

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

2220 JUN 27 P1:37

In the Matter of:

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

FDA DOCKET: 00N-1571

**RESPONDENT BAYER CORPORATION'S
FIRST SET OF INTERROGATORIES TO CVM**

Pursuant to Administrative Law Judge Davidson's April 10, 2002 Order and the parties' June 6, 2002 agreement, Respondent Bayer propounds these Interrogatories, to which CVM shall respond separately and fully, in writing and under oath, on or before July 24, 2002, in accordance with the Instructions and Definitions set forth hereinafter.

INSTRUCTIONS

1. These instructions and definitions should be construed to require answers based upon the knowledge of, and information available to the responding party as well as its agents, representatives, and, unless privileged, attorneys. It is intended that the following discovery requests will not solicit any material protected either by the attorney/client privilege or work product doctrine.
2. These Interrogatories are continuing in character, so as to require that supplemental answers be filed seasonably if further or different information is obtained with respect to any interrogatory.
3. No part of an interrogatory should be left unanswered merely because an objection is interposed to another part of the interrogatory. If a partial or incomplete answer is provided, the responding party shall state that the answer is partial or incomplete.
4. Where a claim of privilege is asserted in objecting to any interrogatory or part thereof, and information is not provided on the basis of such assertion:

- A. In asserting the privilege, the responding party shall, in the objection to the interrogatory, or part thereof, identify with specificity the nature of the privilege (including work product) that is being claimed;
- B. The following information should be provided in the objection, if known or reasonably available, unless divulging such information would cause disclosure of the allegedly privileged information,
 - (1) For oral communications:
 - a. the name of the person making the communication and the names of persons present while the communication was made, and, where not apparent, the relationship of the persons present to the person making the communication;
 - b. the date and place of the communication; and
 - c. the general subject matter of the communication.
 - (2) For documents:
 - a. the type of document,
 - b. the general subject matter of the document,
 - c. the date of the document, and
 - d. such other information as is sufficient to identify the document, including, where appropriate, the author, addressee, custodian, and any other recipient of the document, and where not apparent, the relationship of the author, addressee, custodian, and any other recipient to each other.
- 5. If the responding party elects to specify and produce documents in answer to any interrogatory, the specification shall be in sufficient detail to permit the interrogating party to locate and identify, as readily as the responding party can, the documents from which the answer may be ascertained.
- 6. If, in answering these interrogatories, the responding party encounters any ambiguities when construing a question, instruction, or definition, the responding party's answer shall set forth the matter deemed ambiguous and the construction used in answering.

DEFINITIONS

Notwithstanding any definition below, each word, term, or phrase used in these Interrogatories is intended to have the broadest meaning permitted under the applicable rules and case law.

1. *CVM* shall mean the **FDA Center for Veterinary Medicine** and any person working on its behalf in this matter.
2. **Identify** (with respect to facts or data) means to state the fact or data and reference the document in which it is contained.
3. The present tense includes the past and future tenses. The singular includes the plural, and the plural includes the singular. "All" means "any and all"; "any" means "any and all." "Including" means "including but not limited to." "And" and "or" encompass both "and" and "or." Words in the masculine, feminine or neuter form shall include each of the other genders.

INTERROGATORIES

1. Identify all facts and data on which CVM relies for its position that fluoroquinolone use in chickens (and separately for turkeys) acts as a selection pressure resulting in the emergence and dissemination of **fluoroquinolone-resistant *Campylobacter* spp.** in chickens (and separately for turkeys)

ANSWER:

2. Identify specifically when CVM first understood that **fluoroquinolone use in chickens (and separately for turkeys) could act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys).**

ANSWER:

3. If CVM's answer to Interrogatory No. 2 is earlier than October 4, 1996, please identify in what way, if any, CVM's **current understanding** that fluoroquinolone use in chickens (and separately for turkeys) **can act as a selection pressure resulting in**

the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys) differs from CVM's understanding of the issue prior to October 4, 1996.

ANSWER:

4. Does CVM contend that fluoroquinolone use in chickens (and separately for turkeys) is the only cause of the development of fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys)?

ANSWER:

5. If CVM's answer to Interrogatory No. 4, above, is anything other than an unqualified "yes," please identify in order of relative significance all other causes of the development of fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys) known to CVM.

ANSWER:

6. Identify all facts and data on which CVM relies for its position that fluoroquinolone-resistant *Campylobacter* spp. in chickens (and separately for turkeys) are transferred to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections

ANSWER:

7. Identify when CVM first understood the potential for fluoroquinolone-resistant *Campylobacter* to be transferred from chickens (and separately for turkeys) to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans.

ANSWER:

8. If CVM's answer to Interrogatory No. 7 is earlier than October 4, 1996, identify in what way, if any, CVM's current understanding of the potential for fluoroquinolone-resistant *Campylobacter* to be transferred from chickens (and separately for turkeys) to humans and contribute to fluoroquinolone-resistant *Campylobacter* infections in humans differs from CVM's understanding of the potential prior to October 4, 1996.

ANSWER:

9. Does CVM contend that transfer of fluoroquinolone-resistant *Campylobacter* from chickens (and separately for turkeys) to humans is the only cause of fluoroquinolone-resistant *Campylobacter* infections in humans?

ANSWER:

10. If CVM's answer to Interrogatory No. 9, above, is anything other than an unqualified "yes," please identify in order of relative contribution all other causes of the development of fluoroquinolone-resistant *Campylobacter* spp. in humans known to CVM.

ANSWER:

11. Does CVM contend that transfer of fluoroquinolone-resistant *Campylobacter* from chickens (and separately for turkeys) to humans is a statistically detectable cause of fluoroquinolone-resistant *Campylobacter* infections in humans?

ANSWER:

12. If CVM's answer to Interrogatory No. 11 is anything other than an unqualified "no," identify all statistical tests and data analyses that indicate a causal relation

between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans.

ANSWER:

13. ~~Has~~ CVM performed any formal statistical tests of the causal hypothesis that fluoroquinolone use in chickens causes increases in **fluoroquinolone-resistant *Campylobacter*** infections in humans? If yes, please specify the causal tests, the significance levels used, and the results.

ANSWER:

14. Has CVM performed any formal statistical tests of the causal hypothesis that fluoroquinolone use in chickens *reduces* fluoroquinolone-resistant ***Campylobacter*** infections in humans? If yes, please specify the causal tests, the significance levels used, and the results.

ANSWER:

15. Has CVM performed any Granger-Sims test for causality in any sets of time series that involve fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans? If yes, please specify the significance levels used and the results.

ANSWER:

16. Has **CVM** performed any conditional independence tests for possible causality in any sets of data that involve fluoroquinolone use in chickens and fluoroquinolone-resistant ***Campylobacter*** infections in humans? If yes, please specify the significance levels **used** and the results.

ANSWER:

17. Has CVM developed any causal graph models or path analysis models from data that involve fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans? If yes, please specify the results, especially any finding from the data of a possible causal **relation** between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans.

ANSWER:

18. Has CVM performed any formal statistical tests for omitted explanatory variables and/or confounders in analyