as compound. Bayer/AHI dispute the characterization of the consensus statements.

1225. A WHO consensus statement reads: "*Campylobacter jejuni* is a frequent commensal in poultry and cattle, and *C. coli* is a frequent commensal in swine and poultry. There is a temporal association between the introduction of fluoroquinolones for use in poultry and a substantial rise in the prevalence of quinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones." (World Health Organization 1998 Meeting). Wegener WDT: page 25, lines 18-23

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO consensus statement reads as stated. Bayer/AHI dispute the substance of the quoted statement because in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views.

1226. A WHO consensus statement reads: "*Campylobacter* species are the commonest cause of bacterial gastroenteritis in developed countries. Sporadic cases of campylobacteriosis, which comprise the largest number of reported cases, are predominantly associated with consumption of contaminated food, primarily poultry, in most developed countries." (World Health Organization 1998 Meeting). Wegener WDT: page 25, lines 24-27

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO consensus statement reads as stated. Bayer/AHI dispute the substance of the quoted statement because it does not reflect the current status in the United States, which is the relevant time and location for the issues in this hearing. As relates to the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates (27% between 1996 and 2001). This is the most recent information available on this subject. The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views. This PFOF is also refuted by evidence that chicken is not a major source of campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4;

B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3.

1227. Neimann investigated the duration of illness in patients and found a tendency that patients infected with a quinolone-resistant *Campylobacter* and treated with a fluoroquinolone had a longer duration of illness (average excess duration of 5 days) than the duration of illness in patients with a quinolone-sensitive illness and treated with a fluoroquinolone. Wegener WDT: page 26, lines 1-6; B-561

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Neimann reports that a 5 days longer duration of illness merely "seemed" to be associated with a ciprofloxacin resistant infection. Moreover, Bayer/AHI dispute its applicability to the hearing issues since it does not relate to U.S. data or risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Furthermore, it is unclear if Neimann controlled for foreign travel or prior fluoroquinolone use.

1228. In 2000, the World Health Organization convened a consultation of experts on the increasing incidence of human campylobacteriosis. Twenty-nine internationally recognized scientific experts in *Campylobacter* and campylobacteriosis participated in the consultation., Dr. Wegener participated in the consultation as an expert, speaker, co-chair, and local secretariat. There were agreed-upon conclusions and recommendations from the consultation. Wegener WDT: page 26, lines 7-13

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1229. A WHO agreed-upon conclusion reads: "*Campylobacter* is the leading cause of zoonotic enteric infections in developed and developing countries." (World Health Organization 2000 Meeting). Wegener WDT: page 26, lines 14-15

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO conclusion reads as stated. Bayer/AHI disagree with this statement, however, because the most common **bacterial** cause of traveler's diarrhea is not *Campylobacter*, but *E. coli*. Ohl WDT: P.7 L.25-27; Pasternack WDT: P.18 L. 5-8. In the United States most gastroenteritis is caused by viruses and agents other than *Campylobacter*. Campylobacteriosis accounts for less than 3% of foodborne illnesses in the U. S. Morris WDT: P.3 L.14-18. Furthermore the geographic point of origin is a significant factor in determining what may be a common cause of traveler's diarrhea. B-121 P.1. Also, the causes of zoonotic enteric infections in other countries are not relevant to this proceeding since the domestic use of Baytril and its impact on domestically acquired infections and human health is the issue.

1230. A WHO agreed-upon conclusion reads: "The reported incidence of campylobacteriosis in most developed countries has risen substantially during the past 20 years, and especially since 1990. In developing countries campylobacteriosis is widespread and causes significant morbidity, and even mortality in infants and children. Additional concern is raised by the

increasing number of newly described *Campylobacter* species, as well as the increasing number of antibiotic-resistant strains of the common species, *C. jejuni.* Recently, too, it has been recognized that the paralytic condition, Guillan-Barré Syndrome (GBS), is a serious complication of *Campylobacter* infection. (World Health Organization 2000 Meeting). Wegener WDT: page 26, lines 16-23

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO conclusion reads as stated. Bayer/AHI dispute the substance of the statement as relates to the U.S. As relates to the U. S., this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates (27% between 1996 and 2001). This is the most recent information available on this subject. The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views.

1231. A WHO agreed-upon conclusion reads: "In developed countries, for example, handling and consumption of poultry meat are primary sources of infection and are likely to account for much of the increased incidence of campylobacteriosis." (World Health Organization 2000 Meeting). Wegener WDT: page 26, lines 24-26

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO conclusion reads as stated. Bayer/AHI dispute the substance of the statement as relates to the U.S. because evidence in the record refutes that in the U.S. handling and consumption of poultry meat are primary sources of *Campylobacter* infection. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry constitutes a major source of human campylobacteriosis in the U.S. The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views.

1232. A WHO agreed-upon conclusion reads: "...the most alarming increase in resistance is to the fluoroquinolone group of antimicrobials. This is because adult patients suffering from severe gastrointestinal disease are likely to be treated with a fluoroquinolone prior to confirmation of the diagnosis, and if the strain of *Campylobacter* is fluoroquinolone-

resistant, the duration of the illness may be prolonged. One of the major reasons for the increase in fluoroquinolone-resistant strains in human disease is the use of these antibiotics in poultry." (World Health Organization 2000 Meeting). Wegener WDT: page 26, lines 27-32

Bayer/AHI Response: Bayer/AHI do not dispute that the WHO conclusion reads as stated. Bayer/AHI dispute the substance of the statement as relates to the U.S. The WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views.

1233. Three different World Health Organization meetings with participation from different disciplines and sectors have all reached essentially the same conclusions supporting that poultry is a major source of human *Campylobacter* infections, including quinolone-resistant *Campylobacter* infections: (1) "Following the introduction of fluoroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones."; (2) "*Campylobacter* species are the commonest cause of bacterial gastroenteritis in developed countries. Sporadic cases of campylobacteriosis, which comprise the largest number of reported cases, are predominantly associated with consumption of contaminated food, primarily poultry, in most developed countries."; and (3). "In developed countries, for example, handling and consumption of poultry meat are primary sources of infection and are likely to account for much of the increased incidence of campylobacteriosis." Wegener WDT: page 26, line 33 through page 27, line 9

Bayer/AHI Response: Bayer/AHI object to this PFOF as being compound. Also, the WHO consensus statement reflects the input and views of Dr. Wegener and his colleagues to a considerable extent, and we disagree that the quoted passages should be considered as providing independent confirmation or additional support (beyond mere repetition) of his views. Bayer/AHI dispute statement (1) because evidence in the record shows that in many instances, the appearance of what CVM terms "increasing fluoroquinolone-resistant *Campylobacter* rates in humans" (a term with no official definition and no known clinical relevance) occurred well before the introduction of fluoroquinolones for food animal useand continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone-resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This aspect of the PFOF is refuted by B-1901 P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8. Bayer/AHI dispute statement (2) because as relates to the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject. Bayer/AHI dispute statement (3) because evidence in the record disputes the contention handling and consumption of poultry meat are primary sources of infection. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-

1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that handling and consumption of poultry meat are primary sources of infection in the U.S.

1234. The available scientific evidence supports, beyond reasonable scientific doubt, that poultry products, notably chicken meat, are the major source of human campylobacteriosis infections in industrialized countries. Wegener WDT: page 27, lines 12-27

Bayer/AHI Response: Bayer/AHI dispute this PFOF as inaccurate. Indeed, we have found that available scientific evidence shows, beyond reasonable or statistical scientific doubt, that poultry products, notably chicken meat, are *not* a major source of human campylobacteriosis infections in the US. Evidence in the record disputes the contention that chicken or turkey is a major source of human campylobacteriosis infections in industrialized countries. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of human campylobacteriosis infections in the U.S.

David White (G-1484)

1235. Dr. White is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF at the present time, subject to cross-examination.

1236. Most foodborne illness goes undiagnosed and unreported. White WDT: p. 2, line 27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1237. Nearly 2.4 million cases of foodborne illness are caused by *Campylobacter* each year in the United States. White WDT: p. 2, lines 29-30; G-410; G-1373

Bayer/AHI Response: Bayer/AHI object to this PFOF because it does not accurately reflect the current public health impact of campylobacteriosis in the United States. This PFOF cites G-410 (Mead, et. al 1999) which on its face used data from 1996 and 1997 to estimate the incidence of campylobacteriosis. (G-410 P.3). For example, in the United States, the incidence of *Campylobacter* infections as measured through the Foodborne Disease Active Surveillance Network (FoodNet) decreased by 27% between 1996 and 2001. G-1452 P. 5 L.21-23, Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28.

1238. *Campylobacter* is recognized as one of the leading causes of foodborne gastroenteritis in the United States. White WDT: p. 2, lines 38-40

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Most gastrointestinal infections in the U. S. are viral. CDC has estimated that *Campylobacter* only accounted for 3% of foodborne infections. G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10; B-1042; G-1391. As relates to bacterial infections in the United States, CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject. B-1042 and G-1391.

1239. *Campylobacter* is one of the most frequent causes of acute bacterial enteritis worldwide. White WDT: p. 2, lines 38-40

Bayer/AHI Response: Bayer/AHI agree that *Campylobacter* is a frequent cause of **bacterial** enteritis worldwide, but point out that the cause of enteritis outside the U. S. is not relevant to this proceeding.

1240. In food producing animals such as cattle, poultry and swine, fecal *C. jejuni/C. coli* is regarded as a commensal organism (i.e., does not cause disease). White WDT: p. 2, lines 42-43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1241. Raw poultry meats are commonly contaminated with *Campylobacter*, with prevalence rates reported up to as high as 100%. White WDT: p. 2, lines 46 - p. 3 line 2

Bayer/AHI Response: Bayer/AHI do not dispute that *Campylobacter* can be found on raw retail poultry meat. Bayer/AHI dispute that this constitutes "contamination". Moreover, Bayer/AHI dispute the significance of such a finding since evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5

L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis.

1242. Zhao's study found that 70.7% of raw chicken sampled (n=184) between June, 1999 to July, 2000 in the Greater Washington, DC area were contaminated with *Campylobacter.* White WDT: p. 3, line 7-13; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1243. Zhao's study found that approximately 14% of raw turkey samples (n=172) between June, 1999 to July, 2000 in the Greater Washington, DC area yielded *Campylobacter.* White. WDT: p. 3, lines 7-13; G-727

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1244. Ge's results from antimicrobial susceptibility testing of 135 *Campylobacter* isolates recovered from retail meat (81 *Campylobacter jejuni* isolates: from chickens, 75 from 32 samples; 4 from a beef sample; and, 2 from a pork sample; 39 *Campylobacter coli* isolates: 39 from 14 chickens; 7 from 3 turkeys; and, 8 from 3 pork samples) in the Greater Washington, DC area during the summer and autumn of 1999 show 21.5% resistant to nalidixic acid and 20.7% resistant to ciprofloxacin. White WDT: p. 3, lines 26-35; G-763

Bayer/AHI Response: Bayer/AHI agree to this PFOF. These results represent, in many instances, multiple isolates from single carcasses and are not representative of the carcasses tested. G-763.

1245. 33.3% of *Campylobacter coli* identified in Ge's study were resistant to ciprofloxacin and 31.5% were resistant to nalidixic acid. White WDT: p. 3, lines 26-37; G-763

Bayer/AHI Response: Bayer/AHI agree to this PFOF. These results represent, in many instances, multiple isolates from single carcasses and are not representative of the carcasses tested. G-763.

1246. 12.3% of *Campylobacter jejuni* identified in Ge's study were resistant to ciprofloxacin and 14.8% were resistant to nalidixic acid. White WDT: p. 3, lines 26-37; G-763

Bayer/AHI Response: Bayer/AHI agree to this PFOF. These results represent, in many instances, multiple isolates from single carcasses and are not representative of the carcasses tested. G-763.

1247. *Campylobacter jejuni* and *Campylobacter coli* isolates resistant to antimicrobials used for treating campylobacteriosis are common in retail meats. White WDT: p. 3, lines 41-43; G-763

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is taken out of context and refers to the findings of only one study, conducted in the Washington, DC area in the summer and fall of 1999. G-763; G-1484 P.3 L.26-43. Presented as a finding of fact of general applicability, it is both misleading and not adequately supported.

1248. In 2002, NARMS expanded into surveillance of retail meats to determine the presence of antimicrobial resistance among certain bacteria including *Campylobacter*. White WDT: p. 3, lines 45-47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1249. Preliminary data as of November 2002 for the retail meat arm of NARMS show that 58% of 356 chicken breast samples analyzed and 8% of 372 ground turkey samples were positive. for *Campylobacter*. White WDT: p. 4, lines 12-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1250. In a 1986 study conducted by the Washington State Department of Health, 57% of poultry processing plant samples and 23% of retail chickens carried *C. jejuni*. White WDT: p. 4, lines 24-26; B-387

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1251. In K. Smith's study of retail chicken from September to November 1997, 88% of 91 retail chicken products surveyed in Minnesota by Smith had *Campylobacter*. White WDT: p. 4, lines 29-32; G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF. As stated, this PFOF is misleading and misrepresents the sampling location. The retail samples were taken in the Minneapolis-St. Paul metropolitan area of Minnesota only. As stated, the reader would assume that samples were taken from different places in Minnesota, representative of the entire state, not just in one isolated metropolitan area. G-589 P. 2.

1252. There is an association between molecular subtypes of resistant *C. jejuni* strains that are acquired domestically in humans and those found in retail chicken products. White WDT: p. 4, lines 45-47

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11). Bayer/AHI dispute this PFOF on the grounds that this statement is misleading. The referenced study, G-589 does not establish any "association" between human strains and poultry strains. It can only be said that the strains share the same fla types. It is well established that diverse *Campylobacter* strains may share the same fla types (G-444). Additionally, if the most sophisticated and exacting genetic subtyping showed *Campylobacters* to be "indistinguishable", it would not by itself, imply any causal relationship, since common sources for human and chicken *Campylobacters* (such as water) could not be ruled out. In the absence of epidemiological data no causal inferences can be drawn. In the Smith study (G-589), there is no epidemiological data establishing any causal relationship between chicken *Campylobacters* and human *Campylobacters*. Only foreign travel and prior use of a fluoroquinolone are found to be risks associated with FQ-R infections in the case-comparison study.

1253. The 1994-1995 FSIS baseline study in chickens estimated that the prevalence of *Campylobacter* contaminated chicken broiler carcasses sampled from July, 1994 through June, 1995 was 88%. White WDT: p. 5, lines 4-11; G-652

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1254. The 1996-1997 FSIS baseline study in turkeys estimated that the prevalence of *Campylobacter* contaminated young turkey carcasses sampled from August, 1996 to July, 1997 was 90%. White WDT: p. 5, lines 14-17; G-651

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1255. In 1996, FSIS estimated the national prevalence of *Campylobacter jejuni/coli* on raw ground chicken to be 59.8% in 1996. White WDT: p. 5, lines 25-27;G-653

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1256. In 1996, FSIS estimated the national prevalence of *Campylobacter jejuni/coli* on raw ground turkey to be 25.4% in 1996. White WDT: p. 5, lines 29-32; G-654

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1257. The January-June 1999 FoodNet survey of retail chickens found that 44% of retail chicken meat samples were contaminated with *Campylobacter*. White WDT: p. 5, lines 35-47; G-541; G-1528

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1258. In the January-June 1999 FoodNet survey or retail chickens, overall 11% of retail chicken samples yielded ciprofloxacin-resistant *Campylobacter*; 24% of the *Campylobacter jejuni* contaminated chicken samples were resistant to ciprofloxacin. White WDT: p. 5, lines 35; p. 6, line 2; G-541; G-1528

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1259. Studies have shown that some human clinical *C. jejuni* isolates display PFGE patterns indistinguishable from PFGE patterns observed in *C. jejuni* strains recovered from tested poultry carcasses. White WDT: p. 6, lines 9-12; G-1785

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but do dispute that this is evidence that poultry is a cause of human campylobacteriosis. Genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. B-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

1260. 69.4% of 360 broilers carcasses purchased at a supermarket from January 1994 through December 1994 and tested by Willis were positive for *Campylobacter jejuni*. White WDT: p. 6, lines 15-19; G-701

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1261. Stern found approximately 65% of 2075 poultry carcass rinses contaminated with *Campylobacter*. White WDT: p. 6, lines 25-27; G-791

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1262. Agar dilution involves the incorporation of an antimicrobial agent into an agar medium in a geometrical progression of concentrations followed by the application of a defined bacterial inoculum to the agar surface of the plate. White WDT: p. 7, lines 14-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1263. The standardized agar dilution method for testing *Campylobacter* was developed by scientists at CVM. White WDT: p. 7, lines 26-27

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1264. In the Iowa retail meat study, 20% of 654 retail meats purchased from March, 2001 to March, 2002, were positive for *Campylobacter*. White WDT: p. 6, lines 38-40 and 45-46, and p.7, lines 29-30; G-746; G-1352

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1265. In the Iowa retail meat study, chicken accounted for most (73%) of the *Campylobacter*-positive test results. White WDT: p. 7, lines 29-31; G-746; G-1352

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1266. In the Iowa retail meat study, 20% of retail meats were positive for *Campylobacter;* only 1% of retail pork samples and none of retail ground beef samples yielded *Campylobacter*. White WDT: p. 7, lines 31-33; G-746; G-1352

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1267. 27% of *C. jejuni* isolates recovered from either retail chicken or turkey exhibited ciprofloxacin resistance (MIC $\geq$ 4 μg/ml) and 27% of *C. coli* isolated from retail chicken, turkey and pork exhibited ciprofloxacin resistance in the Iowa retail meat study. White WDT: p. 7, lines 34-37; G-746; G-1352

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1268. *Campylobacter* contamination of retail meats is not limited to poultry raised and slaughtered in the United States. White WDT: p. 8, lines 4-5

Bayer/AHI Response: Bayer/AHI dispute the applicability of this PFOF. This PFOF is not applicable to this case since the results of retail surveys from other countries do not impact

the issues in this hearing, i.e. domestically acquired *Campylobacter* infections by the U.S. population.

1269. The prevalence of *Campylobacter* and fluoroquinolone-resistant *Campylobacter* on retail poultry in other countries is relevant because foreign travel to certain countries has been implicated as a risk factor for acquiring *Campylobacter* and fluoroquinolone-resistant *Campylobacter*. White WDT: p. 8, lines 5-9

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is inapplicable to the issues of this hearing and misleading. The ultimate issue in this hearing whether new evidence shows that enrofloxacin use in poultry in the United States is not shown to be safe. The prevalence of *Campylobacter* and fluoroquinolone-resistant *Campylobacter* on retail poultry in other countries is inapplicable therefore because use of enrofloxacin outside of the United States is not at issue. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore, prevalence of *Campylobacter* and fluoroquinolone-resistant *Campylobacter* on foreign retail poultry has no bearing on the issues in this proceeding.

1270. In the summer of 1994, 1853 fresh chicken breasts of German, Dutch and French origin were purchased at local markets and analyzed for the presence of bacteria. *Campylobacter* was isolated from 28% of the fresh chicken meat. White WDT: p. 8, lines 12-15; A-169

Bayer/AHI Response: Bayer/AHI do not dispute the facts of this PFOF, however Bayer/AHI dispute the PFOF on the grounds that the PFOF is inapplicable to the issues of this hearing for the reasons described in response to PFOF #1269.

1271. Researchers from the United Kingdom looked at a total of 300 raw samples of chicken purchased in New South Wales, U.K. *Campylobacter* was isolated from 68% of the samples and in 34% of the meat packaging. White WDT: p. 8, lines 20-24; G-270

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the ground that the statement is inaccurate in its presentation. With respect to presence of *Campylobacter* on the packaging, the study reports *Campylobacter* was isolated from 3% of external and 34% of whole packaging overall. G-270. In addition, the PFOF is inapplicable to the issues of this hearing for the reasons described in response to PFOF #1269.

1272. In Spain, a group of scientists looked at 198 samples of retail chicken from retail outlets and supermarkets during February 1999 to November 1999 and found that the prevalence of *Campylobacter* in retail chicken was 49.5%. White WDT: p. 8, lines 26-28; G-730

Bayer/AHI Response: Bayer/AHI do not dispute the facts of this PFOF, however Bayer/AHI dispute the PFOF on the grounds that the PFOF is inapplicable to the issues of this hearing for the reasons described in response to PFOF #1269.

1273. The reported rate of *Campylobacter* contamination on pork products is 1.3% in the U.S. and 2% in Belgium. White WDT: p. 8, lines 31-32

Bayer/AHI Response: Bayer/AHI do not dispute the facts of this PFOF, however Bayer/AHI dispute the PFOF on the grounds that the PFOF is inapplicable to the issues of this hearing. The prevalence of *Campylobacter* on pork products in the United States and Belgium is not at issue.

1274. The prevalence of *Campylobacter* in beef is generally low. White WDT: p. 8, lines 33-34

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1275. The majority of studies indicate that poultry meat products are most often contaminated with *Campylobacter* compared with other retail meat commodities. White WDT: p. 8, lines 35-37

Bayer/AHI Response: Bayer/AHI dispute this PFOF on the ground that the statement is inapplicable to the issues of this hearing. The prevalence of *Campylobacter* contamination on poultry compared to other retail meat commodities is not at issue.

1276. Poultry, in particular chicken, represent a major reservoir for human *Campylobacter* infections, including fluoroquinolone-resistant variants, to which humans are routinely exposed through the food supply. White WDT: p. 8, lines 40-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Therefore it is clear that there exist important sources of *Campylobacter* infection other than poultry, and that poultry is not a major reservoir for human *Campylobacter* infections. *See also*, Joint Stipulation 32.

1277. Humans are routinely exposed to *Campylobacter* and fluoroquinolone-resistant *Campylobacter* through the food supply. White WDT: p. 8, lines 41-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, exposure to *Campylobacter* and fluoroquinolone-resistant *Campylobacter* does not necessarily lead to infection since the exposure must lead to ingestion and the dose must be sufficient to cause disease. A number of *Campylobacter* must be ingested to cause a human infection with clinical symptoms. G-70 P.3; G-441 P.3; G-1470 P.4 L. 43 - 46, P.5 L. 1-8. Based on experimental data, the minimum number of *Campylobacter* capable of causing campylobacteriosis has been estimated to be about 500 - 800 organisms (minimum infectious dose). G-70 P.3; G-441 P.3; G-1470 P.4 L. 43 - 46, P.5 L. 1-8. Thus, 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. Second, the evidence demonstrates there are many sources of exposure other than the food supply. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15.. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Therefore it is clear that there exist important sources of *Campylobacter* exposure other than the food supply. *See also*, Joint Stipulation 32.

1278. Poultry constitutes the most important reservoir for human *Campylobacter* infections. White WDT: p. 8, lines 44-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-

1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Therefore it is clear poultry does not constitutes the most important reservoir for human *Campylobacter* infections. *See also*, Joint Stipulation 32.

1279. The use of fluoroquinolones in poultry has played a principal role in increasing resistance to fluoroquinolone among *Campylobacter* isolates recovered from human illness. White WDT: p. 8, lines 5-47

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29. (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a dominant source of *Campylobacter* infection. Second, evidence in the record disputes the contention that there is "increasing resistance to fluoroquinolone[s] among *Campylobacter* isolates recovered from human illness." The national surveillance network designed to monitor human fluoroquinolone-resistant *Campylobacter* infections in the U.S., NARMS, has not produced reliable national prevalence results capable of demonstrating any increasing trend. A-200 P.17 L.23-24 – P.18 L.1-2, P.19 L.16-17, P.19 L.23 – P.20 L.1-2, P.20 L.14-15, P.21 L.10-13, P.25 L.18-22, P.27 L.5-24, P.55 L.6-7, P.30 L.1 – P.33 L.17. Human NARMS does not show a national prevalence. A-199 P.11-13. Moreover, in the U.S. there is no reliable baseline to compare pre-approval and post-approval levels of human fluoroquinolone-resistant *Campylobacter*. B-1900 P.3 L.35-37.

Christopher Ohl (G-1485)

1280. Dr. Ohl is qualified as an expert to testify as to the matters set forth in his written direct testimony submitted on December 9, 2002.

Bayer/AHI Response: Bayer/AHI disagree that Dr. Ohl is qualified to testify as an expert regarding whether poultry is a significant source of *Campylobacter* infections in the United States. See Ohl WDT: P.6 L.12-15, 20-22.

1281. Bacterial enteritis is a very common cause of traveler's diarrhea. Ohl WDT: p. 4, lines 20 to 22

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that traveler's diarrhea is contracted outside the United States, is most commonly caused by agents other than *Campylobacter*, is longer in duration than diarrhea associated with domestically acquired *Campylobacter*, and may be a marker for some other risk factor, and is a confounding factor that must be corrected for in considering the potential effects of Baytril use on poultry in the United States. Ohl WDT: P.7 L.24-29; Burkhart WDT: P.4 L.16-18, P.13 L.20-46, P.14 L.1-22, P.36 Table 8; G-1711, P.5, 6; Feldman WDT: 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; Cox WDT: P.5 L.14-21, P.22, P.31, Attachment 1.

1282. Gastroenteritis is the medical term for inflammation of the stomach and intestine. Ohl WDT: p. 4, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1283. Gastritis refers to such disorders of the stomach and is predominately a vomiting illness, while enteritis involves the small or large intestine and manifests with diarrhea. Ohl WDT: p. 4, lines 7-9

Bayer/AHI Response: Bayer/AHI disagree with this finding of fact. "Enteritis" means inflammation of the intestines; it may or may not involve diarrhea or other symptoms. Kist WDT: P.4 L.17-18; Pasternack WDT: P.3 L.23, P.4 L.1-3, 5; G-70 P.3, 4.

1284. Gastroenteritis is an acute illness afflicting both the stomach and intestines. Ohl WDT: p. 4, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1285. Gastroenteritis is a common disease with up to 1 billion cases per year worldwide causing 3.3 million deaths, mostly due to severe dehydration. Ohl WDT: p. 4, lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that most gastroenteritis is caused by viruses and agents other than *Campylobacter* (which accounts for less than 3% of foodborne illnesses in the United States), and death related to campylobacteriosis in the United States is rare and almost always related to serious underlying diseases. Morris WDT: P.3 L.14-18; Kist WDT: P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4.

1286. In the United States there are an estimated 100 to 375 million gastroenteritis episodes, ~3000 attributable deaths, and depending on the patient's age, 1.5 to 5 episodes per person per year. Ohl WDT: P.4, lines 18-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is based on older data; whereas with specific regard to campylobacteriosis alone, the incidence of disease declined 27% between 1996 and 2001. Ohl WDT: P.4 L.20; Angulo WDT: P.5 L.21-23; G-1452 Attachment 3

P.82; CVM Response to Bayer Interrogatory 28. CDC estimates the US incidence of *Campylobacter* infections in 1999 was 1.4 million and since then has declined. CVM proposed finding of fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. Angulo (G-1452) P.7 L.13-14, L.16-18, P.17 L.10.

1287. Gastroenteritis is the third most common syndrome seen in general practice. Ohl WDT: p. 4, lines 24-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons given in their response to proposed finding of fact 1286, that is, the study referenced by Ohl is out dated as it was published in 1988.

1288. In 1985, 8.2 million Americans visited a physician and 250,000 persons required hospitalization because of diarrhea. More recent data show 28 million health care provider visits, 45 million physician phone calls and 1.8 million hospitalizations that are associated with 116 million antidiarrheal and 19 million antibiotic medication prescriptions. Ohl WDT: p. 4, lines 25-30; reference 4

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons given in their response to proposed finding of fact 1286.

1289. Military populations are particularly at risk for diarrheal illness. Ohl WDT: p. 4, line 32

Bayer/AHI Response: Bayer/AHI do not disagree with this finding of fact; however they point out that the evidence for the proposed finding of fact relates to illnesses acquired outside the United States. Ohl WDT: P.4 L.34.

1290. Diarrheal illness is one of the most common nontraumatic reasons for military population hospitalizations in peace as well as wartime. Ohl WDT: p. 4, lines 32-34

Bayer/AHI Response: See response of Bayer/AHI to proposed finding of fact 1290.

1291. *Campylobacter jejuni* is the most common cause of bacterial enteritis in the United States. Ohl WDT: p. 4, lines 41-42

Bayer/AHI Response: Bayer/AHI dispute the proposed finding of fact because it is based on older data, while more recent data show that *Campylobacter jejuni* is not the most common cause of bacterial enteritis in the United States. B-1042 P.2. Furthermore, by far the largest number of cases of bacterial enteritis even in the older data are of unknown etiology or cause, rendering the proposed finding of fact seriously misleading. B-515 P.1,6,7,9,10. Further in this regard, it should be noted that CVM's and CVM's witnesses's analyses and conclusions are repeatedly based on data from reported cases, which necessarily biases the sample toward the small percentage of cases where treatment is sought, in all probability because the illness is more severe or prolonged. In other words, their analyses and conclusions are based on a sample cohort self-selected by people who seek treatment, rather than on a cohort selected by researchers as

being representative of all *Campylobacter* cases, the vast majority of which are not reported and can be expected to be generally milder than the relative few that are reported.

1292. Bacterial gastroenteritis is acquired through swallowing viable bacteria and subsequent passage of the bacteria from the stomach to the intestines. Ohl WDT: p. 5, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that a number of *Campylobacter* organisms must be ingested to cause illness, with the minimum infectious dose having been estimated to be 500-800 organisms. G-70 P.3; G-441 P.3; Nachamkin WDT: P.4 L.43-46, P.5 L.1-8.

1293. Person to person spread with *Campylobacter* is unusual. Ohl WDT: p. 5, lines 7-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because person to person spread of *Campylobacter* depends on the circumstances. Ohl WDT: P.5 L.4-7.

1294. The predominate symptom of bacterial gastroenteritis or enteritis is diarrhea accompanied by cramping abdominal pain. Ohl WDT: p. 5, lines 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1295. Persons afflicted with bacterial gastroenteritis may have between 3 and 15 loose or watery stools per day. Ohl WDT: p. 5, line 14

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that they do so because the proposed finding says "may" – diarrhea occurs in some, but not all cases of *Campylobacter* enteritis, and as many as 25% of *Campylobacter* infections may be asymptomatic. Pasternack WDT: P.3 L.23, P.4 L.1-3, 5, G-70 P.3.

1296. Additional symptoms of bacterial gastroenteritis may include fever, headache, muscle aches, rectal pain with defecation, weakness, fatigue, malaise, and occasionally vomiting. Ohl WDT: p. 5, lines 15-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they note that these are symptoms of enteritis, not gastroenteritis.

1297. In most cases people are not able to function normally or be productive until their illness begins to resolve. Ohl WDT: p. 5, lines 32-33

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Most persons with campylobacteriosis do not even seek treatment (perhaps 1 in 18), so there is no basis for knowing the condition of "most cases" insofar as campylobacteriosis is concerned. G-615 P.3; Pasternack WDT: P.4 L.4-6. Moreover, as this observation suggests, many if not most cases of campylobacteriosis are mild, and "[i]n mild cases afflicted people may be able to perform their usual daily tasks". Ohl WDT: P.5 L.30-31.

1298. Patients who seek medical care for bacterial enteritis due so in order to obtain treatment to relieve their symptoms and hasten the resolution of their illness. Ohl WDT: p. 5, lines 33-35.

Bayer/AHI Response: Bayer/AHI disagree with the proposed statement of fact because the witness's testimony is expressly based only on his personal experience. Common sense equally suggests that patients also, or instead, may seek treatment to make sure that they do not have a more serious illness or condition (e.g., blood in the stool is cited by CDC as being a warning sign for colon cancer: http://www.cdc.gov/cancer/screenforlife/fs_basic.htm), and many patients may decline antibiotic treatment for personal reasons or as a result of, e.g., CDC's campaign to reduce unnecessary use of antibiotics, which advises persons seeking care, among other things, to "[a]sk what else you can do to feel better sooner." http://www.cdc.gov/drugresistance/community/

1299. It is estimated that there are probably more than 2 million *Campylobacter jejuni* infections in the U.S. annually. Ohl WDT: p. 6, lines 7-9

Bayer/AHI Response: Bayer/AHI disagree with the finding of fact because it is based on old data; more recent data show that the incidence of campylobacteriosis in the United States declined by 27% from 1996-2001, and that as of 1999, the number of cases in the United States was estimated to be about 1.4 million, or about 0.5% of the US population. Angulo WDT: P.5 L. 21-23, P.17 L.10.

1300. *Campylobacter jejuni* is the most common organism that is grown from stool specimens of patients with inflammatory diarrhea. Ohl WDT: p. 6, lines 9-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness's testimony expressly is based only on his personal experience. In addition, they point out that the extrapolation of this observation beyond the witness's personal experience is called into question by the fact that, *Campylobacter* is not now the most common cause of bacterial enteritis. See Bayer/AHI response to proposed finding of fact 1291.

1301. Most patients acquire *Campylobacter* infection from contaminated food, milk, or water. Ohl WDT: p. 6, lines 12-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness's testimony is expressly based only on his personal experience and the witness is not a qualified as a expert in this area.

1302. The majority of patients become infected with *Campylobacter* through the ingestion of undercooked or post-cooking contaminated poultry including chicken, and turkey. Ohl WDT: p. 6, lines 13-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is beyond the scope of the witness's expertise and because it is factually incorrect. See, e.g., Bayer/AHI's response to proposed finding of fact 50 and Patterson WDT: P.6 L.8-11, P.8 L.3-4, P.27 L.8-11, P.28 L.1-2.

1303. *Campylobacter* is a common cause of traveler's diarrhea, particularly for visitors to southeast Asia. Ohl WDT: p. 6, lines 17 and 18

Bayer/AHI Response: Bayer/AHI disagree with this statement because the most common cause of traveler's diarrhea is not *Campylobacter*, but *E. coli*. Ohl WDT: P.7 L.25-27; Pasternack WDT: P.18 L. 5-8. Furthermore the geographic point of origin is a significant factor in determining what may be a common cause of traveler's diarrhea. B-121 P.1. Also, the causes of Traveler's diarrhea are not relevant to this proceeding since the domestic use of Baytril and its impact on domestically acquired infections and human health is the issue.

1304. *Campylobacter jejuni* causes moderate to severe inflammation of the small and large intestine resulting in the secretion of large amounts of fluid. Ohl WDT: p. 6, lines 20-21

Bayer/AHI Response: Bayer/AHI dispute this PFOF because such inflammation and secretion is not present in all cases of campylobacteriosis; as many as 25% of all cases are asymptomatic. Pasternack WDT: P.3 L.23, P.4 L.1-3, 5, G-70 P.3. Furthermore, the low reporting rate for *Campylobacter* strongly suggests that the vast majority of *Campylobacter* infections are mild. See Bayer/AHI response to proposed finding of fact 1297.

1305. Patients with campylobacteriosis are usually dehydrated and in the elderly and young. infants this dehydration can be profound and cause death if not treated with fluids. Ohl WDT: p. 6, lines 28-30

Bayer/AHI Response: Bayer/AHI dispute this PFOF because campylobacteriosis usually resolves itself without treatment in less than 5 days (Thielman WDT: P.2 ¶ 3) and death in campylobacteriosis is rare and almost always related to serious underlying disease. Kist WDT: P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4. Moreover, as pointed out in Bayer/AHI's responses to proposed findings of fact 1297 and 1304, many *Campylobacter* infections are asymptomatic and most are likely to be mild.

1306. In 10 percent of cases, particularly those not treated with antibiotics, *Campylobacter* intestinal infection can relapse and cause recurrent diarrheal illness, with or without associated systemic symptoms. Ohl WDT: p. 6, lines 38-41

Bayer/AHI Response: Bayer/AHI dispute this PFOF because relapses in untreated patients occurs in only about 5-10% of cases. ThielmanWDT: P.2 ¶ 3. Furthermore, even these data are biased in an upward direction because many *Campylobacter* infections are asymptomatic and most are mild. See Bayer/AHI response to findings of fact 1304 and 1305.

1307. Cases in which *Campylobacter* invades the bloodstream always require antibiotic treatment. Ohl WDT: p. 7, lines 2-4

Bayer/AHI Response: Bayer/AHI dispute this PFOF because most *Campylobacter jejuni* and *coli* stains are susceptible to the bactericidal activity of blood serum, campylobacteremia is usually self-limited without treatment (Kist WDT: P.5 L.7-9), and in any event, antibiotic

treatment of campylobacteremia uses other classes of antibiotics, not fluoroquinolones (Pasternack WDT: P.8 L.21-22, P.9 L.1-3; Iannini WDT: P.5 L.6-8; B-273 P.7; B-742 P.5).

1308. Children less than one year of age, the elderly or patients with cancer, HIV infection, or low levels of antibodies are always treated for *Campylobacter* infection if confirmed or suspected in order to alleviate symptoms, reduce the rate of reoccurrence and prevent complications. Ohl WDT: p. 7, lines 11-15

Bayer/AHI Response: Bayer/AHI dispute this PFOF because complications and relapses of campylobacteriosis are generally unrelated to antibiotic treatment. Kist WDT: P.7 L.11-13, P.9 L.17-20, P.13 L.15/21, P.14 L.18-19; G-1616 P.3; G-422 P.3; B-127 P.2; G-497 P.2-4; Pasternack WDT: P.19 L.6-8; G-1661 P.4. Furthermore, fluoroquinolones, which are the subject of this proceeding, are not approved in the United States for treatment of children under 18, pregnant women and lactating women (JS 25; Pasternack WDT: P.4 L.19; G-529, P.3; B-121 P.2) and should not be used for treatment if hemorragic *E. coli* is confirmed or suspected (Iannini WDT: P.3 L.19-21, P.4 L.1-2; Pasternack WDT: P.5 L.8-17, P.8 L.18-21; B-1559 P.1, 3, 4, 6).

1309. Inflammatory, bacterial enteritis is usually suspected in patients who have more diarrhea than vomiting and accompanying fever and systemic symptoms. Ohl WDT: p. 8, lines 2-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1310. Physical examination of the patient is usually not that helpful in differentiating a bacterial cause from viral or parasitic cause of illness. Ohl WDT: p. 8, lines 5-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF because patients that have mostly vomiting, an absence of or low fever and a short duration of symptoms are much more likely to have viral rather than bacterial or parasitic gastroenteritis. Ohl WDT: P.7 L.46 – P.8 L.12.

1311. A culture of stool for the specific types of bacteria that cause diarrhea is required to confirm the diagnosis and identify the exact bacterium responsible for the illness. Ohl WDT: p. 8, lines 14-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF because a recently introduced test allows the identification of *Campylobacter* infections within 2 hours. B-1143 P.1-3.

1312. Many offices and some hospitals currently send out laboratory specimens to a large centralized lab which delays the plating of the culture and decreases the chances of it growing. Ohl WDT: p. 8, lines 25-27

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no basis for the statement is provided by the witness.

1313. *Campylobacter,* in particular, is difficult to culture from stool as many hospital and clinical laboratories do not have the filter apparatus and special incubation jars that have been shown to yield optimal culture results. Ohl WDT: p. 8, lines 28-30

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1311. Moreover, as they pointed out in connection with the potential bias produced by use of selective media with inhibitory antibiotics, many, if not most, laboratories utilize such selective media rather than filter apparatus for *Campylobacter jejuni* and *coli.*

1314. The perception of many clinicians is that stool cultures are not cost effective. Ohl WDT: p. 8, lines 30-32

Bayer/AHI Response: Bayer/AHI dispute this PFOF because no basis for the statement is provided by the witness. On the contrary, the IDSA Guidelines point out that yields and cost-effectiveness are significantly improved by selective testing, and that "the cost per positive stool culture is an incomplete and misleading measure of the value of diagnostic testing." G-261 P.8. The ALJ has ruled against the use of economic considerations.

1315. Many health-care providers will treat infectious diarrhea without the use of stool cultures. Ohl WDT: p. 8, lines 33-34

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, they point out that many health care providers do obtain a stool culture (see, e.g., Morris WDT: P.5 L.13-15), and that CDC and other experts recommend against administration of antibiotic agents to persons in the United States with bloody diarrhea, at least without testing a stool culture for *E. coli* O157. G-261 P.4, 8, 11.

1316. Studies of the efficiency of stool cultures have confirmed their expense and a low yield between approximately 1 and 15%. Ohl WDT: p. 8, lines 37-38

Bayer/AHI Response: Bayer/AHI dispute this PFOF because limiting stool cultures to patients with inflammatory diarrhea and/or certain epidemiological risks can raise both yield and cost-effectiveness, and recent guidelines recommend cultures. Ohl WDT: P.9 L.38-46; G-261 P.8, 11. The ALJ has ruled against the use of economic considerations.

1317. Most physicians treating adults or older adolescents do not wait for the results of an *E. coli* 0157:H7 culture or toxin test before prescribing an antibiotic unless the patient has a known risk for this specific illness in the setting of an epidemic. Ohl WDT: p. 9, lines 8-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness expressly bases his statement only on his personal experience and because the statement is inconsistent with the witness's opinion and recent guidelines and CDC recommendations. Ohl WDT: P.9 L.2-8; G-261 P.8, 11.

1318. *E. coli* 0157:H7 is a rare illness and outside of children the risk of HUS is very small. Ohl WDT: p. 9, lines 12-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the risk is still important enough that testing is required before treatment. Ohl WDT: P.9 L.2-8; Iannini WDT: P.3 L.19-21, P.4 L.1-2; Pasternack WDT: P.5 L.8-17, P.8 L.18-21; B-1559 P.1, 3, 4, 6. They also point out that Mead et al. project over 73, 000 deaths annually due to this bacterium and a mortality rate that is greater than 8 times the rate that they calculate for *Campylobacter*. B-515 P.4.

1319. Most cases of HUS occur in children, and fluoroquinolone antibiotics (including ciprofloxacin), the most commonly used antibiotic for inflammatory diarrhea, are contraindicated for this age group. Ohl WDT: p. 9, lines 17-19

Bayer/AHI Response: Bayer/AHI dispute this PFOF because ciprofloxacin is not the most commonly used antibiotic for *Campylobacter*. Iannini WDT: P.4 L.3-21; Pasternack WDT: P.4, 10-17, P.13 L.11-12, P.14 L.1-16; Ohl WDT, P.13 L.20-31.

1320. For moderate to severe cases of inflammatory diarrhea, most medical care providers will start treatment with an antibiotic before stool culture results are available. Ohl WDT: p. 10, lines 28-30

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however they point out that 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 2 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 (Pasternack WDT: P.13 L.11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16, P.6 L.1-5).

1321. 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, lines 43-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is inconsistent with Joint Stipulation 42. It also is inconsistent with the IDSA guidelines, which say that antibiotic treatment for most persons with febrile diarrheal illnesses should be "considered" only after obtaining a fecal specimen. G-261 P.11-13.

1322. Patients benefit symptomatically from antibiotic therapy, recover from illness more quickly and are able to return to work earlier. Ohl WDT: p. 10, line 46; - p. 11, line 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the witness's testimony expressly relates only to perceptions (Ohl WDT: P.10 L. 46), and actual studies are in conflict with one another on the effectiveness of antibiotic therapy (Pasternack WDT: P.11 L.19-22, P.12 L.1-22, P.13 L.1-8; B-44 P.7; G-705 P.1; B-816 P.2-3; G-188 P.1, 3, 4, 5; G-172 P.3. In addition, the IDSA guidelines classify the evidence underlying even their recommendation for selective antibiotic treatment for *Campylobacter* as being "moderately" supportive and not based on a properly randomized, controlled clinical trial. G-261 P.2-3.

1323. Antibiotic therapy hastens recovery from traveler's diarrhea. Ohl WDT: p. 11, lines 2-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF because antibiotic therapy does not help with viral or parasitic travelers diarrhea; they also point out that traveler's diarrhea is contracted outside the United States, is usually not caused by *Campylobacter*, and insofar as *Campylobacter* is concerned, has longer duration and may be a marker for another risk factor. See response of Bayer/AHI to proposed finding of fact 1281. Also, traveler's diarrhea is not relevant to this proceeding since the domestic use of Baytril and it's impact on domestically acquired infections and human health is the issue.

1324. Guidelines of the Infectious Diseases Society of America (ISDA) recommend that immunocompromised patients, including those with antibody deficiencies, cancer, organ transplants, and human immunodeficiency virus infection; infants; and patients who are pregnant, elderly, or ill with diabetes or chronic liver or intestinal disease, should be treated with antibiotics for inflammatory diarrhea presumed to be due to a bacterial infection. Ohl WDT: p. 11, lines 11-18; G-261

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the IDSA guidelines do not say this, and on the contrary state that "any consideration of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences", and treating physicians must always make a prudent judgment whether in an individual case, the benefits of treatment will outweigh the risks. Ohl WDT: P.9 L.36-46, P.10 L.1-7; Pasternack WDT: P.18. L.12-22, P.19 L.1-22, P.20 L.1-2; G-261 P.11, G-250 P.1.

1325. Soldiers and sailors are likely to be treated for milder symptoms of gastroenteritis. Ohl WDT: p. 11, line 26

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the statement is expressly based only on the witness's personal experience.

1326. Many times antibiotic therapy is started without specific knowledge of the cause of the bacteria because of the lack of submitted stool culture or the institution of therapy before culture results are available. Ohl WDT: p. 11, lines 31-34

Bayer/AHI Response: See response of Bayer/AHI to proposed finding of fact 1320.

1327. The most appropriate antibiotic for suspected bacterial enteritis of unknown etiology is one that has the appropriate spectrum to cover the usual bacteria that cause the syndrome. Ohl WDT: p. 11, lines 38-40

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it neglects the importance of considering the characteristics of the host (e.g., fluoroquinolones are not appropriate for patients under 18, pregnant women, and lactating women). JS 25; Pasternack WDT: P.4 L.19; G-529 P.3; B-121 P.2.

1328. The ISDA guidelines recommend the fluoroquinolone antibiotic ciprofloxacin as the preferred empiric treatment for bacterial enteritis and traveler's diarrhea in adults if therapy is required. Ohl WDT: p. 11, line 44-p. 12, line 2; G-261

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the IDSA guidelines in fact say that treatment of patients with febrile diarrheal with quinolones should be "considered" after obtaining a fecal specimen and, further, indicate that the evidence supporting their recommendation is "moderate" and not based on a properly controlled, randomized clinical study. G-261 P.2-3, 11-13. Also, traveler's diarrhea is not relevant to this proceeding since the domestic use of Baytril and it's impact on domestically acquired infections and human health is the issue.

1329. In addition to better efficacy, there are fewer side effects for patients who take ciprofloxacin than alternative drugs for treatment of bacterial enteritis. Ohl WDT: p.12, lines 10-12

Bayer/AHI Response: Bayer/AHI dispute this PFOF because azithromycin is of comparable or higher efficacy and is well tolerated. Pasternack WDT: P.13 L.11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16, P.6, 1-5; Ohl WDT: P.13 L.31-33.

1330. Studies of patients with moderate to severe diarrhea due to *Campylobacter* who received antibiotics early in their illness (~2 days) have shown that antibiotic treatment shortens the duration of illness, decreases severity of symptoms, and reduces the number of diarrheal stools in addition to decreasing the number of days of shedding of the bacterium. Ohl WDT: p. 12, line 43-p. 13, line 1; G-172; G-707; G-399

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1322, and for the reason that the most significant treatment effect was seen in a study in which the patients received treatment on average 4 or more days after the onset of diarrhea (B-1127 P.1; G-172 P.3; Pasternack WDT: P.12 L.14-20.

1331. Most authorities now recommend that moderate to severe symptomatic infectious diarrhea due to *Campylobacter* be treated with antibiotics, particularly if it is accompanied by bloody stools, fever, chills, and worsening or non-resolving symptoms. Ohl WDT: p. 13, lines 5-8

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it is inconsistent with Joint Stipulation 42; they also point out that it is not specific to empiric therapy and that "most authorities" recommend a number of antibiotics, not just fluoroquinolones (see, e.g., Ohl WDT: P.13 L.23-31). Finally, they point out that some experts recommend against antibiotic therapy for persons with bloody diarrhea in the United States, and CDC recommends stool testing for *E. coli* O157 in such cases. G-261 P.4, 8.

1332. Antibiotic treatment in campylobacteriosis cases decreases the duration of diarrhea symptoms by 2-3 days. Ohl WDT: p. 13, lines 2-3

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1322.

1333. Antibiotic therapy of *Campylobacter* enteritis considerably reduces the chances of relapse of the illness. Ohl WDT: p. 13, lines 14-16

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the basis for the statement is limited to the witness's personal experience and no data are presented.

1334. For *Campylobacter jejuni* bacteria that are not resistant to antibiotics, erythromycin, ciprofloxacin, and azithromycin have been shown to be effective antibiotics for killing the bacterium in the test tube and improving the symptoms and duration of diarrheal illness. Ohl WDT: p. 13, lines 20-23

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1322.

1335. Dr. Bartlett, in his guide *Therapy of Diarrhea, Community Acquired Acute*, recommends erythromycin or ciprofloxacin for *Campylobacter* enteritis. Ohl WDT: p. 13, lines 26-27

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the cited reference is not in evidence and available for review, and they cannot assume that the witness's characterization is accurate and not misleading due to the witness's mischaracterization of the Sanford and IDSA references. See Bayer/AHI responses to proposed findings of fact 1280, 1328, 1336.

1336. The Sanford Antibiotic Guide recommends ciprofloxacin or azithromycin as the preferred therapy and erythromycin as alternative therapy. Ohl WDT: p. 13, lines 27-29

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the cited reference in fact recommends antimotility agents and fluids, not antibiotics, as the empiric treatment for moderate cases of *Campylobacter* diarrhea. G-244.

1337. Dr. Cunha recommends in his guide book either ciprofloxacin, doxycycline, or erythromycin and as alternative therapy azithromycin or clarithromycin. Ohl WDT: p. 13, lines 29-31

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the cited reference is not in evidence and available for review, and they cannot assume that the witness'' characterization is accurate and not misleading due to the witness's mischaracterization of the Sanford and IDSA references. See Bayer/AHI responses to proposed findings of fact 1280, 1328, 1336.

1338. Ciprofloxacin or azithromycin is tolerated better by adult patients, with less side effects than erythromycin, and requires fewer administered doses per day. Ohl WDT: p. 13, lines 32-33

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1339. Most cases of bacterial enteritis are treated empirically without the identification of a causative bacteria, and that the majority of these cases will be undiagnosed *Campylobacter* enteritis. Ohl WDT: p. 13, lines 40-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF because *Campylobacter* enteritis usually resolves within 5 days without treatment, only a small number of persons even seek treatment (perhaps 1 in 18), routine empiric treatment is not recommended, *Campylobacter* is not the most likely cause of bacterial enteritis, and much empiric therapy is for traveler's diarrhea which must be excluded as a confounder from the present controversy. See responses of Bayer/AHI to proposed findings of fact 1305, 1297, 1300, 1281 and Pasternack WDT: P.18 L.5-8.

1340. Ciprofloxacin, the antibiotic indicated for empiric therapy of bacterial enteritis due to an unknown bacterium, will be used for treatment of the majority of cases of *Campylobacter* enteritis. Ohl WDT: p. 13, lines 42-45

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1339.

1341. Many patients with campylobacteriosis treated with ciprofloxacin will benefit with reduced symptom severity and duration and a faster return to a functional status. Ohl WDT: p. 13, lines 45-46

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1322.

1342. The treatment of *Campylobacter* enteritis is becoming complicated by the development of antibiotic resistance of this bacterium to ciprofloxacin, erythromycin and azithromycin. Ohl WDT: p. 14, lines 4-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF because resistance to erythromycin and azithromycin remain low, fluoroquinolone resistance is not a significant treatment problem in the United States because the mean durations for domestically acquired susceptible and resistant *Campylobacter* are not statistically different, and the occurrence of "treatment failures" for susceptible and resistant *Campylobacters* is similar. Pasternack WDT: P.12 L.20-22, P.13 L.1, 11-21, P.14 L.1-16; Iannini WDT: P.4 L.9-16; P.6 L.1-15; Burkhart WDT: P.36 table 8; B-50 P.2; B-1920 P.4; B-20 P.2; G-354 P.3; Cox WDT: P.78.

1343. Patients with inflammatory bacterial enteritis due to antimicrobial resistant *Campylobacter* are less likely to realize the benefits of treatment with antibiotics than patients infected with an antibiotic sensitive *Campylobacter*. Ohl WDT: p. 14, lines 11-13

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1342.

1344. Symptomatic relapse developing during or after treatment with ciprofloxacin has been described with *Campylobacter* infection due to ciprofloxacin resistance in this bacterium. Ohl WDT: p. 14, lines 18-20

Bayer/AHI Response: Bayer/AHI dispute this PFOF because clinical and bacterial relapses are seen in untreated patients, as well as in fluoroquinolone treated patients with *Campylobacter* initially susceptible to fluoroquinolones. Kist WDT: P.13 L.15-21; G-1616 P.3; G-422 P.3; B-127 P.2; G-497 P.2-4.

1345. In Marano's multistate surveillance study, patients treated with a fluoroquinolone antibiotic for *Campylobacter* enteritis had diarrhea that lasted significantly longer amongst those infected by a fluoroquinolone-resistant strain than by a fluoroquinolone-sensitive strain (8 days vs 6 days, p=0.02). Ohl WDT: p. 14, lines 23-27; G-394

Bayer/AHI Response: Bayer/AHI dispute this PFOF because there is no statistical difference between the mean durations of fluoroquinolone-resistant and susceptible campylobacteriosis when the Marano and Smith studies are corrected for confounding by foreign travel/traveler's diarrhea and prior use of fluoroquinolones. Burkhart WDT: P.35 L.4-6, P.36 L.4-5 and table 8; B-50 P.2.

1346. In K. Smith's study, patients treated with a fluoroquinolone for *Campylobacter* enteritis caused by a fluoroquinolone-resistant strain showed a slower response to therapy by 3 days (p=0.03). Ohl WDT: p. 14, lines 27-30;G-589

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1345.

1347. Data show that the morbidity of ciprofloxacin-resistant *Campylobacter* gastroenteritis is higher than that of ciprofloxacin-sensitive illness due to this bacterium. Ohl WDT: p. 14, lines 32-34

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their response to proposed finding of fact 1345.

1348. A recent analysis of attributable morbidity and mortality due to antimicrobial resistance in *Campylobacter jejuni* infections in the United States calculated that each year 22,085 infections, hospitalizations and 1 death are attributable to fluoroquinolone-resistant *Campylobacter jejuni.* Ohl WDT: p. 14, lines 34-38

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the following reasons:

First, the analysis referred to, by Barza and Travers, calculates "attributable morbidity and mortality" using the following incorrect equation: $[(OR - 1) \times P]/\{1 + [(OR - 1) \times P]\}$, where P is the proportion of the general population with exposure to antimicrobial agents and OR is the odds ratio, unadjusted for confounders or for the presence of multiple risk factors. Barza and Travers are incorrect in interpreting this quantity as "The proportion of all cases that would not

rates. It simply assumes that the associations created by confounders can be attributed to *Campylobacter.*

In summary, the numbers relied on by the witness are based on hypothetical calculations, incorrect underlying data on causes, and an incorrect (univariate, unadjusted for confounders or other causes) formula for calculating attributable risks.

1349. The increasing rate of fluoroquinolone resistance in *Campylobacter jejuni* will make treatment more and more difficult for afflicted patients and deprive them of an opportunity for treatment to reduce the severity and duration of symptoms and an earlier return to work. Ohl WDT: p. 14, lines 38-42

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1342 and 1345.

1350. For patients who are at higher risk for complications of *Campylobacter species* enteritis, such as invasion of the blood stream or other organs, fluoroquinolone-resistance is potentially life-threatening. Ohl WDT: p. 14, lines 42-44

Bayer/AHI Response: Bayer/AHI dispute this PFOF because CVM does not have any facts or data demonstrating any increase in the rate or extent of complications from infections caused by fluoroquinolone-resistant *Campylobacter* as compared to infections caused by fluoroquinolone-susceptible *Campylobacter* (CVM Interrogatory Answer 60); there are no data associating either complications or increased mortality with fluoroquinolone-resistant *Campylobacter* infections as compared to infections with susceptible *Campylobacter* (Kist WDT: P.16 L.6-7, P.18 L.6-7, 12-13; Newell WDT: P.47 L.23-24, P.48 lines 1-2); Guillain-Barre Syndrome and reactive arthritis are not affected by prior antibiotic treatment (Kist WDT: P.7 L.11-13, P.14 L.18-19; Pasternack WDT: P.19 L.6-8; G-1661 P.4); and if and when campylobacteremia and infections of other organs require treatment by antibiotics, drugs other than fluoroquinolones are used (Pasternack WDT: P.8 L.21-22, P.9 L.1-3; Iannini WDT: P.5 lines 6-8; B-273 P.7; B-742 P.5).

1351. Most medical providers will initiate empiric therapy based on treatment guidelines or guide books in the hopes of reducing the severity and duration of diarrhea and its associated symptoms. Ohl WDT: p. 15, lines 19-22

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1315, 1317, 1320 and 1324.

1352. The empiric therapy of presumed bacterial enteritis is ciprofloxacin for adults. Ohl WDT: p. 15, lines 22-23

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1320, 1329 and 1342.

1353. If treatment with ciprofloxacin is initiated early in the course of illness, many patients will realize benefits in terms of lessened severity and duration of illness. Ohl WDT: p. 15, lines 23-25

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1322 and 1330.

1354. The development of ciprofloxacin-resistance in *Campylobacter* species is complicating the treatment of this illness and resulting in treatment failures. Ohl WDT: p. 15, lines 35-37

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1342 and 1345.

1355. Continued development of antimicrobial resistance in this *Campylobacter* will increase the morbidity and mortality of infections due to this bacterium. Ohl WDT: p. 15, lines 37-39

Bayer/AHI Response: Bayer/AHI dispute this PFOF for the reasons stated in their responses to proposed findings of fact 1342 and 1345.

Gregory Burkhart (B-1900)

1356. The retail and slaughter data confirm that fluoroquinolone-resistant *Campylobacter* can contaminate poultry intended for human consumption. Burkhart WDT: p. 3, line 8-9.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, with the caveat that the phrase "fluoroquinolone-resistant *Campylobacter*" is ambiguous in general and is not meant here to refer to or have any implications for clinical resistance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

1357. When used in poultry, enrofloxacin is administered in the drinking water to all birds in the same housing unit as those birds with a suspected *E. coli* or *Pasteurella* infection. Burkhart WDT: p. 6, line 11-12.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF. We note that there is nothing improper or imprudent about treating birds in this manner. Water medication is an approved method of delivery for fluoroquinolone use in poultry, see Joint Stipulation 18. Evidence in the record shows that by the time a 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 illness and exposing more birds. A-202 P.13 L.15-22; B-1915 P.4 L.15 – P.5 L.2. CVM's own witness Carey acknowledges that due to their common housing, feeding, drinking and litter exposure, an entire flock has exposure to the challenge. G-1456 P.4 L.34-37.

1358. Several publications have provided bacteriological sampling data from retail chicken products in the United States as well as from carcasses sampled in slaughter houses and these data confirm the presence of fluoroquinolone-resistant *Campylobacter* at the retail at surprisingly high rates given the fairly low rate of use of enrofloxacin in poultry production. Burkhart WDT: p. 9, 10-14.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, with the caveat that the phrase "fluoroquinolone-resistant *Campylobacter*" is ambiguous in general and is not meant here to refer to or have any implications for clinical resistance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Moreover, the phrase "surprisingly high rates" is specifically intended to refer to the context of enrofloxacin being used in poultry production at a "fairly low rate" and to the prior expectation, based on CVM's theories and statements [Bartholomew, G-1454, p. 9, lines 28 and 29)] that enrofloxacin is the main or only source of "fluoroquinolone-resistant *Campylobacter*" in domestic chickens. It is specifically not intended to deny that resistant *Campylobacter* are found in poultry (as well as wild birds) or on chicken products as a consequence of ciprofloxacin-contaminated water in the environment and other factors other than the treatment of poultry flocks. B-1908. P.15 L.12-13, P.16 L.24 – P.17 L.6 (citing B-609); B-1851. Dr. Burkhart recognizes that, CVM's assumptions and statements to the contrary not withstanding (e.g., Bartholomew, G-1454 P.9 L.28, 29), fluoroquinolone use in chickens and turkeys is not the only cause, or necessarily even the most frequent cause, of the development of fluoroquinolone-resistant *Campylobacter* species in sampled chickens and turkeys (CVM Response to Bayer's Interrogatory 4) and that 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) and, indeed, prior to 1985. B-1901 P.79.

1359. The most likely exposure to fluoroquinolone-resistant *Campylobacter*, given all current evidence, would be uncooked or undercooked food that contains fluoroquinolone-resistant *Campylobacter*. Burkhart WDT: p. 9, line 42-43.

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but subject to the caveat that phrase "the most likely exposure" is intended to mean "the most likely food-borne source of exposure", and that "exposure" is not here intended to mean or imply "exposure leading to or capable of causing illness or infection". Evidence in the record disputes the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-

30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of either fluoroquinolone-sensitive or fluoroquinolone-resistant *Campylobacter* infections.

1360. The 1996-1998 database from Minnesota (i.e., the Smith study) is a source of multi-year data in the United States on fluoroquinolone-resistant *Campylobacter* that is: (a) derived from a well-defined denominator; (b) not based upon non-random sampling of reported cases; and (c) captured data on foreign travel and prior fluoroquinolone use. Burkhart WDT: p. 16, line 40-44.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, subject to the caveats that (a) the phrase "source of multi-year data in the United States" is not meant to suggest or imply that the Smith data are in any way representative of the general US population (or even of the general Minnesota population); and (b) the phrase "fluoroquinolone-resistant *Campylobacter*" is ambiguous in general and is not meant here to refer to or have any implications for clinical resistance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16;. B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

1361. The Minnesota data from 1996-1998 (i.e., the Smith study) are probably the most robust multiyear dataset in the United States, and perhaps the world, containing information on foreign travel and prior fluoroquinolone use. Burkhart WDT: p. 17, line 12-14.

Bayer/AHI Response: Bayer/AHI agree to this PFOF. The CDC case-control data set is larger and potentially even more useful, and also contains information on foreign travel and prior fluoroquinolone use. However, CDC has recently raised questions about its own performance in delivering that data accurately. Pending the resolution of that issue, the Smith data may be more reliable.

1362. If there is no increased virulence, there is no reason to believe that the total *Campylobacter* incidence would change at all if domestic fluoroquinolone-resistant cases could be eliminated; resistant cases would simply be replaced by non-resistant cases. Burkhart WDT: p. 33, line 7-11.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, subject to the usual caveat that the phrase "fluoroquinolone-resistant *Campylobacter*" is ambiguous in general and is not meant here to refer to or have any implications for clinical resistance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

1363. Irrespective of foreign travel or prior fluoroquinolone use, resistant cases with no use of an antidiarrheal agent tended to have a longer duration of diarrhea by 1-2 days. Burkhart WDT: p. 37, line 6-8.

Bayer/AHI Response: Bayer/AHI do not dispute this statement, provided that it is read in the full context of Dr. Burkhart's testimony, which makes clear that this "longer duration" does *not* refer to a statistically significant difference after correcting for multiple testing bias arising from multiple sub-group analysis. As noted by Dr. Burkhart, partitioning the data into multiple sub-groups makes it essentially certain that some groups will have longer mean durations of exposure than others (i.e., the probability that all have exactly the same mean duration quickly approaches zero as the number of sub-groups analyzed increases). Thus, as stated by Dr. Burkhart, non-significant or "meaningless" differences, including the one noted in this PFOF, are bound to occur by chance and should not be misinterpreted as true or statistically significant effects. In context Burkhart's testimony reads as follows "My findings are similar to those reported by Marano. Irrespective of foreign travel or prior FQ use, resistant cases with no use of an AD agent tended to have a longer duration of diarrhea by 1-2 days. *However, Marano leaves an important statement out of her abstract. Resistant cases who used an AD agent tended to have 1-2 days less diarrhea.* Hence, Marano focused on one subgroup basically ignoring the fact the findings were contradictory across the subgroups. Why would resistant cases respond better if treated with an AD agent but fare worse if untreated? Even if one believed this, it's not clear what to do with the finding since one needs to compute a summary measure of morbidity. *It's much more likely that the variation in days of diarrhea when subgrouping on AD use is just due to chance, as happens in many subgroup analyses.*" Burkhart WDT P.37 L.6-15 (emphasis supplied.)

1364. The 1996-1998 Minnesota data (i.e., the Smith study) are likely to be the most valid data in the United States that are available to study the issue of increasing domestically acquired fluoroquinolone-resistant *Campylobacter*. Burkhart WDT: p. 45, line 14 through p. 46, line 2.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, subject to the caveat that the phrase "are likely to be the most valid data in the United States" does not imply that the Smith data are in any way representative of the general US population (or even of the general Minnesota population).

1365. There is good evidence to support the conclusion that enrofloxacin use in poultry can select for fluoroquinolone-resistant *Campylobacter*, and that such selection, leads to fluoroquinolone-resistant *Campylobacter* on poultry at slaughter and at the retail level. Burkhart WDT: p. 48, line 4-6.

Bayer/AHI Response: Bayer/AHI agree to this PFOF, with the caveat that the phrase "fluoroquinolone-resistant *Campylobacter*" is ambiguous in general and is not meant here to refer to or have any implications for clinical resistance. The clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

Louis Anthony Cox, Jr. (B-1901)

1366. Cox determined his figure for population-attributable risk (PAR) for chicken consumption by treating the absence of a response to a yes-or-no survey question as a "no". This had the effect of reducing that calculation of that PAR from 11% to 3.1%. Later he concedes that the estimate of a 24% or 25% PAR for eating chicken in restaurants depends heavily on how such missing data are treated. Cox WDT: p. 56, first of three "Note" paragraphs; Cox WDT: p. 57, first full paragraph.

Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as falsely suggesting that Dr. Cox determined a single value ("his figure") for chicken-associated PAR. In reality, Dr. Cox presented the results from several alternative methods and testified that "Thus, the PAR specifically for chicken eaten in restaurants, as opposed to other meats (hamburger) in restaurants, might be estimated as 25% - 14% = 11% if missing responses are ignored. The 3.1% estimate is more plausible, but 11% may be used for sensitivity analyses."

1367. After substituting some values pursuant to his testimony, and using his (Cox-Popken) model, Cox testified that the baseline version of his model predicts that 2,814 treatment failures per year would be averted by a "ban" [withdrawal of approval] of enrofloxacin. Cox WDT: p. 84, last three lines.

Bayer/AHI Response: Bayer/AHI Response: Bayer/AHI disagrees with this PFOF as being inaccurate and taking testimony out of context. The full context is as follows: "The baseline version of the Cox-Popken (B-1260) model predicts 2,814 treatment failures per year averted by a ban of enrofloxacin, using most of CVM's assumptions, but with a corrected prh value of 0.064 and a 20% chicken-attributable risk." ... (In reality, however, recall that FQ-r CP cases may not create any excess days of illness). Thus, under CVM's assumptions about days of illness, the human health harm-to-benefit ratio from the proposed ban of enrofloxacin is estimated to be at least one to three orders of magnitude (25 to 1000), depending on how the probability of treatment failure is modeled (effectively 100% according to CVM, or 2.5% suggested by the one data point reported in Piddock, 1999.)"

Thus, the full context clearly shows that the "2,814 treatment failures" referred to in this PFOF are specifically and explicitly contingent on using input assumptions made by CVM (such as 100% treatment failure probability) which Dr. Cox has testified are unrealistic and not supported by (or are refuted by) data. This contrasts with the out-of-context quote in the PFOF, which states only that "Cox testified that the baseline version of his model predicts that 2,814 treatment failures per year would be averted".

Roger Feldman (B-1902)

1368. The majority of *Campylobacter* cases are sporadic. Feldman WDT: p. 15, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1369. In the Harris study, excluding travel to underdeveloped nations and consumption of raw milk did not alter the association of *Campylobacter* enteritis with unprocessed poultry or processed turkey consumption. Feldman WDT: p. 19, lines 18-20; G-268

Bayer/AHI Response: Bayer/AHI do not dispute that this is stated in Dr. Feldman's testimony but dispute that the Harris findings are probative of the issues in this hearing. Evidence in the record more recent than Harris's outdated 1986 study refutes that retail poultry eaten by consumers at home is a major source of campylobacteriosis (B-1901 P.19, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24). This PFOF is also refuted by recent epidemiological evidence in the record 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. B-1901 P.29 (citing G-1644). Moreover, the Harris study did not isolate 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. B-1901 P.38-39. P.57-64.

1370. The Niemann case control study finds a major risk of campylobacteriosis with eating undercooked chicken. Feldman WDT: p. 20, lines 5-7; B-561

Bayer/AHI Response: Bayer/AHI do not dispute that this is stated in Dr. Feldman's testimony but dispute that the Niemann findings are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that chicken is a major risk for campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis.

1371. The Oosterom study reports an increased risk of campylobacteriosis with eating chicken at home or in barbecue. Feldman WDT: p. 21, lines 4-7; G-474;

Bayer/AHI Response: Bayer/AHI do not dispute that this is stated in Dr. Feldman's testimony but dispute that the Oosterom findings are probative of the issues in this hearing. Evidence in the record more recent than Oosterom's 1984 study refutes that chicken is a major risk for campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover,

recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that poultry is a major source of campylobacteriosis.

1372. The Eberhart-Philips study found an increased risk of *Campylobacter* infection with eating chicken. Feldman WDT: p 21, lines 8-10; G-182

Bayer/AHI Response: Bayer/AHI do not dispute that this is stated in Dr. Feldman's testimony but dispute that the Eberhart-Philips findings are probative of the issues in this hearing. Evidence in the record refutes that there is an increased risk of *Campylobacter* infection with eating chicken . B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is an increased risk of *Campylobacter* infection with eating chicken.

1373. The Studahl study found an increased risk of campylobacteriosis from eating chicken and from contact with chickens. Feldman WDT: p 21, lines 16-19; G-602

Bayer/AHI Response: Bayer/AHI do not dispute that this is stated in Dr. Feldman's testimony but dispute that the Studahl findings in Sweden are probative of the issues in this hearing. The ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Moreover, evidence in the record refutes that there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that there is an increased risk of campylobacteriosis from eating chicken and from contact with chickens.

1374. Case control studies are an acceptable way to investigate risk factors of sporadic disease in a population. Feldman. WDT: p 23, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

John R. Glisson (B-1903)

1375. Baytril (enrofloxacin) is delivered to chickens and turkeys through the drinking system in a water soluble form. Glisson WDT: p. 3, lines 20-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1376. Administration via water is typical of therapeutic antibiotic usage in the poultry industry. Glisson WDT: p. 3, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1377. For commercially grown broiler chickens and turkeys in the United States, it is neither feasible nor practical to administer enrofloxacin, or other therapeutic antibiotics, on an individual bird basis. Glisson WDT: p. 3, line 22 – p. 4, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1378. The label instructions for Baytril allow a dosage of 25 ppm - 50 ppm for 3-7 days. Glisson WDT: p. 5, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1379. Enrofloxacin usage is by prescription only and only under veterinary supervision. Glisson WDT: p. 5, lines 16-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1380. Enrofloxacin is used for therapeutic purposes and is not used for growth promotion. Glisson WDT: p. 5, lines 17-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Charles Haas (B-1904)

1381. Bayer Witness Haas concedes that the epidemiological studies used by Vose [in the CVM *Campylobacter* resistance risk assessment] to estimate the poultry related fraction of campylobacteriosis were peer reviewed in refereed journals. Haas WDT: p. 17, lines 11-12

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Haas' testimony contains this statement. Dr. Haas goes on to explain about the cited articles, however, that "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." B-1904 P.17 L.12-14. More recent data, particularly in the U.S. show that poultry is not a source of campylobacteriosis. Evidence in the record disputes the contention that chicken or turkey is a major (let alone "dominant") source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 – P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44. Moreover, recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Recent studies in the United Kingdom also now question whether chicken is a major source of fluoroquinolone-resistant campylobacteriosis. B-1909 P.40. L.20-22. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a dominant source of *Campylobacter* infection.

1382. Manfred Kist (B-1906)
CVM did not proffer a PFOF #1382.

1383. *Campylobacter jejuni* is a common cause of bacterial diarrhea worldwide. Kist WDT, p. 2, line 15

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF. However, as this issue relates to the current U.S. incidence of campylobacteriosis, which is the relevant time and location for the issues in this hearing CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates (B-1042 and G-1391). This is the most recent information available on this subject.

1384. Most cases of campylobacteriosis are sporadic in nature. Kist WDT: p. 3, line 7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1385. Symptoms of campylobacteriosis includes headache, back pain, general malaise, fever, cramps and frequent bowel movements, loose or watery diarrhea and bloody diarrhea in about half the cases. Kist WDT: p. 3, lines 10-14

Bayer/AHI Response: Bayer/AHI disagree with this PFOF because it is taken out of context, is inaccurate and misleading, implying that symptoms of campylobacteriosis are worse than stated by Dr. Kist. The WDT cited by CVM states, "Campylobacteriosis establishes itself after an incubation period of 24 to 72 hours, with prodromic symptoms of headache, back pain, and general malaise. This develops into fever, sometimes with temperatures up to 40 C, which in most cases does not last longer than 24 hours. Simultaneously, abdominal symptoms start, with cramps and frequent bowel movements, loose or watery diarrhea, developing into bloody diarrhea in half the cases." Clearly, Dr. Kist does not state that all symptoms listed by CVM occur in half the cases. He then goes on to say, "Symptoms last for less than one week in most cases and the illness is self-limiting in nature for otherwise healthy individuals." P.3, L.14-16.

1386. People can die from *Campylobacter* infections. Kist WDT: p. 3, line 21 – p. 4, line 7

Bayer/AHI Response: Bayer/AHI agree to this PFOF. However, as stated it is out of context and does not imply or suggest that a fatal outcome from campylobacteriosis is frequent or caused by fluoroquinolone- resistant *Campylobacter*. A fatal outcome of campylobacteriosis is rare and is usually confined to very young or elderly patients, almost always with an underlying serious disease. B-1906 P.3 L.19-20; B-44 P.1; G-580 P.4; G-1644 P.4; (B-742) P.3-5. In the most thoroughly reported case study, the deaths of 3 HIV-infected patients were attributed to *Campylobacter* jejuni bacteremia 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.

1387. Campylobacteriosis establishes itself after an incubation period of 24 to 72 hrs. Kist WDT: p. 3, line 10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1388. Extraintestinal infections do occur as a complication of campylobacteriosis. Kist WDT: p. 4, lines 17-18

Bayer/AHI Response: Bayer/AHI agree that this statement appears in Kist's WDT. However, as stated in the PFOF it is taken out of context and misleading if it leads one to conclude that Kist believes or that the literature supports a conclusion that such infections are (i) anything other than rare, (ii) in any manner (more frequent, more severe) related to whether the *Campylobacter* is resistant or susceptible to fluoroquinolones, or (iii) mostly not treatable with antibiotics, and most not life threatening and/or self limiting. Kist P.8 L.12-17. See also CVM answer to Bayer's Interrogatory 60. Additionally, in the rare instances of bacteremia and extraintestinal infections requiring antibiotic treatment, particularly among those patients with underlying immunodeficiency states, parenteral (intramuscular or intravenous, not oral, treatment) combination therapy with imipenem and gentamicin is the recommended treatment.

Pasternack (B-1909) P.8 L.21-22, P.9 L.1-3; Iannini (B-1905) P.5 L.6-8; (B-273) P.7; (B-742) P.5.

1389. *Campylobacter* infection may lead to symptomatic sequelae. Kist WDT: p 4, lines 20-21

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is misleading and irrelevant, as stated. As stated, the PFOF is misleading because it is taken out of context. Dr. Kist concludes his discussion of this subject with, "In conclusion, generally campylobacteriosis is self-limiting and uncomplicated. In a very small number of cases, complications such as those identified can occur." P.8. L.12-13. See also reply to PFOF # 1388.

1390. Complications of *Campylobacter* infection include bacteremia, cholecystitis, pancreatitis, appendicitis, meningitis, encephalopathy, septic abortion, hemolytic uremic syndrome, reactive arthritis, and Guillain-Barre syndrome. Kist WDT: p. 5, line 1 – p. 8, line 17

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF for the reasons stated in the response to PFOF 1388 and 1389.

1391. Neonatal meningitis can be a life-threatening complication of *Campylobacter* bacteremia of the pregnant mother. Kist WDT: p. 6, lines 6-7

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF for the reasons stated in the response to PFOF 1388 and 1389. In addition this rare complication is not relevant, as fluoroquinolones are not approved for use by pregnant women. B-121 P.2.

1392. In the United States, more than 99% of reported infections with *Campylobacter* are with *Campylobacter jejuni*. Kist WDT: p. 8, line 19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1393. Indications for antimicrobial treatment are high fever for more than 2 days, bloody stools, prolonged illness, pregnancy, infection with HIV, other immunocompromised states, and living in an institution. Kist WDT: p. 10, lines 2-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1394. In Germany, the decrease of *C. coli* relative to *C. jejuni* is probably due to increased consumption of poultry in that period. Kist WDT: p. 9, lines 3-5

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is taken out of context. The paragraph to which this PFOF is cited points out the large differences between countries, suggesting that that one cannot extrapolate such information from one country to another.

1395. In Sweden and Belgium, fluoroquinolones are not recommended to treat *Campylobacter* infections because of the high rates of *Campylobacter* resistance to fluoroquinolones. Kist WDT: p. 11, lines 3-5

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is taken out of context and is therefore incomplete and misleading. To put this PFOF in its proper context it should include the full sentence of Kist and not as the PFOF does omit the important qualifier, "presumed" high resistance, and should also include the sentence that follows it: "In Sweden and Belgium, fluoroquinolones are in no case recommended for treatment of campylobacteriosis because of *presumed* high resistance quotes against these drugs. In addition the possibility was considered, that strains could become quinolone-resistant during antimicrobial treatment, a phenomenon which was observed in a couple of earlier studies (Wistrom et al., 1992; Wretlind et al., 1992; Adler Mosca et al., 1991; Petrucelli et al., 1992; Segreti et al., 1992; Smith et al., 1999)."

1396. Some countries have already lost the use of fluoroquinolones to treat campylobacteriosis because of high resistance rates. Kist WDT: p. 11, lines 3-5

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is a characterization of the text cited in PFOF 1395, and is similarly misleading and out of context. The "Some countries" refer only to Sweden and Belgium, based on the cite to Kist's WDT.. Bayer/AHI therefore disagree with this PFOF for the same reasons given in the response to PFOF 1395.

1397. Quinolones are prescribed as an empiric treatment to treat diarrhea without knowledge of its causative agents. Kist WDT: p. 11, lines 13-15

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it misrepresents the testimony. The WDT cited states, "Quinolones, though not the antibiotic of first choice for *Campylobacter*, *can be* prescribed (500 mg every 12 hrs) as empiric treatment to treat diarrhea without knowledge of the causative agents (such as *Salmonella, Shigella*)."

1398. In the US, quinolones are prescribed in approximately 5.2% of all food-borne bacterial diarrhea cases. Kist WDT: p. 11, lines 15-16

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is taken out of context and is therefore misleading. The PFOF neglects the conclusions the witness draws, i.e., that quinolones are prescribed in only 0.32% of all foodborne illness cases, including viral causes, that only about 14,442 *Campylobacter* patients in the US would receive empiric fluoroquinolone treatment, and that at most only 144 patients would not be effectively treated with ciprofloxacin, "in case *in vitro* resistance corresponds to clinical resistance." Kist WDT: P.11 L.20-22 – P.12 L.1-11.

1399. At least some patients who need antibiotics are prescribed fluoroquinolones that are ineffective because they have fluoroquinolone-resistant *Campylobacter*. Kist WDT: p. 12, lines 1-11

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it totally misrepresents the testimony of Dr. Kist. Dr. Kist initiates this discussion by stating, "I estimate the number of people who receive quinolones **potentially** ineffective, since they were infected with a fluoroquinolone-resistant *Campylobacter*...". He then concludes, "at most 20% (144 patients) would not have been effectively treated with ciprofloxacin, **in case *in vitro* resistance corresponds to clinical resistance."** To characterize this testimony as, "some patients who need antibiotics are prescribed fluoroquinolones that are ineffective" seriously distorts the witness's statement.

1400. Ciprofloxacin is effective in shortening the duration of diarrhea in patients with *Campylobacter* infection whose pretreatment *Campylobacter* isolates are susceptible to ciprofloxacin. Kist WDT: p. 13, lines 16-18

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it misrepresents the testimony of Dr. Kist. In this case, Dr. Kist is simply citing the results of a single study reported by Goodman et al., 1990. Dr. Kist does not conclude from this study that, "Ciprofloxacin is effective in shortening the duration of diarrhea in patients with *Campylobacter* infection whose pretreatment *Campylobacter* isolates are susceptible to ciprofloxacin." Moreover, the results from this study show that the percentage of "treatment failures" for fluoroquinolone-susceptible *Campylobacter* is in the same range as for fluoroquinolone-resistant *Campylobacter*. See Bayer/AHI response to PFOF 1342.

1401. Erythromycin has a narrow spectrum of activity. Kist WDT: p. 12, lines 16-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1402. There is a rising incidence of quinolone resistance in human *Campylobacter* infections. Kist WDT: p. 14, lines 5-6

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is taken out of context and misrepresents the testimony of Dr. Kist. The PFOF is derived from the following sentence, "In view of the rising incidence of quinolone resistance in *Campylobacter* (**with different frequencies in different countries) and the possibility of resistance developing as a result of treatment**, quinolones should not be used to prevent or treat *Campylobacter* complications."

1403. Patients with fluoroquinolone-resistant *Campylobacter* infections are more likely to be hospitalized than patients with fluoroquinolone-susceptible *Campylobacter* infections. Kist WDT: p. 15, lines 16-19

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF because it is misleading and seriously misrepresents the testimony of Dr. Kist. The paragraph upon which this PFOF was drawn actually states: "In a 1997 study of *Campylobacter* isolates from humans in 4 states in the US, 20 of 164 were resistant to ciprofloxacin. Of 16 patients who were interviewed, 5 were hospitalized overnight, compared with only 1 of 31 patients with fluoroquinolone-

sensitive *Campylobacter* infection (Smith et al., 2000). **Although the data presented appear suggestive, there is no evidence based on a comprehensive reanalysis of the raw data that campylobacteriosis is more severe when the bacteria are resistant. There is also no evidence that complications are more severe, or more frequent, in countries with high prevalence of fluoroquinolone resistance, such as Thailand, Taiwan or Spain (Gallardo et al., 1998; Hoge et al., 1998; Li et al., 1998).** The high incidence of fluoroquinolone-resistant *Campylobacters* and *E. coli* in Spain is likely the result of overmedication with this antimicrobial in human medicine (Ena et al., 1998). **There is also no reported increase in complications such as bacteremia, hepatitis, or reactive arthritis related to *Campylobacter* infections over the last 15 years, when fluoroquinolone resistance was on the rise. Thus, it can be concluded that, based on the data available, there is no evidence for increased risk of complications due to quinolone-resistant *Campylobacters*." P.15 L.16-22 and P.16 L.1-7.**

1404. In a study of *Campylobacter* isolates from humans in 4 states in the U.S., 20 of 164 were resistant to ciprofloxacin. Of 16 patients who were interviewed, 5 were hospitalized overnight, compared with only 1 of 31 patients with fluoroquinolone-sensitive *Campylobacter* infection. Kist WDT: p. 15, lines 16-19; B-1803

Bayer/AHI Response: Bayer/AHI cannot agree to this PFOF as it is misleading and seriously misrepresents the testimony of Dr. Kist. See Bayer/AHI response to PFOF 1403.

Diane Newell (B-1908)

1405. *Campylobacter jejuni* and the related organism *C. coli* are motile, thermophilic, microaerophilic, Gram negative bacteria, which can colonize the intestinal mucous of a range of hosts, including humans and poultry. Newell WDT: p. 3, lines 14-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1406. Most published information is derived from studies in broiler chicken flocks for *Campylobacter* colonization. The prevalence of flock infection varies worldwide from 10% to over 90%. Flock colonization is seasonal and can vary between countries. Newell WDT: p. 3, lines 17-23

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include the next following clause in the first sentence "but because of differences in sampling and culture methodology accurate comparison of such surveys is difficult." Additionally the second above referenced sentence is concluded with the phrase "and the seasonal peaks can vary between countries." B-1908, P. 3 L. 20-21, L. 22-23. The complete sentences make clear that Newell is saying that one cannot readily aggregate or compare studies between countries.

1407. 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. Newell WDT: p. 4, lines 1-3

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include the several following sentences which significantly qualify the conclusion that the ecology and physiology "in all birds is the same" and lead to the conclusion "Overall these observations suggest that *Campylobacter* colonization in broilers and turkeys may have significant host-specific differences." The full text following the PFOF states: 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). 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). Overall these observations suggest that *Campylobacter* colonization in broilers and turkeys may have significant host-specific differences. B-1908 P. 4 L. 3-12.

1408. *C. jejuni* in particular appears to have evolved to preferentially colonize the avian gut as part of the normal gut flora. Newell WDT: p. 4, lines 23-24

Bayer/AHI Response: Bayer/AHI agree that this statement is in Newell's WDT, however, it is taken out of context and is misleading to the extent it is understood as supporting that the avian gut is the source of human C. *jejuni*. Newell clearly does not support the conclusion suggested by this PFOF. For example, Newell also refers to a recent US study (Dickins et al 2002) where only a small overlap was found between human and poultry strains using the very discriminating PFGE typing, Newell P.35 L.7-10. Additionally, Newell concludes (P.43 L.6-9) that epidemiology and molecular biotechniques raise serious questions about the assumption of poultry as source of human *Campylobacter* infections.

1409. In chickens reared under intensive conditions, there are few natural restrictions to *Campylobacter* growth. Newell WDT: p. 5, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1410. Once the birds have become detectably infected at about 2-3 weeks of age, colonization can reach high level in such birds (about 10^8 per g caecal contents) and is chronic for the life of the bird (usually 6-7 weeks). Newell WDT: p. 5, lines 3-6

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include the several following sentence which significantly qualifies the conclusion that colonization "is chronic for the life of the bird." The text qualifying the PFOF states "Nevertheless, the organism is not an essential component of the avian gut flora as broiler flocks from many countries may be *Campylobacter*-free at slaughter (Newell and Wagenaar, 2000). B-1908 P.5 L. 8-9.

1411. Surveys undertaken with turkeys indicate that colonization occurs by 7 days of age and is persistent with between 80-100% of birds detectably colonized at slaughter. Newell WDT: p. 5, lines 10-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1412. Longitudinal epidemiological investigations indicate that naturally-acquired *Campylobacter* infection in broilers is age-dependent. Most flocks become infected only 2-3 weeks after placement into a house. Once the first positive birds are detected transmission is extremely rapid which may reflect enhanced colonization potential. Newell WDT: p. 5, lines 13-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1413. Published epidemiological evidence indicates that chicks are *Campylobacter*-free on hatching. Newell WDT: p. 6, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1414. Potential horizontal sources of *Campylobacter* contamination for poultry include feed, water, air and an environment contaminated by previous flocks. Newell WDT: p. 7, lines 1-3 .

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include several additional sources listed by Newell and inaccurately leads to the conclusion that the only sources of *Campylobacter* are those listed. Among the other factors identified by Newell are poultry production and service provider staff, wild life, domestic animals. B-1908 P.7 L.1-3.

1415. *Campylobacters* can be isolated from environmental sources around broiler houses. Newell WDT: p. 8, line 24 and page 9, line 1

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include several additional sources listed by Newell such as water coming into the poultry house and does not include Newell's conclusion: These results support the evidence from previous studies that the majority of flocks are infected by strain external to the poultry house environment. It seems likely that carriage into the house from the puddle on the boots of farm staff was the source of infection in this case. Contamination of the puddle may have occurred via a variety of routes including from wild bird feces. B-1908 P.9 L.4-8.

1416. Colonization in turkeys is also chronic and most birds are colonized at slaughter though shedding may be intermittent. Newell WDT: p. 10, lines 13-14

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that does not include Newell's discussion of the several significant differences between broilers and turkeys with

respect to *Campylobacter* colonization, including earlier infection, vertical transmission, loner period for colonization throughout the flock, diversity of colonization strains in a flock, and ending with the statement that "with the longer period of colonization host immunity, which can apparently reduce overall levels of colonization in experimentally infected chickens (Newell and Wagenaar, 2000), should be more consistently developed in turkeys but this has yet to be investigated." B-1908 P.10 L.20-23.

1417. As early as 1981 the development of *Campylobacter* resistance to antimicrobials, including erythromycin and nalidixic acid was being reported. In 1985 cross-resistance between nalidixic acid and enoxacin, a first generation fluoroquinolone, was reported. Newell WDT: p. 11, lines 4-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1418. Resistance to the fluoroquinolones has only become of major interest since the 1995 International *Campylobacter* Workshop as the reports of increasing resistance have emerged. Newell WDT: p. 11, lines 8-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1419. Bayer witness Newell uses in her testimony "resistance" for *Campylobacter* to mean a MIC of 4 μg/mL, measured *in vitro*. Newell WDT: p. 11, footnote 1

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and does not imply or otherwise suggest that a MIC of 4 μg/mL, measured *in vitro* equates to clinical resistance. For fluoroquinolones and *Campylobacter*, a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14) and the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

1420. In *C. jejuni/coli* it appears that the major molecular basis of fluoroquinolone resistance is by a single point mutation in the *gyr*A gene. Newell WDT: p. 12, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1421. *Campylobacter* resistance to fluoroquinolones occurs naturally as a point mutation in the *gyr*A gene and is selected by the presence of fluoroquinolones. Newell WDT: p. 12, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1422. Fluoroquinolone-resistant *Campylobacters* may be isolated from poultry as a direct result of either the fluoroquinolone treatment of *Campylobacter*-infected poultry or the acquisition by poultry of already fluoroquinolone-resistant organisms. Newell WDT: p. 13, lines 13-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1423. There are no standardized methods for the measurement of fluoroquinolone resistance in *Campylobacters*. Newell WDT: p. 13, lines 17-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1424. In the United Kingdom, the Public Health Laboratory Service has adopted a MIC of 1 µg/mL as resistant for *Campylobacter*. Newell WDT: p. 13, lines 21-22

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and does not imply or otherwise suggest that a MIC of 4 µg/mL, measured *in vitro* equates to clinical resistance. The context of Newell's statement makes this clear: "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 and even within laboratories in the same country, is difficult. Variations in MICs of 2-fold can occur within replicates (A Ridley, personal communication). In the United Kingdom, the Public Health Laboratory Service has adopted a MIC of 1 ug/ml as resistant (Thwaites & Frost, 1999) but studies in our laboratory indicate that at this level not all strains may have the *gyr*A mutation. As validated breakpoints have not yet been established, although, MICs of 4ug/ml may be considered resistant, MICs of 1-2ug/ml should be interpreted with caution. Crucially, the clinical importance of "resistant" isolates *in vivo* remains unknown. B-1908 P.13 L.17 – P.14 L.2. For fluoroquinolones and *Campylobacter*, a NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. (Joint Stipulation 14) and the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50).

1425. In Denmark 6% of *C. jejuni* but no *C. coli* strains were ciprofloxacin-resistant during the 2001 abattoir survey. Diane G. Newell, Exhibit B-1908, page 14, lines 5-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1426. The levels of fluoroquinolone resistance in poultry at slaughter varies; studies have found 32% were resistant in chicken strains in Japan; 19% in Germany, and 99% in Spain. Newell WDT: p. 14, lines 7-10.

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and does not imply or otherwise suggest that there is a causal relationship, that in many countries resistance in human isolates does not precede

resistance in *Campylobacter* isolated from poultry, or that fluoroquinolone resistant *Campylobacter* are not seen in countries without use of fluoroquinolones to treat poultry. B-1908 P.14 L.3-20.

1427. Emerging fluoroquinolone resistance in poultry *Campylobacters* worldwide has been reported subsequent to the licensing of fluoroquinolones for use in poultry. Newell WDT: p. 14, lines 11-12

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that it leads one to believe that Newell concludes that the studies are valid or that she supports the conclusion that there is a temporal trend or cause and effect between licensure of fluoroquinolones in poultry and *Campylobacter* resistance to fluoroquinolones in human isolates, when in fact in context the PFOF is inaccurate. "Emerging fluoroquinolone resistance in poultry *Campylobacters* worldwide has been reported subsequent to the licensing of fluoroquinolones for use in poultry. However, few studies have been to compare resistance in poultry strains isolated pre- and post-licensing. Such studies are confined to small samples of poultry meat isolates. For example 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. Such data provides a very limited opportunity for comparison with resistance levels in modern isolates. Thus there is no clear evidence that resistance to fluoroquinolones has increased over time, especially post. licensing, in poultry *Campylobacters*. Moreover, this limited data indicates that resistant poultry isolates were present even before the licensing of fluoroquinolones for use in poultry. B-1908 P.14 L.11-20.

1428. NARMS data suggests that between 1997-2000 25% of 180 retail chickens carried fluoroquinolone-resistant *Campylobacters*. Smith *et al.* found a similar level (19%) of resistance in 91 retail chicken products while Ge *et al* (2002) found 25% resistance in 155 isolates from chicken and turkey meat. Newell WDT: p. 14, lines 22-24, page 15, line 1

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is misleading in that it leads one to believe that Newell believes the NARMS data are valid or that the results are generalizable, when in fact in context the PFOF is inaccurate. Newell in fact in the sentence immediately preceding the CVM's PFOF that "The prevalence of fluoroquinolone resistance in poultry *Campylobacters* in North America is unclear." She goes on to say after the sentence quoted in the PFOF that "Smith *et al.* (Smith *et al.*, 1999) found a similar level (19%) of resistance in 91 retail chicken products while Ge *et al* (2002) found 35% resistance in 155 isolates from chicken and turkey meat. Both of these are relatively small studies using isolates from unstructured surveys and from poultry meats rather than poultry flocks at slaughter with no indication as to the domestic or foreign source of the birds," discusses other studies and concludes "This clearly shows that resistant *Campylobacter* can be present on chicken products as a consequence of factors other than the treatment of domestic flocks." B-1908 P.14 L.21-22, 23 – P.15 L.13.

1429. Turkey *Campylobacters* may be more exposed to fluoroquinolones than strains from broilers. Newell WDT: p. 15, lines 22-23

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context in that it takes only part of the sentence and thereby distorts the predicate to the conclusion, and does not state or imply that turkeys are exposed to higher levels of fluoroquinolones. Rather in context it is clear that Newell is saying that it may be economically more justifiable for turkey producers to use fluoroquinolones to treat disease than broiler producers: "For turkeys their longer life and greater value makes use of such [fluoroquinolone] treatment more cost effective and therefore Turkey *Campylobacters* may be more exposed to fluoroquinolones than strains from broilers." B-1471 P.15 L.20-23.

1430. The treatment of broiler flocks, which are already colonized with *Campylobacter,* can result in the selection of resistant organisms, which will naturally occur during bacterial growth. Jacobs-Reitsma *et al* clearly demonstrated that resistant *Campylobacters* are readily recovered from experimentally-infected chickens exposed to fluoroquinolones. Newell WDT: p. 16, lines 13-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1431. Bayer witness Newell acknowledges that "treatment of broiler flocks with fluoroquinolones does result in the selection of resistant organisms." Newell WDT: p. 16, lines 23-24

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context in that it takes only part of the paragraph, leaving out the sentences that qualify the statement and leaving the misinterpretation that Newell believe that treatment of broilers with fluoroquinolones is the only source or a predominant source of fluoroquinolone resistant *Campylobacter* in poultry and in humans. Rather, and in context it is clear that Newell is saying that "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 (Piddock, 1995). This indicates that resistant *Campylobacter* can be acquired by broiler flocks, other than by treatment. As mentioned previously the sources of *Campylobacter* infection in broiler flocks is unclear but is thought to be predominantly horizontal primarily from environments contaminated with feces from domestic and wild animals and birds. Few *Campylobacters* from such environmental sources have been investigated but fluoroquinolone-resistant organisms have been recovered from wild birds including sparrows (Sorum & Abee-Lund, 2002) (Chuma *et al*, 2000) and domestic animals like pigs and cattle (DANMAP 2001, 2001) (Table 1). Thus the phenotype of such strains appears to be stable in the environment and could cause poultry infections." B-1908 P.16 L.23 – P.17 L.13.

1432. Newell concludes that "In poultry flocks reared under intensive conditions colonization with *Campylobacters* can reach extremely high levels and during processing such gut contents can contaminate poultry meat." Newell WDT: p. 17, lines 17-19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1433. The importance of thermophilic *Campylobacters* as a cause of acute human bacterial enteritis was first recognized in 1977. Newell WDT: p. 19, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1434. Most human *Campylobacter* infections are due to *C. jejuni*. Newell WDT: p. 19, lines 7-8

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the PFOF does not include Newell's observation that this fact was recognized in 1981 nor "Most infections are due to *C. jejuni* but, in most industrialized countries, about 10% were caused by *C. coli*" and "In some human populations *C. coli* infections, and even other non-*jejuni/coli Campylobacter* species, have an increased importance as causes of enteritis." B-1908 P.19 L.6-10.

1435. *Campylobacter jejuni* and *C. coli* colonize the intestinal mucous of a range of hosts, including humans and poultry. In susceptible humans, particularly in the industrialized world, colonization with *Campylobacter* is associated with disease. Newell WDT: p. 19, lines 18-21

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context, and is misleading in that it leads one to believe incorrectly that infection in humans with *Campylobacter* automatically and always or frequently, leads to disease, by omitting the next following and additional sentences which make clear that "Nevertheless, excretion of *Campylobacters* in symptomatic humans is well-recognized." B-1417 P.19 L.22-23.

1436. Surveillance has shown that campylobacteriosis is the major cause of acute bacterial intestinal infectious disease in many industrial countries. Newell WDT: p. 20, lines 3-5

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, this statement is taken out of context and does not conflict with the current status in the United States, which is the relevant time and location for the issues in this hearing. As relates to the United States, B-1042, and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject and the 27% decrease in U.S. campylobacteriosis rates from 1996 to 2001 is also expressly acknowledged by Newell. B-1908 P.20 L.15-18.

1437. In Great Britain campylobacteriosis is the most common cause of acute bacterial enteritis. Newell WDT: p. 20, lines 5-6

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context, and is misleading in that it leads one to believe incorrectly that the annual incidence rates of campylobacteriosis in Great Britain are rising, when

in fact such rates, according to Newell, are currently decreasing and have been since 1998. B-1908 P.20 L.6-10.

1438. CDC has estimated the incidence of campylobacteriosis infections in the United States at 2.4 million cases per year, including non-reported cases. Newell WDT: p. 20, lines 15-16

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context in that it deletes the sentence following the quoted statement, which reads "However, more recently CDC has reported a 27% reduction in campylobacteriosis rates between 1996 and 2001." P.20 L.15-16. It is clear in the full context that Newell is merely acknowledging that CVM reported the 2.4 million figure and not that she thinks it is a valid or current estimate of the number of annual cases of campylobacteriosis in the U.S.

1439. Campylobacteriosis is generally considered to be foodborne. Newell WDT: p. 21, line 16

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context in that it deletes the next sentences which qualify the statement in its entirety and makes the finding of fact inaccurate and misleading. Newell goes on to say, after the PFOF: "However, a range of other sources, including exposure to pets and livestock, recreational waters, foreign travel, are well documented from epidemiological studies (Friedman, *et al.*, 2000) and may be significant contributors. Thus, the sources and routes of transmission, and the relative contribution of all these potential sources, remain unclear. B-1908 P.21 L.16-20.

1440. Because of their fastidious growth requirements *Campylobacters* only naturally multiply within the intestinal tract of a suitable host such as poultry and humans. Newell WDT: p. 21, lines 21-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF; however, Newell also lists as suitable hosts wild birds, pets and livestock. B-1908 P.21 L.21-23.

1441. The ability of *Campylobacters* to survive and be disseminated around the domestic kitchen is acknowledged as a risk factor. Newell WDT: p. 22, lines 10-11

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context in that it does not include the multiple other risk factors for, and sources of, human infection with *Campylobacter*, including soils, surface waters, sewage, vegetables and fruit, pet dogs and cats, horses, rabbits, wild birds, including pigeons and Newell herself concludes that poultry persists as a perceived risk factor for campylobacteriosis "even in the face of contradictory evidence." Newell concludes " Thus humans can come into contact with *Campylobacters* from a range of hosts and via a range of routes. The relative contributions of these to human infections are undetermined but may vary depending on country, region, life style and food preference. Although there are many potential sources of human infections it is widely assumed that the handling and consumption of contaminated meat, especially poultry meat, is the major source (Friedman, *et al.*, 2000). It is difficult to ascertain

why this assumption exists or even why such entrenched views persists even in the face of clearly contradictory evidence (Tam et a., 2002; Allos, 2002). B-1908 P.22 L.6 – P.23 L.8.

1442. One compelling argument for poultry as a source of infection is the contamination of retail poultry products with *Campylobacters*. The level of this contamination can be high; between 10^2 – 10^5 CFU per chicken carcass. The levels of contamination on other retail meats are significantly lower. Newell WDT: p. 23, lines 10-14

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is clearly misleading. The sentences in the PFOF are preceded by the following sentences which make clear that in context Newell does not find the purported high levels of *Campylobacter* contamination reported in retail survey as "compelling." Newell states, just prior to the PFOF "Although there are many potential sources of human infections it is widely assumed that the handling and consumption of contaminated meat, especially poultry meat, is the major source (Friedman, *et al.*, 2000). It is difficult to ascertain why this assumption exists or even why such entrenched views persists even in the face of clearly contradictory evidence (Tam et a., 2002; Allos, 2002)." B-1908 P.23 L.6-10. And Newell goes on to conclude: "These levels vary dependant on the sampling and culture methods used (Corry & Atabay, 2001). ..... Nevertheless, as knowledge about *Campylobacter* epidemiology has accumulated since 1977 the evidence has become less convincing. For example there have been several natural human experiments associated with campylobacteriosis, which have generated contradictory results. B-1908 P.23 L.6-10 P.13-18. Further Newell goes on to say: "Thus these naturally-occurring epidemiological experiments give no clear indication that poultry is a major source of human campylobacteriosis." B-1908 P.24 L.17-19.

1443. On average, the delay between exposure to *Campylobacter* and illness is 3-5 days and diagnosis by culture can take a further 3-5 days. Newell WDT: p. 25, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1444. Many studies have used genotyping techniques, like fla-typing, ribotyping or PFGE, to compare isolates from humans and poultry or livestock to determine the degree of population overlap. Newell, WDT: p. 30, lines 20-22

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is clearly misleading. Newell spends the better part of almost ten pages (B-1908, P.26-36) discussing the difficulties in using various genetics techniques and their limitations. She concludes this discussion with the following sentences: "Thus, although the results of epidemiological and molecular studies have been used to implicate poultry as the major source of human disease, more realistically, these results indicate that poultry is one of several sources. It remains impossible to determine the contribution of poultry as a source of human campylobacteriosis because representative populations from structured surveys have not yet been undertaken. However, it seems likely that the role of poultry has been overestimated, on the basis of these studies, as contributing disproportionally to human campylobacteriosis. The importance of other potential sources, such

as sheep, cattle and pets, and environmental contamination is now increasingly recognized at least in Europe (Tam *et al.*, 2002). B-1908 P.36 L.16-24.

1445. From 35-80% of the *Campylobacter* strain types found in poultry are the same as the types of strains recovered from humans with disease. Newell WDT: p. 35, lines 1-2

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but dispute that this overlap shows any causal relation between poultry consumption and campylobacteriosis. As Dr. Newell's testimony points out, genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

1446. The population structure studies confirm that the lineage of many of the *Campylobacter* strains isolated from poultry is the same as strains isolated from humans with disease. Newell WDT: p. 35, lines 16-17.

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT. However, the statement is taken out of context and is clearly misleading. Newell spends the better part of almost ten pages (B 1908, P. 26-36) discussing the difficulties in using various genetics techniques and their limitations. She does in fact make the statement in the PFOF but it is immediately followed and entirely qualified by the following two sentences which demonstrate clearly that the PFOF is misleading and incorrect, as stated: concludes this discussion with the following sentences: However, for the first time such studies have also investigated reasonable numbers of strains from other domestic animals. This data has shown that the lineage of strains from cattle, sheep and pets is also in common with strains from both humans and poultry. B-1908 P.35 L.18-21. See also reply to PFOF # 1444.

1447. In Clow's study, the proportion of *Campylobacter* types in poultry not associated with disease in humans was estimated to be about 10%. Newell WDT: p. 36, lines 7-9

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but dispute that this overlap shows any causal relation between poultry consumption and campylobacteriosis. As Dr. Newell's testimony points out, genetic typing analysis showing overlapping *Campylobacter*

genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11). See also reply to PFOF # 1444.

1448. A proportion of patients, probably ranging from 5-10% of those with *Campylobacter* infections may require hospitalization. Newell WDT: p. 37, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1449. In the past, the drug of choice for patients who may benefit from antimicrobial therapy for *Campylobacter* infections was Erythromycin but increasingly Ciprofloxacin and other fluoroquinolones are prescribed, as these have activity against most enteric bacterial pathogens. Newell WDT: p. 37, lines 8-14

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but note that Newell does not state, suggest or otherwise imply that *Campylobacter* should be routinely treated with antibiotics. In fact she believes such use is and should be limited. B-1908 P.37 L.8-12.

1450. An observed increase in resistance of *Campylobacters* infecting humans to antimicrobials has recently caused concern. Skirrow and Blaser have stated that the use of fluoroquinolones for treatment of campylobacteriosis has been severely compromised by increasing resistance rates in some countries. These concerns are realistic. Newell WDT: p. 37, lines 15-21, G-580

Bayer/AHI Response: Bayer/AHI agree that the statement is in Newell's WDT *with the exception of the last sentence concluding* "These concerns are realistic." This last sentence added by CVM is not in accord with Newell's testimony, is not correct and makes Newell's statement as stated in the PFOF misleading and inaccurate. Newell spends the better part of ten pages (B-1908 P. 37-46) of her testimony refuting the last line of this PFOF, and concludes: " In conclusion there is no significant data that the clinical outcome of infection with a fluoroquinolone-resistant *Campylobacter* is affected as a result of enhanced virulence of the organism. To the contrary data from Sentinal Surveillance Study Group (2002) indicates that resistant organisms may cause less severe illness. B-1908 P.46 L.23 – P.47 L.2.

1451. Because the mechanism of resistance is primarily a single point mutation and is not known to be horizontally transferred, fluoroquinolone-resistant *Campylobacters* may be isolated from humans as a direct result of either the fluoroquinolone treatment of *Campylobacter* infected humans or the acquisition by humans of already fluoroquinolone-resistant organisms from another treated host. Newell WDT: p. 37, lines 23-24, p. 38, lines 1-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1452. Transmission of *Campylobacter* from human to human is rare. Newell WDT: p. 38, line 15

Bayer/AHI Response: Bayer/AHI agree that this statement is in Newell's WDT. However, as stated it is out of context and therefore misleading because the human-to-human transfer of C. *jejuni* and C. *coli*, either by direct or indirect pathways, has been documented in other documents than those quoted by the witness. For example, G-1697 describes an outbreak of *C. jejuni* infections associated with food handler contamination, G-1692 describes the intrafamilial spread of *Campylobacter* in five separate households, G-580 describes a "persistent outbreak of *Campylobacter* infection in a day care nursery in Israel, and B-213 reviews nine different studies that point to person-to-person contact as being the main transmission route. The rate of human-to-human transmission in the United States is unknown, but such transmission is not necessarily as uncommon as has been supposed. G-1452 P.9 L.28-29. In addition, sewage treatment plants which process domestic, commercial, and industrial wastewater that received human waste discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of bacteria, including fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9; G-580 P.14. This PFOF is also refuted by B-1901 P.57, 80; B-1445; B-214. CVM witness Ohl also recognizes that person to person spread depends on the circumstances, Ohl WDT. P.5 L.4-7.

1453. Infection of susceptible humans with *C. jejuni* or *C. coli* can cause severe symptoms: in one study in England, published in 2000, all adults presenting to general practitioners with campylobacteriosis had diarrhea; severe in 65% of the cases, and bloody in 17% of them. Ninety-two percent of the patients had abdominal pain and 76% had fever. Their mean duration of illness was 6 days. Newell WDT: p. 42, line 21 – p. 43, line 2.

Bayer/AHI Response: Bayer/AHI agree that this statement is in Newell's WDT. However, as stated it is out of context, misleading and contradicts the conclusion of the witness if it is meant to suggest or otherwise imply that anything other than a small fraction of persons with campylobacteriosis seek medical treatment and visit a physician for treatment.

James Patterson (B-1910)

1454. Fluoroquinolone resistance among *Campylobacter* strains is worrisome with regard to the treatment of human *Campylobacter* infections. Patterson WDT: p. 6, lines 12-13

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. 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, and resistance to erythromycin and azithromycin, the preferred antimicrobials, remain low. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

1455. Waste products associated with animal husbandry and meat products processing contain *Campylobacter*, including fluoroquinolone-resistant *Campylobacter*. Patterson WDT: p. 10, lines 15-16

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that evidence in the record demonstrates that 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. B-1910 P.3 L.22 – P.4 L.3; B-1908 P.9 L.18-21, P.19 L.18-20; B-1902 P.15 L.5-10; G-1470 P.4 L.608; G-1483 P.8 L.15-17. Nearly all animals, wild and domesticated, harbor *Campylobacter* as a normal inhabitant of the gastrointestinal tract. G-1483 P.4 L.14-15. *Campylobacter* contaminate the water environment via wild and domestic animal excretions, urban and agricultural drainage, and sewage and industrial wastewater discharges. B-1910 P.4 L.12-13; B-1908 P.8 L.1-3. *Campylobacter* has been demonstrated to be ubiquitous in the water environment, present both in surface waters and ground waters. B-1910 P.4 L.4-6; B-1908 P.7 L.24 – P.8 L.1; CVM Response to Bayer's Interrogatory 1. *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. B-1910 P.4 L.8-12. Predominant routes of fluoroquinolone resistant *Campylobacter* infection in humans are other than associated with poultry. B-1910 P.7 L.20-22.

1456. Farm drainage can transport *Campylobacter* into surface waters and ground waters. Patterson WDT: p. 10, lines 16-17

Bayer/AHI Response: Bayer/AHI agree that this statement appears in Patterson's WDT, but as stated in PFOF 1456 it is out of context and misleading in that Patterson identifies many other sources of both fluoroquinolone-susceptible and resistant *Campylobacter* (Patterson WDT P.9 L.13-14), provides numerous non-poultry examples of causes of both a fluoroquinolone

susceptible and resistant *Campylobacter* in surface and ground waters and concludes that "waterborne transmission of *Campylobacter* accounts for the majority of campylobacteriosis cases in the U.S., and that poultry "as a route of human infection is insignificant." See Patterson WDT, generally, and P.22 L.14-16 (with supporting documentation cited.)

1457. Most *Campylobacter* infections in humans occur as sporadic isolated cases or as part of a small cluster of cases. Patterson WDT: p. 22, lines 17-18

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1458. Most documented waterborne instances of campylobacteriosis are associated with outbreaks. Patterson WDT: p. 23, lines 15-16

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that the vast majority of *Campylobacter* infections occur sporadically, not as part of an outbreak. Tauxe (G-1475) P.6 L.14-16; Angulo (G-1452) P.9 L.18-19.

Michael Robach (B-1911)

1459. Most human *Campylobacter* illness is caused by *Campylobacter jejuni*. Robach WDT: p. 5, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1460. The most common bacterial causes of food borne disease in the United States are *Salmonella* and *Campylobacter*. Robach WDT: p. 4, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1461. Most people who become ill from *Campylobacter* develop diarrhea 2-5 days after exposure to the organism. Robach WDT: p. 4, lines 10-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1462. Campylobacteriosis usually occurs in single, sporadic cases. Robach WDT: p. 5, line 17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1463. Chickens colonized with *Campylobacter* usually show no signs of illness. Robach WDT: p. 5, line 20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1464. When an infected bird is slaughtered, *Campylobacter* can be transferred from the intestinal tract to the skin or to the meat. Robach WDT: p. 5, lines 22-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1465. Many chicken flocks are infected with *Campylobacter* but show no signs of illness. Robach WDT: p. 5, line 20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1466. *Campylobacter* can easily spread from bird to bird through a common water source, or through contact with infected feces. Robach WDT: p. 5, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1467. When an infected bird is slaughtered, *Campylobacter* can be transferred from the intestinal tract to the skin or to the meat. Robach WDT: p. 5, lines 22-23

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1468. Foods of animal origin are an important cause of human illness. Robach WDT: p. 7, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1469. During the slaughtering process, workers, equipment, and the processing environment can serve as sources of contamination for the finished product. Robach WDT: p. 8, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1470. *Campylobacter* are naturally occurring bacteria that reside in the gut of healthy birds. Robach WDT: p. 9, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1471. *Campylobacter* organisms are capable of causing foodborne illness in humans. Robach WDT: p. 9, line 10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1472. The two human enteropathogens most frequently associated with poultry are *Salmonella* and *Campylobacter jejuni*. Robach WDT: p. 10, lines 19-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1473. The intestines of poultry are easily colonized with *Campylobacter*. Robach WDT: p. 10, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1474. *Campylobacter* grows best at 37 – 42 C. Robach WDT: p. 11, line 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1475. *Campylobacter* grows best in a microaerophillic environment (5% O_2, 10% CO_2, and 85% N_2). Robach WDT: p. 11, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1476. *Campylobacter* is rarely found in chickens until after the third or fourth week of grow-out. Robach WDT: p. 12, lines 1-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1477. Once *Campylobacter* is introduced in the poultry house, almost the entire house will be colonized in the span of a few days, and remain that way through slaughter. Robach WDT: p. 12, lines 1-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1478. Evisceration can be a major source of fecal contamination, particularly if the intestines are cut. Robach WDT: p. 14, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1479. Adding chlorine to chill tank water does not kill all bacteria. Robach WDT: p. 14, lines 18-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1480. High pre-chill contamination of poultry with bacteria results in high post-chill contamination of poultry with bacteria. Robach WDT: p. 14, lines 20-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1481. Foods of animal origin are an important source of the enteric organisms that cause human illness. Robach p. 17, lines 5-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Scott Russell (B-1912)

1482. Broilers (chickens) are typically raised on broiler farms comprised of two or three houses per farm with 20,000 to 25,000 broilers per house. Russell WDT: p. 3, lines 14-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1483. Broilers are reared to 42-58 days. Russell WDT: p. 3 lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1484. Scalders have water between 130 - 132°F. Russell WDT: p. 4, lines 13-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1485. Fecal contamination of chickens at the evisceration stage is easily spread to adjacent birds due to the bird to bird contact on the hang line. Russell WDT: p. 5, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1486. Chill tank water is about 33 - 34°F. Russell WDT: p. 6, lines 3- 4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1487. Campylobacteriosis usually occurs in single, sporadic cases. Russell WDT: p. 10, lines 7-8 and p. 10, line 14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1488. *Campylobacter* has been associated with handling raw poultry. Russell WDT: p. 10, line 9

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. Bayer/AHI do not agree that in the U.S. handling raw poultry is a major source of *Campylobacter* infection. Recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a major source of *Campylobacter* infections in the U.S.

1489. *Campylobacter* has been associated with eating raw or undercooked poultry. Russell WDT: p. 10, lines 9-10

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. Bayer/AHI do not agree that in the U.S. poultry is a major source of *Campylobacter*

infection. Recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contact with and consumption of chicken and turkey is a major source of *Campylobacter* infections in the U.S.

1490. A very small number of *Campylobacter* organisms can cause illness in humans. Russell WDT: p. 10, lines 10-11

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. "Very small" is a relative term. The statement must be put in context. The risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *Campylobacter* ingested. Joint Stipulation 27. 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. Evidence in the record shows that "Based on experimental data, the minimum number of *Campylobacter* capable of causing campylobacteriosis has been estimated to be about 500 - 800 organisms (minimum infectious dose)." B-1901 P.23, citing B-748/G-629 and G-628; G-67.

1491. As few as 500 *Campylobacter* organisms can cause illness in humans. Russell WDT: p. 10, lines 10-11

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. The statement must be put in context, however. The risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *Campylobacter* ingested. Joint Stipulation 27. 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. Evidence in the record shows that "Based on experimental data, the minimum number of *Campylobacter* capable of causing campylobacteriosis has been estimated to be about 500 - 800 organisms (minimum infectious dose)." CVM's PFOF may be interpreted to mean that the infective dose for all people is 500 organisms, which is not accurate. B-1901 P.23, citing B-748/G-629 and G-628; G-67.

1492. Campylobacteriosis is estimated to affect over 2 million persons every year. Russell WDT: p. 10, line 18

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. Bayer/AHI dispute this as a finding of fact, however, because it is outdated. CDC estimates that campylobacteriosis incidence since 1996 has decreased 27% (1996 to 2001) and the estimate for *Campylobacter* infections in 1999 was 1.4 million. CVM proposed finding of

fact #36, G-1452 Attachment 3 P.82; CVM Response to Bayer's Interrogatory 28. G-1452 P.7 L.13-14, L.16-18, P.17 L.10

1493. People can die from campylobacteriosis. Russell WDT: p. 11, lines 1-2

Bayer/AHI Response: Bayer/AHI do not agree to this PFOF because it is misleading without further qualification. The lethality of campylobacteriosis is "extremely rare, and always related to underlying conditions". Kist WDT: P.4. L.14-16. Also, this PFOF is irrelevant to this proceeding as it is the human health impact of **resistant** *Campylobacter* that is at issue, not campylobacteriosis.

1494. During viscera removal, opportunities exist for the digestive tract to be cut or torn, releasing fecal material onto the interior or exterior surfaces of the carcass. Russell WDT: p. 13, lines 4-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1495. Line speeds at chicken slaughter plants are 70 broilers per minute or higher. Russell WDT: p. 15, lines 16-17

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1496. Only a certain percentage of bacteria will be susceptible to chlorine in the chiller. Russell WDT: p. 15, line 22

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, with the caveat that the use of the phrase "susceptible to chlorine" does not reflect "susceptibility" in the context of antimicrobial resistance.

1497. Some bacteria on the chicken is protected from the chiller by the chicken fat, location on the carcass, or because they are lodged in a feather follicle. Russell WDT: p. 16, lines 1-2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1498. Highly contaminated pre-chiller carcasses will result in highly contaminated post chiller carcasses. Russell WDT: p. 16, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1499. Chickens in a chiller are susceptible to cross-contamination. Russell WDT: p. 16, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1500. In the chiller, bacteria from carcasses contaminated with feces can spread to other carcasses. Russell WDT: p. 16, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1501. The chiller does not reduce high bacterial count numbers. Russell WDT: p. 19, line 14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1502. The chiller will reduce bacteria by a certain degree but the number of bacteria does not change significantly if the numbers are high or low going into the chiller. Russell WDT: p. 19, lines 14-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1503. *Campylobacter jejuni* is a leading cause of diarrhea disease and foodborne gastroenteritis worldwide. Russell WDT: p. 24, lines 18-19

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. Bayer/AHI do not dispute this PFOF but disagree that it reflects the current status in the United States, which is the relevant time and location for the issues in this hearing. As relates to the United States, this PFOF is refuted by B-1042 and G-1391, in which CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. This is the most recent information available on this subject.

1504. Contaminated poultry is a common vehicle of transmission of *C. jejuni* in humans. Russell WDT: p. 24, lines 20-21

Bayer/AHI Response: Bayer/AHI do not dispute that Dr. Russell's testimony makes this statement. Bayer/AHI do not agree that in the U.S. contaminated poultry is a common vehicle of transmission of *C. jejuni* in humans. Recent epidemiological data in the U.S. demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that retail poultry eaten by consumers at home is a major source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Therefore the best, most recent epidemiological evidence in the record does not show or even merely suggest that contaminated poultry is a common vehicle of transmission of *C. jejuni* in humans in the U.S.

Terry TerHune (B-1915)

1505. The current label dose for enrofloxacin is 25 to 50 ppm for broiler chickens and turkeys. TerHune WDT: p. 5, line 16 – p. 6, line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Anthony E. van den Bogaard (B-1916)

1506. Selection and dissemination of resistance is an inevitable result of any antibiotic use. van den Bogaard WDT: p. 3, lines 5-6.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1507. In most cases, two mutations in the genome of a bacterium are required in order to cause clinically relevant resistance against fluoroquinolones but only one mutation is necessary to cause resistance in *Campylobacter*. van den Bogaard WDT: p. 3 lines 10-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1508. Bayer witness Dr. van den Bogaard testified that data and information has demonstrated that fluoroquinolone use in poultry acts as a selection pressure resulting in the emergence of fluoroquinolone-resistant *Campylobacter* spp. in poultry that may be transferred to humans cause therapy failures in humans when those infections are treated with a fluoroquinolone. van den Bogaard WDT: p. 5, lines 2-11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This finding of fact is inaccurate and misleading in its statement of what Dr. van den Bogaard actually testified. A review of the testimony indicates that Dr. van den Bogaard stated that "CVM was aware of data and information demonstrating (and had concluded) that" fluoroquinolone use in poultry acts as a selection pressure resulting in the emergence of fluoroquinolone-resistant *Campylobacter* spp. in poultry that may be transferred to humans cause therapy failures in humans when those infections are treated with a fluoroquinolone. Unlike CVM's proposed finding of fact, Dr. van den Bogaard is not testifying himself to these facts. van den Bogaard (B-1916) P. 5 L. 1-11.

1509. The emergence of fluoroquinolone-resistance of *Campylobacter spp.* in chickens was first suggested by Endtz et al as isolates from chicken meats were frequently found resistant to fluoroquinolones. van den Bogaard WDT: p. 5 line 29 – p. 6, line 1, G-755, G-190

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1510. An experiment by Jacobs-Reitsma et al experimentally infected broiler chickens with quinolone-sensitive *C. jejuni*, and then treated the birds with enrofloxacin, which did not eradicate the *Campylobacter* colonization of the broilers, but caused the emergence of quinolone-resistant strains that persisted until slaughter. *Campylobacters* in chicks of a control group, not receiving enrofloxacin treatment, remained fluoroquinolone-sensitive. van den Bogaard WDT: p. 6, lines 4-11, B-432

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1511. Recent studies confirm 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 WDT: p. 7, lines 17-21, B-868

Bayer/AHI Response: Bayer/AHI dispute this PFOF because it does not accurately reflect the actual testimony at page 7, lines 17-21, including that this information was know to CVM prior to licensing of fluoroquinolones for poultry. In the actual testimony, van den Bogaard does not state that "recent studies confirm," rather he merely states that "these studies have not revealed new premises." The actual testimony states: "Indeed, information published since the time of approval merely confirms those conclusions known at the time prior to approval. Specifically, 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.15-21.

1512. Endtz et al. documented the prevalence of ciprofloxacin resistance bracketing the introduction of fluoroquinolones into human medicine and enrofloxacin into veterinary medicine. van den Bogaard WDT: p. 8, lines 18-22

Bayer/AHI Response: Bayer/AHI agree that this statement is contained in van de Bogaard's WDT. However, as stated the PFOF is taken out of context and is misleading, if it leads one to conclude other than CVM was aware this data (as well as others specified by van de Bogaard) before licensure of fluoroquinolones for poultry in the U.S. van den Bogaard WDT: P.4-10.

1513. Among human *Campylobacter* isolated examined by Endtz et al., no ciprofloxacin resistance was found during 1982 to 1983 or in 1985. The percentage of ciprofloxacin-resistant isolated increased to 8% during 1987 to 1988 and to 11% in 1989. In a follow-up study in humans, the prevalence of fluoroquinolone-resistant *Campylobacter* isolates amounted to approximately 25% in 1990. van den Bogaard WDT: p. 8, lines 24-28

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that it only reflects the results of an initial study. As previously stated, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint-indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. 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, and resistance to erythromycin and azithromycin, the preferred antimicrobials, remain low. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant

difference in the mean duration's of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L.4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

1514. Among poultry isolates examined by Endtz et. al., no resistance was found in poultry isolates from 1982 to 1983; the percentage of resistant isolates increased to 8% during 1987 to 1988 and to 14% during 1989. van den Bogaard WDT: p.8 lines 18-28. G-755, B-22

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF, but note that it only reflects the results of an initial study. As previously stated, the clinical significance of *Campylobacter* isolates deemed to be "fluoroquinolone-resistant" *in vitro* has not been demonstrated. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Joint Stipulation 14; see also B-1909 P.17 L.4-6, P.14 L.19 – P.15 L.16; B-1913 P.12-13, P.17 L.15-23; B-1908 P.14 L.1-2; B-1900 P.4 L.22-24, P.10 L.1-2; and B-1901 P.78 (citing B-50). Without a clinical breakpoint for *Campylobacter*, it is not possible to determine what level of resistance is necessary to produce clinical resistance. 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, and resistance to erythromycin and azithromycin, the preferred antimicrobials, remain low. Analysis of United States data from the CDC 1998-1999 *Campylobacter* case-control study and Smith et al. there is no significant difference in the mean durations of diarrhea for susceptible and resistant cases when appropriate adjustments are made to exclude foreign travel and prior treatment. B-1900 P.35 L. 4-6; P.36 L. 4-5, P.36 (Table 8), P.49 L.12-14; B-50 P. 2; B-1901 P.24, P.30-31; B-1908 P.46 L.10-13.

1515. Fluoroquinolones are very important for human patients with life-threatening bacterial infections. van den Bogaard WDT: p. 14, lines 22-23

Bayer/AHI Response: Bayer/AHI do not agree to this PFOF because as stated it is too broad and, therefore, misleading. Although it is agreed that fluoroquinolones can be important for human patients with some life-threatening bacterial infections, the evidence does not support that they are important for *Campylobacter* infections. Pasternack (B-1909) P.8 L.21-22, P.9 L.1-3; Iannini (B-1905) P.5 L.6-8; (B-273) P.7; (B-742) P.5. See also Bayer/AHI response to PFOF 1342.

1516. Like with other foodborne pathogenic bacteria, the colonization of *Campylobacter* spp. in animals, the high rate of contamination of meat products and inappropriate handling at home as well as in commercial kitchens are the basic problems. van den Bogaard WDT: p.15, lines 16-18

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context, thereby affecting its true and intended meaning. The actual testimony states: "Finally, I believe that the intervention measures taken in production, processing and food handling to reduce the burden of *Campylobacter* in the United States and elsewhere, is by far, more promising to reduce campylobacteriosis in humans than focusing on the fluoroquinolone resistance issue. The resistance "per se" is not the problem. Like with other foodborne

pathogenic bacteria, the colonization of *Campylobacter* spp. in animals, the high rate of contamination of meat products and inappropriate handling at home as well as in commercial kitchen are the basic problems. In this respect, it should also be noted that the new macrolides such as azithromycin or clarithromycin are the drugs of first choice in the rare cases where campylobacteriosis need to be treated with antibiotics." van den Bogaard (B-1916) P.15 L.12-21.

Dennis P. Wages (B-1917)

1517. Toms are raised until 16 - 22 weeks of age and weight 32- 40 pounds; hens are raised from 14-20 weeks of age and weigh 14 - 20 pounds. Wages WDT: p. 3, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1518. The typical turkey grow-out complex has two brooder houses and four grow-out houses per farm. Wages WDT: p. 3, lines 20-21

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1519. Turkey brooder and grow-out houses are usually 40-50 feet wide and 300-400 feet long. Wages WDT: p. 4, line 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1520. Turkey brooder and grow-out houses are usually oriented east-west. Wages WDT: p. 4, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1521. Turkey brooder and grow-out houses are usually curtain sided, wood constructed with tin roofs. Wages WDT: p. 4, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1522. Inside the turkey house, there are usually two automatic feed lines in a brooder house and one automatic feed line in the grow-out houses. Wages WDT: p. 4, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1523. There are usually two rows of automatic, Plasson type (open) drinkers in turkey houses. Wages WDT: p. 4, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF but notes that there is additional evidence in the record that "poultry houses also have one of several nipple drinkers," that waterers are generally washed with iodine every 1-2 days to control microbial contamination,"

and that "all water systems in poultry houses must be managed to avoid spillage and keep the litter as dry as possible" for the health of the birds. A-201, P.7 L.2-13.

1524. There are typically 8,000 -12,000 turkeys raised in a brooder house. Wages WDT: p. 4, line 7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1525. There are normally 4,000 to 6,000 turkeys raised in the grow-out houses. Wages WDT: p. 4, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1526. All turkey feed in the U.S. industry is pelleted. Wages WDT: p. 4, line 11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1527. Baytril 3.23% concentrate oral solution was approved for control of turkey mortality associated with *E. coli* and *Pasteurella multocida* (fowl cholera) susceptible to enrofloxacin. Wages WDT: p. 8, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1528. Baytril is administered in the drinking water of the infected house. Wages WDT: p. 18, lines 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1529. In the United States, enrofloxacin is approved for use only by prescription and only under veterinary supervision. Wages WDT: p. 18, lines 7-8

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1530. In the United States, enrofloxacin is approved for therapeutic use only and is not approved for growth promotion. Wages WDT: p. 18, lines 8-9

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1531. In the United States, extra-label use of enrofloxacin is prohibited by law for food producing animals. Wages WDT: p. 18, lines 9-10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1532. Extra-label use of enrofloxacin is prohibited in the United States. Wages WDT: p. 18, line 11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1533. Labeled dosage of enrofloxacin for turkeys is 25 ppm - 50 ppm. Wages WDT: p. 18, line 12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1534. Typical dosage of enrofloxacin for turkeys is 50 ppm. Wages WDT: p. 18, line 12

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context, thereby affecting its true and intended meaning. The actual testimony at P.18 L.12 states: "Labeled dosage for turkeys is 25 ppm – 50 ppm (A-54). Typical dosage for turkeys is 50 ppm." Evidence in the record supports the position that a dose of 25 ppm is frequently used. A-201 P.27 L.6-8.

Richard Carnevale (A-199)

1535. It is currently not possible, even under the most hygienic conditions, to produce raw poultry that is sterile, or at least completely free of any harmful pathogens. Carnevale WDT: p. 21, line 1-2.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1536. Millions of bacteria may be carried by birds upon entry to a slaughter establishment. Carnevale WDT: p. 20, line 17 through p. 21, line 3.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1537. *Campylobacter* contamination of raw poultry carcasses is considered unavoidable; this is true regardless of the antimicrobial susceptibility profile of the *Campylobacter*. Carnevale WDT: p. 21, line 10-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Bradley DeGroot (A-200)

1538. Seasonal variation explains only a small proportion of the number of resistant isolates submitted by Minnesota to the human NARMS surveillance program, beyond what can be expected based on overall resistance measured for the state. DeGroot WDT: p. 24, line 1-7.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1539. If participating laboratories do not change culture and isolation methods and if the relative contribution of laboratories using various methods remain consistent through time, any differences in laboratory methods will have minimal effect on comparisons of resistant rate estimates over time. DeGroot WDT: p. 28, line 15-18.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1540. The intent of the slaughter sampling component of the animal NARMS surveillance program is sound. DeGroot WDT: p. 64, line 12-13.

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Eric Gonder (A-201)

1541. The traditional turkey housing system includes a farm with a brooder house and 1-3 grow-out houses. Gonder WDT: p. 4, line 13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1542. Turkeys start in the brooder house, move to the grow-out houses at 5-7 weeks of age, and are replaced by a new group in the brooder house after several weeks. Gonder WDT: p. 4, lines 13-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1543. Two ages of turkeys may be present on the farm at the same time. Gonder WDT: p. 4, lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1544. Most turkey farms have 2 to 4 houses while the national range is 2 to 10 houses. Gonder WDT: p. 6, line 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1545. Brooder houses, where the turkeys reside for the first several weeks of life, are 32-70 feet wide and 250-600 feet long. Gonder WDT: p. 6, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1546. Brooder houses will contain 10,000-20,000 turkey poults, although some very large houses used in a few locations may contain 70,000 turkey poults. Gonder WDT: p. 6, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1547. Finishing or grow-out houses usually contain one-third to one-half as many turkey as brooder houses due to the need to provide additional space for the birds to grow. Gonder WDT: p. 6, lines 11-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1548. Typically, the number of turkeys in a grow-out house is on the order of 10,000 to 20,000 birds. Gonder WDT: p. 6, lines 13-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1549. CDC reports that 95 - 99% of human *Campylobacter* infections are caused by C. *jejuni.* Gonder WDT: p. 13, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Chuck Hofacre (A-202)

1550. The US turkey (272 million) and broiler chicken (8.5 billion) industries are similar to each other. The integrated company purchases the parent breeders at 1 day of age or hatching eggs from a primary breeder or genetic selection company. These birds are raised on farms contracted by the company under specific company guidelines for antibiotic usage. The offspring (broiler chickens or commercial turkeys) of these breeders are hatched in company-owned hatcheries, and placed on a contract or company-owned farm, where the farmer must follow strict company guidelines for all aspects of raising the birds, including antibiotic usage. All feed that is fed to the breeders, broiler chickens or commercial turkeys is manufactured in a company-owned feedmill under specific guidelines of a company. The company nutritionist specifies the nutritional composition of the feed, and the veterinarian determines any antibiotic usage requirements. The birds are then slaughtered in a company-owned processing plant. Hofacre WDT: p. 32, lines 4-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1551. The typical US broiler chicken farm typically has on the order of 100,000 chickens, divided equally into four houses. Hofacre WDT: p. 3, lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1552. Day old broiler chicks are delivered to a contract broiler grower farm where they go into an environmentally controlled house that is on average 40 feet wide and 500 feet long with approximately 25,000 broilers per house. Hofacre WDT: p. 5, lines 20-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1553. The label dose for Baytril is 25 to 50 ppm for 3 to 7 days for the treatment of *E. coli* infections in chickens and turkeys plus *Pasteurella multocida* infections of turkeys. Hofacre WDT: p. 22, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Ronald Prucha (A-203)

1554. About one-half of foodborne bacterial infections from the major bacterial pathogens are attributable to meat and poultry sources. Prucha WDT: p. 4, lines 3-5

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1555. In 1993, 50% of *Campylobacter* cases were attributed to meat and poultry sources. Prucha WDT: p. 4, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1556. In 1995, 41% to 53% of *Campylobacter* cases were due to meat and poultry sources. Prucha WDT: p. 4, lines 6-7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1557. The number of *Campylobacter* cases attributed to meat and poultry are rising. Prucha p. 4, lines 5-7

Bayer/AHI Response: Bayer/AHI dispute this PFOF because by deleting the time periods, stated in Prucha's testimony the PFOF is a misleading characterization and generalization from a non-current, clearly time limited period (1993 and 1995) limited and does not accurately reflect either the actual testimony or relevance to this proceeding. The actual testimony at P.4 L.5-7 states: "For example, in 1993, 50% of *Campylobacter* cases were attributable to meat and poultry sources, and in 1995, 41 to 53% of *Campylobacter* cases were due to meat and poultry sources." Prucha (A-203) P.4 L.5-7.

1558. The skin and feathers of live birds are highly contaminated during their grow-out periods, and their intestinal tracts contain millions of bacteria, some of which may be pathogenic to humans. Prucha WDT: p. 7, lines 18-20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1559. The evisceration process can release heavy bacteria loads through fecal contamination to poultry carcasses. Prucha WDT: p. 8, lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1560. Fecal contamination in chill tanks can cross-contaminate thousands of other carcasses. Prucha WDT: p. 8, lines 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Robert Tompkin (A-204)

1561. A multistate survey between 1996-1997 found that only 1.5% of people drink raw milk. Tompkin WDT: p. 12 line 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1562. *Campylobacter* is now recognized as the leading cause of zoonotic enteric infections in most developed and developing countries. Tompkin WDT: p. 14, lines 11-12

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF. However, as with respect to the current status in the United States, which is the relevant time and location for the issues in this hearing most gastrointestinal infections in the U. S. are viral. As relates to bacterial infections in the United States, CDC reports that for 2001 *Salmonella* is the most commonly reported bacterial cause of foodborne illness in the United States and notes declining campylobacteriosis rates. B-1042 and G-1391. This is the most recent information available on this subject.

1563. Campylobacteriosis is usually caused by *C. jejuni* or to a lesser extent by *C. coli.* Tompkin WDT: p. 14, lines 12-13

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1564. Most human *Campylobacter* infections are classified as sporadic single cases. Tompkin WDT: p. 14, line 13

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context, thereby affecting its true and intended meaning. The actual testimony beginning on P.14 L.13 states: "Most human *Campylobacter* infections are classified as sporadic single cases or as part of small family related outbreaks."

1565. FoodNet is the most sensitive means employed by the public health community to document the extent of diarrheal disease in the U.S. Tompkin WDT: p. 15, lines 14-15

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1566. Vertical transmission of *Campylobacter* is an unlikely source of infection. Tompkin WDT: p. 44, line 19

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1567. Once a poultry flock has been exposed to colonization, water and feed play an important role in the dissemination of colonization throughout the flock. Tompkin WDT: p. 45, lines 5-6

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context, thereby affecting its true and intended meaning. Among other things, the

testimony clarifies that "[c]hlorination of the water supply was shown to slow the intra-flock transmission of the organism." Tompkin (A-204) P.45 L.12-13.

1568. There is contamination of the exterior of a large proportion of birds in the transport vehicle. Tompkin WDT: p. 46, lines 15-16

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1569. As birds enter the scald tank there may be involuntary defecation, leading to accumulation of fecal matter in the tank. Tompkin WDT: p. 49, lines 13-14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1570. Scalding may lead to external contamination if an uncontaminated poultry carcass is passed through contaminated scald water. Tompkin WDT: p. 49, lines 21-22

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1571. Defeathering machines are major sites of potential cross-contamination in primary processing. Tompkin WDT: p. 50, lines 5-6

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1572. The spinning action of the plucker heads during mechanical defeathering produces aerosols which spread contamination. Tompkin WDT: p. 50, lines 9-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1573. The process of defeathering has been demonstrated to generally increase the number of carcasses contaminated with organisms. Tompkin WDT: p. 50, lines 11-12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1574. For birds colonized with *Campylobacters,* gross contamination may result if damage occurs to the viscera during evisceration. Tompkin WDT: p. 51, lines 3-4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1575. As the carcasses move through the operation, the major source of contamination can result during mechanical evisceration. Tompkin WDT: p. 51, lines 10-11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1576. The majority of campylobacteriosis in humans is due to *C. jejuni.* Tompkin WDT: p. 57, line 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Joint Stipulations

1577. Fluoroquinolone use in chickens and turkeys can act as a selection pressure for fluoroquinolone-resistant bacteria in the chicken and turkey digestive tract. Revised Joint Stipulation No. 7

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1578. The parties do not have any facts or data demonstrating horizontal gene transfer for fluoroquinolone resistance in *Campylobacter*. Revised Joint Stipulation No. 10

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1579. The National Committee for Clinical Laboratory Standards (NCCLS) is a standards-developing organization that develops and disseminates standards, guidelines and best practices for medical testing in clinical laboratories. Revised Joint Stipulation No. 11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1580. NCCLS has established guidelines for susceptibility testing of certain bacteria to certain antimicrobial agents. Revised Joint Stipulation No. 12

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1581. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans. Revised Joint Stipulation No. 14

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1582. Many persons sick with gastroenteritis do not seek medical care. Revised Joint Stipulation No. 20

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1583. 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. Revised Joint Stipulation No. 36

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1584. In the United States, a broiler grow-out house typically contains on the order of 20,000 to 25,000 broilers. Revised Joint Stipulation No. 37

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1585. In the United States, a turkey grow-out house typically contains on the order of 10,000 to 20,000 turkeys. Revised Joint Stipulation No. 38

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1586. Baytril 3.23% concentrate oral solution was approved in the United States on October 4, 1996 for control of chicken mortality associated with *Escherichia coli* susceptible to enrofloxacin and for control of turkey mortality associated with *E. coli* and *Pasteurella multocida* (fowl cholera) susceptible to enrofloxacin. Revised Joint Stipulation No. 39

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1587. The horizontal transfer of genes conferring fluoroquinolone resistance in *Campylobacter* has not been demonstrated. Revised Joint Stipulation No. 40

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1588. *Campylobacter jejuni* and *Campylobacter coli* can be human pathogens. Revised Joint Stipulation No. 41

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1589. 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. Revised Joint Stipulation No. 42

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1590. In 2001, there were 8.6 billion broilers (chickens) raised for slaughter in the United States. Revised Joint Stipulation No. 43

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1591. In 2000, there were 270 million turkeys raised for slaughter in the United States. Revised Joint Stipulation No. 44

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1592. The use of enrofloxacin in chickens and turkeys can exert a selection pressure that can lead to fluoroquinolone resistance. Revised Joint Stipulation No. 45

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1593. SaraFlox WSP was approved in the United States on August 18, 1995 for the control of mortality in growing turkeys and broiler chickens associated with *Escherichia coli* organisms susceptible to sarafloxacin. Revised Joint Stipulation No. 47

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1594. SaraFlox Injection was approved in the United States on October 12, 1995 for the control of early mortality in day old broiler chickens associated with *E. coli* organisms susceptible to sarafloxacin. Revised Joint Stipulation No. 48

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1595. Bayer's ciprofloxacin product was first registered in Austria on June 26, 1987; Bayer's enrofloxacin product for poultry was first registered in Austria on May 3, 1988. Revised Joint Stipulation No. 51

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1596. Bayer's ciprofloxacin product was first registered in Belgium on January 20, 1989; Bayer's enrofloxacin product for poultry was first registered in Belgium on January 19, 1988. Revised Joint Stipulation No. 52

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1597. Bayer's ciprofloxacin product was first registered in Denmark on March 23, 1988; Bayer's enrofloxacin product for poultry was first registered in Denmark on December 27, 1991. Revised Joint Stipulation No. 53

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1598. Bayer's ciprofloxacin product was first registered in Finland on July 8, 1987. Revised Joint Stipulation No. 54

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1599. Bayer's ciprofloxacin product was first registered in France on July 24, 1987; Bayer's enrofloxacin product for poultry was first registered in France on December 31, 1991. Revised Joint Stipulation No. 55

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1600. Bayer's ciprofloxacin product was first registered in Germany on January 30, 1987; Bayer's enrofloxacin product for poultry was first registered in Germany on January 17, 1990. Revised Joint Stipulation No. 56

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1601. Bayer's ciprofloxacin product was first registered in Greece on April 6, 1988; Bayer's enrofloxacin product for poultry was first registered in Greece on January 22, 1990. Revised Joint Stipulation No. 57

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1602. Bayer's ciprofloxacin product was first registered in Ireland on December 20, 1988; Bayer's enrofloxacin product for poultry was first registered in Ireland on October 1, 1988. Revised Joint Stipulation No. 58

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1603. Bayer's ciprofloxacin product was first registered in Italy on March 1, 1989; Bayer's enrofloxacin product for poultry was first registered in Italy on September 19, 1990. Revised Joint Stipulation No. 59

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1604. Bayer's ciprofloxacin product was first registered in Luxembourg on June 16, 1987; Bayer's enrofloxacin product for poultry was first registered in Luxembourg on February 23, 1990. Revised Joint Stipulation No. 60

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1605. Bayer's ciprofloxacin product was first registered in The Netherlands on August 15, 1988; Bayer's enrofloxacin product for poultry was first registered in The Netherlands on April 8, 1987. Revised Joint Stipulation No. 61

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1606. Bayer's ciprofloxacin product was first registered in Portugal on August 23, 1988; Bayer's enrofloxacin product for poultry was first registered in Portugal on June 20, 1994. Revised Joint Stipulation No. 62

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1607. Bayer's ciprofloxacin product was first registered in Spain on May 26, 1988; Bayer's enrofloxacin product for poultry was first registered in Spain on October 1, 1990. Revised Joint Stipulation No. 63

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1608. Bayer's ciprofloxacin product was first registered in Sweden on February 4, 1988; Bayer's enrofloxacin product for poultry was first registered in Sweden on Septembers, 1989. Revised Joint Stipulation No. 64

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1609. Bayer's ciprofloxacin product was first registered in the United Kingdom on February 2, 1987; Bayer's enrofloxacin product for poultry was first registered in the United Kingdom on November 11, 1993. Revised Joint Stipulation No. 65

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1610. Bayer's ciprofloxacin product was first registered in Australia on December 18, 1987. Revised Joint Stipulation No. 66

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1611. Bayer's ciprofloxacin product was first registered in New Zealand on February 4, 1988. Revised Joint Stipulation No. 67

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1612. Bayer's ciprofloxacin product was first registered in Thailand on May 23, 1988; Bayer's enrofloxacin product for poultry was first registered in Thailand on November 30, 1988. Revised Joint Stipulation No. 68

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1613. Bayer's ciprofloxacin product was first registered in Taiwan on July 3, 1990; Bayer's enrofloxacin product for poultry was first registered in Taiwan on November 1, 1990. Revised Joint Stipulation No. 69

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1614. Bayer's ciprofloxacin product was first registered in Japan on March 29, 1988; Bayer's enrofloxacin product for poultry was first registered in Japan on November 15, 1991. Revised Joint Stipulation No. 70

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1615. Bayer's ciprofloxacin product was first registered in Vietnam on July 16, 1994. Revised Joint Stipulation No. 71

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1616. Bayer's ciprofloxacin product was first registered in Israel on September 1, 1988; Bayer's enrofloxacin product for poultry was first registered in Israel in July 1991. Revised Joint Stipulation No. 72

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1617. Bayer's ciprofloxacin product was first registered in Turkey on March 16, 1989; Bayer's enrofloxacin product for poultry was first registered in Turkey on March 20, 1989. Revised Joint Stipulation No. 73

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1618. Bayer's ciprofloxacin product was first registered in the Russian Federation on September 26, 1996; Bayer's enrofloxacin product for poultry was first registered in the Russian Federation on October 25, 1989. Revised Joint Stipulation No. 74

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1619. Bayer's ciprofloxacin product was first registered in Norway on October 9, 1990. Revised Joint Stipulation No. 75

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1620. Bayer's ciprofloxacin product was first registered in Canada on January 9, 1989; Bayer's enrofloxacin product for poultry was first registered as a turkey egg dip in Canada on December 5, 1988. Revised Joint Stipulation No. 76

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1621. Bayer's ciprofloxacin product was first registered in Mexico on November 3, 1987; Bayer's enrofloxacin product for poultry was first registered in Mexico on September 18, 1992. Revised Joint Stipulation No. 77

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1622. Bayer's ciprofloxacin product was first registered in Switzerland on May 21, 1987; Bayer's enrofloxacin product for poultry was first registered in Switzerland on October 10, 1991. Revised Joint Stipulation No. 78

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Exhibits

1623. Fluoroquinolone resistance rates in Denmark are low because relatively little Baytril is being used in Denmark. B-454

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF presumes that fluoroquinolone resistance rates are linked to Baytril usage. Evidence in the record demonstrates that resistant *Campylobacter* can be present in poultry or on chicken products as a consequence of factors other than the treatment of domestic flocks. B-1908 P.15 L.12-13, P.16 L.24 - P.17 L.6 (citing B-609); B-1851. Fluoroquinolone use in chickens and turkeys is not the only cause of the development of fluoroquinolone-resistant *Campylobacter* species in chickens and turkeys. CVM Response to Bayer's Interrogatory 4. 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. Moreover, Bayer/AHI dispute its applicability to the hearing issues since it does not relate to U.S. data or risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30.

1624. Fluoroquinolone-resistant *Campylobacter* rates in retail samples may be lower than those assessed in flocks, owing to a low persistence. B-454

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1625. More than 50% of sporadic cases of *Campylobacter* enteritis are linked to eating or handling poultry. B-288, p. 1

Bayer/AHI Response: Bayer/AHI dispute this PFOF. B-288, P.1 only indicates that 50% of sporadic cases of *Campylobacter* enteritis is an estimate.

1626. In Denmark, the public health burden associated with the 4161 registered cases of campylobacteriosis in 1999 comprised more than 41,000 days of illness, 820 hospitalizations (and approximately 3800 bed days), and 1800 general practitioner consultations. B-561, p. 7

Bayer/AHI Response: Bayer/AHI dispute this PFOF based on its applicability to the hearing issues since it does not relate to U.S. data or risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30.

1627. In Neimann's case control study of campylobacteriosis in Denmark in 1999, among cases treated with antimicrobials (mainly fluoroquinolones) a 5 days longer duration of illness seemed to be associated with a ciprofloxacin-resistant infection, compared to a ciprofloxacin susceptible infection. B-561, p. 191, and p. 200

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Neimann reports that a 5 days longer duration of illness merely "seemed" to be associated with a ciprofloxacin resistant infection. Moreover, Bayer/AHI dispute its applicability to the hearing issues since it does not relate to U.S. data or risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Furthermore, it is unclear if Neimann controlled for foreign travel or prior fluoroquinolone use.

1628. In Neimann's case control study, consumption of undercooked poultry was identified as a risk factor for acquiring campylobacteriosis. B-561, p. 50

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI dispute its applicability to the hearing issues since it does not relate to U.S. risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Recent U.S. epidemiological data refute the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644 , G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

1629. Goodman and Gillman's The Pharmacological Basis of Therapeutics, 9th Edition, recommends ciprofloxacin or ofloxacin as a treatment for *Campylobacter* enteritis. B-656, p. 2-3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1630. Fluoroquinolones are the therapy of choice for human enteric infections caused by foodborne *Campylobacter jejuni*. B-147, p. 1

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1631. Human to human transmission of *Campylobacter jejuni* is almost nonexistent. B-147, p. 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is refuted by B-1901 P.57, 80; B-1445; B-214. Human-to-human transfer of *C. jejuni* and *C. coli*, either by direct or indirect pathways, has been well-documented. For example, G-1697 describes an outbreak of *C. jejuni* infections associated with food handler contamination, G-1692 describes the intrafamilial spread of *Campylobacter* in five separate households, G-580 describes a "persistent" outbreak of *Campylobacter* infection in a day care nursery in Israel, and B-213 reviews nine different studies that point to person-to-person contact as being the main transmission route. The rate of human-to-human transmission in the United States is unknown, but such transmission is not necessarily

as uncommon as has been supposed. G-1452 P.9 L.28-29. In addition, sewage treatment plants which process domestic, commercial, and industrial wastewaters that received human waste discharge into waters used for recreation and drinking water sources, and therefore likely constitute a major source of bacteria, including fluoroquinolone-susceptible and fluoroquinolone-resistant *Campylobacter*, to human populations in the United States. B-1910 P.13 L.12-14; B-1900 P.4, L.4-9.

1632. By far the largest contributor to individual or sporadic cases of campylobacteriosis is the consumption of improperly cooked or improperly handled poultry which may be associated with more than 60% of the cases. B-147, p. 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF since U.S. epidemiological data refute the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644 , G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

1633. In a quantitative risk assessment, a lack of data and adequate scientific studies at critical points in the processing steps that precede the final retail product would introduce a large degree of uncertainty into a comprehensive model entailing all steps of production. B-147, p. 2

Bayer/AHI Response: Bayer/AHI disagree with this PFOF as being inaccurate in general. For example, suppose that the comprehensive model consists of a product of factors, some of which are very uncertain due to "a lack of data and adequate scientific studies at critical points in the processing steps that precede the final retail product" while one or more factors are zero. Then these large uncertainties would introduce no uncertainty at all into the result of the "comprehensive model entailing all steps of production": the product of all factors would be exactly zero. More generally, sensitivity analysis often reveals that the uncertainty in the outputs of a comprehensive model is far less than the uncertainties in its inputs (Cox and Popken, 2001).

As a practical application in the current case, if enrofloxacin use in chickens does not cause ciprofloxacin-resistant campylobacteriosis in people, we believe that the risk of excess human illness-days of illness or complications due to failure of ciprofloxacin treatment caused by

enrofloxacin use in chickens should be acknowledged to be exactly zero, no matter what other uncertainties are present. If treatment of ciprofloxacin-resistant campylobacteriosis cases with realistic doses of ciprofloxacin is just as clinically effective as treatment of ciprofloxacin-susceptible campylobacteriosis cases, we believe that the risk of excess human illness-days due to enrofloxacin use in chickens should be acknowledged to be zero, no matter what other uncertainties are present. In these cases, "a lack of data and adequate scientific studies at critical points in the processing steps that precede the final retail product" would not "introduce a large degree of uncertainty into a comprehensive model entailing all steps of production": the answer is still zero.

1634. Years of research have demonstrated that the selective pressure of fluoroquinolones, even delivered in a controlled therapeutic capacity, leads to the emergence of resistant organisms. B-147, p. 11

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI do not dispute that selective pressure occurs but do dispute the extent to which it is occurring through the controlled therapeutic use in poultry.

1635. Of 442 human strains of *Campylobacter jejuni* investigated by Clow, 77% of these strains came from genotypes common to human and chicken strains of *Campylobacter jejuni*. B-250, p. 3

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF but do dispute that it shows a causal connection between poultry and campylobacteriosis. Evidence in the record shows that genetic typing analysis showing overlapping *Campylobacter* genotypes between *Campylobacter* isolated from poultry and *Campylobacter* isolated from humans do not necessarily mean that one is the source of the other. There may be a common third source of *Campylobacter* for both the humans and poultry flocks. G-1908 P.26 L.20. Common source routes of infection cannot be ruled out for populations that have overlapping *Campylobacter* genotypes. B-1908 P.38 L.17-20; G-1473 P.14 L.20-25. For example, 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. B-1901 P.20 (citing G-1670). 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. B-1901 P.28. 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). B-1901 P.28 (citing G-1458, P.7 ¶ 11).

1636. In Australia, where there is a relatively low use of fluoroquinolones in humans and animals ciprofloxacin-resistant *Campylobacter* are uncommon. B-255, p. 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. First, whether fluoroquinolone resistance among poultry or human *Campylobacter* isolates is "low" or "high" is subjective.

Bayer/AHI also dispute its applicability to the hearing issues since it does not relate to U.S. data or risk factors. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30.

1637. In an experiment of 50 4-day old *Campylobacter* free broilers were divided into 4 groups: one group was challenged with *Campylobacter jejuni* and not treated with enrofloxacin; one group was challenged with *Campylobacter jejuni* and treated with 25 ppm enrofloxacin via drinking water for 5 consecutive days; one group was challenged with *Campylobacter jejuni* and treated with 50 ppm enrofloxacin via drinking water for 5 consecutive days; and, one group was not challenged with *Campylobacter* or treated with enrofloxacin. Nearly all the isolates from the 2 enrofloxacin treated groups showed MICs of > 32 μg/ml. *Campylobacter* isolates from the group challenged with *Campylobacter* but not treated with enrofloxacin were sensitive to ciprofloxacin during the entire experiment. A-190, p. 1

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the results of the experiment were derived (in part) from administration of the E-test. It has been concluded that the use of E-test as a method for monitoring susceptibility of poultry isolates should be reconsidered as it has been shown not to be as good as the microdilution broth test when compared to the standard agar dilution method. Silley (B-1913) P.11 L.10-12. The E-test is somewhat difficult to read with many *Campylobacter* isolates. The E-test tends to overestimate MICs in the resistant range and underestimate MICs in the susceptible range. All human and poultry *Campylobacter* NARMS. isolates are MIC tested using the E-test. Silley (B-1913) P.11 L.13-16.

1638. Fluoroquinolone treatment does not eradicate *Campylobacter* in broilers. A-190, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF. Bayer acknowledges that fluoroquinolone treatment may not entirely eliminate *Campylobacter* from the intestinal tract of chickens, and may select for fluoroquinolone-resistant isolates.

1639. Fluoroquinolone-resistant *Campylobacter jejuni* develops very quickly in fluoroquinolone treated broilers. A-190, p. 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. The meaning of the term "very quickly" is not defined and thus Bayer is unable to adequately interpret this sentence. Moreover, this finding of fact is repetitive of other findings of fact where Bayer has already agreed that use of fluoroquinolones may act as a selective pressure leading to the presence of fluoroquinolone-resistant *Campylobacter* in broilers. Various studies have found this effect at varying times, depending on when the susceptibility testing has been performed. A-190; G-868.

1640. In Zhang's experiment, fluoroquinolone-resistant *Campylobacter* isolates from broilers showed the PFGE pattern identical to the inoculated fluoroquinolone sensitive strains which indicates that fluoroquinolone isolates did not come from environmental contamination but evolved from the original fluoroquinolone sensitive *Campylobacter jejuni* inoculated. A-190, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1641. In 1996, 7,598,000,000 broilers were raised in the United States. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1642. In 1997, 7,764,000,000 broilers were raised in the United States. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1643. In 1998, 7,934,000,000 broilers were raised in the United States. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1644. In 1999, 8,146,000,000 broilers were raised in the United States. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1645. In 2000, 8,263,000,000 broilers were raised in the United States. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1646. In 2001, the projected 2002 number of broilers were raised in the United States was 8,650,000,000. A-158, p. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1647. Per capita poultry consumption in the United States (in pounds) was 69.8 in 1995; 70.8 in 1996; 71.8 in 1997; 72.4 in 1999; 77.6 in 1999; and, 81.7 in 2000. A-101, p. 1

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1648. Gaudreau studied the antimicrobial susceptibility in *Campylobacter jejuni* strains isolated in Quebec, Canada in 1995-1997 compared to *Campylobacter jejuni* strains isolated in 1992-1993 and 1985-1986 and found that 13.9% were resistant to nalidixic acid in 1995-1997 while 4.7% were resistant to nalidixic acid in 1992-1993 and 0% were resistant to nalidixic acid in 1985-1986, and 12.7% were resistant to ciprofloxacin in 1995-1997 while 3.5% were resistant to ciprofloxacin in 1992-1993 and 0% were resistant to ciprofloxacin in 1985-1986. G-239

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1649. In a case-control study conducted in Norway in 1989-1990, poultry consumption of poultry produced in Denmark or Sweden was strongly associated with *Campylobacter* illness whereas poultry consumption of poultry produced in Norway was not. G-334

Bayer/AHI Response: Bayer/AHI dispute this PFOF. This PFOF is not applicable to the issues in this hearing. Recent, robust U.S. epidemiological data refute the contention that

chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644 , G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

1650. There is a relatively low prevalence of *Campylobacter* in Norwegian broiler chicken flocks. G-334

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the meaning of "relatively low prevalence" is subjective and no frame of reference is given.

1651. During the period of time that Belgian poultry was withdrawn from market in June 1999 due to the dioxin crisis, no other events that could explain the decline in *Campylobacter* numbers were known to have occurred. G-672, p. 3

Bayer/AHI Response: Bayer/AHI dispute the PFOF. The causal attribution (Belgian poultry was withdrawn from market and caused a decline in *Campylobacter* numbers) is speculation, not fact. The decline in infection during 1999 was similar to that in other years and has no apparent connection with chicken consumption. This PFOF is refuted by B-1901 P.36, P.94; B-1908 P.23 L.18-21.

1652. In June 1999, the decline in the number of *Campylobacter* infections in Belgium by 40% was due to the withdrawal of Belgian poultry from the market. G-672, p. 4

Bayer/AHI Response: Bayer/AHI dispute the PFOF. The causal attribution (Belgian poultry was withdrawn from market and caused a decline in *Campylobacter* numbers) is speculation, not fact. The decline in infection during 1999 was similar to that in other years and has no apparent connection with chicken consumption. This PFOF is refuted by B-1901 P.36, P.94; B-1908 P.23 L.18-21.

1653. In a double blind placebo-controlled study of the use of norfloxacin or a placebo to treat traveler's diarrhea, norfloxacin was found to reduce the duration of diarrhea. The difference in duration of diarrhea among those treated with norfloxacin and those treated with placebo was 1.8 days vs. 5.0 days ($P < .01$). G-399

Bayer/AHI Response: Bayer/AHI agree with this PFOF.

1654. In a study of retail meat in the United States, 44% yielded *Campylobacter* and 24% of the *Campylobacter* isolated were resistant to fluoroquinolones. In all, 11% of the chickens tested yielded fluoroquinolone-resistant *Campylobacter.* G-541

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1655. An industry summary of fluoroquinolone use indicates that from August 1995 to March 1998, approximately 1.1 percent of broilers were treated with fluoroquinolones. A-192

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1656. An industry summary of fluoroquinolone use indicates that from August 1995 to March 1998, approximately 3.7 percent of breeders were treated with fluoroquinolones. A-192

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1657. The Sanford Guide to Antimicrobial Therapy, 2000, lists ciprofloxacin, norfloxacin and azithromycin as suggested primary regimens for *Campylobacter jejuni* infection. G-244

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1658. The Sanford Guide to Antimicrobial Therapy, 2000, lists ciprofloxacin and norfloxacin as suggested primary regimens for the empiric treatment of severe diarrhea associated with gastroenteritis. G-244

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1659. In the Netherlands, among human *Campylobacter* isolates, no ciprofloxacin resistance was found during 1982 to 1983 or 1985. The percentage of resistant isolates increased to 8% during 1987 to 1988 and to 11% during 1989. Ciprofloxacin resistance among *Campylobacter* isolates from poultry products closely paralleled that found among human isolates. No resistance was found in poultry isolates from 1982 to 1983; the percentage of resistant isolates increased to 8.4% during 1987 to 1988 and to 14% during 1989. G-586, p. 2

Bayer/AHI Response: Bayer/AHI dispute this PFOF. Bayer/AHI object to this PFOF as compound. Data from other countries is not applicable to the issues in this hearing because the ecology of *Campylobacter* differs throughout regions of the world. G-1470 P.5 L.29-30. Evidence in the record also shows that in many instances, the trend of increasing fluoroquinolone resistant *Campylobacter* rates in humans occurred *before* the introduction of fluoroquinolones for food animal use and continued without change after fluoroquinolones were introduced. Also, there is evidence that the increase in fluoroquinolone resistant *Campylobacter* rates has been comparable in countries with and without fluoroquinolone use in broilers. This PFOF is refuted by B-1901

P.27 citing B-119 and B-29; B-1901 P.42; B-1900 P.3 L.27-29, P.8 L.34-36, P.8 L.44 – P.9 L.1, P.8 L.30-34, P.8 L.37-38, P.8 L.38-40; B-1908 P.14 L.17-20, P.39 L.6-8.

1660. Eberhart-Phillips' case-control study of risk factors for campylobacteriosis in New Zealand found the strongest associations for food exposures were with recent consumption of chicken, particularly raw or undercooked chicken, or chicken prepared at a sit-down restaurant. Barbecued chicken and fried chicken were positively associated with disease, while consumption of baked or roasted chicken seemed to be protective, as was chicken purchased frozen. G-182, p. 3

Bayer/AHI Response: Bayer/AHI dispute this PFOF since U.S. epidemiological data refute the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644 , G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

1661. Eberhart-Phillips' case-control study of risk factors for campylobacteriosis in New Zealand confirmed a leading role for poultry in human *Campylobacter* infections. The combined population attributable risk percentage for the chicken related variables in the multivariate model exceed 50% suggesting that consumption of chicken lies behind more cases of campylobacteriosis in New Zealand than all other risk factors combined. G-182, p. 4

Bayer/AHI Response: Bayer/AHI also dispute this PFOF since U.S. epidemiological data refute the contention that chicken or turkey is a major source of campylobacteriosis. Chicken is not a major source B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Turkey is not a major source either A-201 P.13 L.6-7; A-204 P.15 L.11-15; G-1452 P.10 L.36-44; G-1452 Attachment 3. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644). Finally, evidence in the record shows that restaurant dining, rather than chicken consumption per se, appears to be the major human health threat for getting campylobacteriosis. B-1901 P.29 (citing U.S. studies G-1644 , G-185 and G-1711 and international studies G-10, G-182), G-1460 P.8; B-1908 P.25 L.15-18.

1662. Ciprofloxacin, a fluoroquinolone, is active against all the recognized bacterial causes of gastroenteritis. G-172, p. 1

Bayer/AHI Response: Bayer/AHI do not dispute that Ciprofloxacin is a broad spectrum antibiotic with good efficacy against many recognized bacterial causes of gastroenteritis. Whether it is "active" depends on the bacteria, the MIC and the concentration of the drug.

1663. In a randomized control trial, Dryden 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. G-172, p. 4

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1664. In Rodrigues' case-control study, consumption of chicken in a restaurant was identified as a risk factor for intestinal infection with *Campylobacter jejuni*. Rodrigues' study was conducted in England and enrolled 229 cases and 229 controls matched on age, sex, and general practitioner practice. G-1711

Bayer/AHI Response: Bayer/AHI do not dispute this PFOF.

1665. Deming's case-control study identified eating fully cooked chicken and eating chicken reported to be raw or undercooked as risk factors for *Campylobacter* enteritis. Deming's study was conducted at the University of Georgia during the fall and winter quarters of the 1983-1984 academic year. Deming enrolled 45 case-control pairs matched on age, sex, and residence. G-162

Bayer/AHI Response: Bayer/AHI dispute this PFOF because of the limitations in the Deming study. G-162 (Deming 1987) is outdated and epidemiologically flawed. The Deming study did not isolate 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. B-1901 P.38-39, P.57-64. Moreover, Bayer/AHI disagree with the applicability of the Deming study to the issues in this hearing. The population in the Deming study is not representative of the current U.S. population in terms of age, income, travel habits, dietary habits, and other relevant risk factors. B-1901 P.38, P.57-64. The attributable fractions calculated in Deming cannot correctly be applied to U.S. population case rates. B-1901 P.38, P.57-64. Recent U.S. epidemiological data refute the contention that chicken is a major source of campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent

epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644).

1666. Consumption of chicken was associated with more than a doubling of the risk of *Campylobacter jejuni/coli* enteritis in Harris' case-control study; the consumption of raw or rare chicken was even more strongly associated with *Campylobacter* infection. Harris' study was conducted between April 1982 and September 1983 in Washington State and enrolled 218 cases and 526 controls. G-268

Bayer/AHI Response: Bayer/AHI dispute this PFOF because of the limitations in the Harris study. G-268 (Harris 1986) is outdated and epidemiologically flawed. The Harris study did not isolate 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. B-1901 P.38-39, P.57-64. Moreover, Bayer/AHI disagree with the applicability of the Harris study to the issues in this hearing. The population in the Harris study is not representative of the current U.S. population in terms of age, income, travel habits, dietary habits, and other relevant risk factors. B-1901 P.38, P.57-64. The attributable fractions calculated in Harris cannot correctly be applied to U.S. population case rates. B-1901 P.38, P.57-64. Recent U.S. epidemiological data refute the contention that chicken is a major source of campylobacteriosis. B-1901 P.14, P.20, P.21 P.27-28, P.36, P.37, P.38, P.49, P.57-64, P.79; B-1904 P.7 L.21 - P.8 L.4; B-1908 P.36 L.18-24, P.40 L.20-22; B-1902 P.35 L.1 – P.36 L.11; B-1910 P.5 L.15-19; B-1913 Attachment 1 P.40 ¶ 2; G-1483 P.15 L.28-30. Moreover, recent epidemiological data demonstrate that retail chicken handled or prepared at home is associated with a statistically significant *reduction* in risk of campylobacteriosis, refuting that the handling and consumption of poultry meat at home is a dominant source of campylobacteriosis. B-1901 P.15 (citing G-1644, G-185 and B-1252, *see also* G-1488 and G-1489), P.19, P.24, P.29 (citing G-1644), P.29-30 (citing G-185 and G-1711); B-1900 P.9, L.39-41; *See also* G-1457 P.4 L.23-24. Even 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. B-1901 P.29 (citing G-1644).

1667. In 2001, there were 8.6 billion broilers raised in the United States. Bayer Narrative Statement, p. 3

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1668. Large chilling tanks are used to cool the birds after evisceration, creating the potential to further cross-contaminate carcasses with various bacteria. Bayer's Narrative Statement, p. 4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1669. *Campylobacter* are commensal organisms in poultry. Bayer's Narrative Statement, p. 4

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1670. To the extent that poultry is a source of campylobacteriosis in humans, there is no reason to believe that poultry could not also be a source of fluoroquinolone-resistant infections in humans. Bayer's Narrative Statement, p. 5

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context and omits the very significant qualifying phrase at the end of the sentence that demonstrates the very limited nature of fluoroquinolone-resistant *Campylobacter* that may be transmitted to humans from broilers. As a result, the true and intended meaning of the statement has been altered. The actual testimony states: "To the extent poultry is believed to be a significant source of *Campylobacter* infections in humans, there is no reason to believe that poultry could not also be a source of fluoroquinolone-resistant infections in humans, although the amount of poultry's contribution to fluoroquinolone-resistant *Campylobacter* infections in humans is significantly less than that estimated by CVM." Bayer's Narrative Statement P.5.

1671. The use of enrofloxacin in chickens and turkeys exert selection pressure that leads to fluoroquinolone-resistant *Campylobacter*. Bayer's Narrative Statement, p. 11

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1672. Chickens that harbor *Campylobacter* quickly develop fluoroquinolone-resistant *Campylobacter* once a fluoroquinolone is administered in laboratory conditions. Bayer's Narrative Statement, p. 12

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context. As a result, the true and intended meaning of the statement has been altered. The actual testimony states: "2. The fact that chickens that harbor *Campylobacter* quickly develop fluoroquinolone-resistant *Campylobacter* once a fluoroquinolone is administered in laboratory conditions was well known by FDA at the time of approval.
> Prior to the approval of enrofloxacin there was evidence from laboratory studies that chickens that harbor *Campylobacter* quickly develop fluoroquinolone-resistant *Campylobacter* once a fluoroquinolone is administered. More recent laboratory studies merely reach the same result and are not new evidence.
> Nevertheless, these laboratory results do not take into account possible recolonization of susceptible *Campylobacter* in the field, nor the pathogen load at slaughter..." Bayer's Narrative Statement P.12.

1673. Bayer does not dispute the fact that fluoroquinolone-resistant *Campylobacter* spp. from chickens and turkeys can be transferred to humans. Bayer Narrative Statement, p. 16

Bayer/AHI Response: Bayer/AHI dispute this PFOF because the sentence is improperly taken out of context. As a result, the true and intended meaning of the statement has been altered. The actual testimony states: "Bayer does not dispute that fluoroquinolone-resistant *Campylobacter* spp. from chickens and turkeys can be transferred to humans. Bayer does dispute the extent and significance of any such transfer and whether fluoroquinolone-resistant *Campylobacter* from chickens and turkeys are a significant cause of fluoroquinolone-resistant *Campylobacter* infections in humans." Bayer's Narrative Statement P.16.

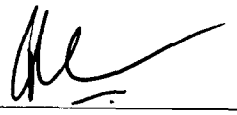
1674. Approximately 1.6% of all broilers raised in the United States in 1999 were treated with Baytril. Bayer's response to CVM's Interrogatory No. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

1675. Approximately 4% of all turkeys raised annually in the United States are treated with Baytril. Bayer's response to CVM's Interrogatory No. 2

Bayer/AHI Response: Bayer/AHI agree to this PFOF.

Respectfully submitted,



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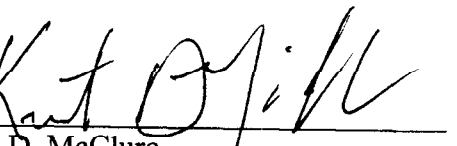

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CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of Bayer's and Animal Health Institute's Joint Response To The Center For Veterinary Medicine's 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 the foregoing Joint Response was 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 the foregoing Joint Response was e-mailed and mailed via first-class mail, postage pre-paid, 14th day of April 2003 to:

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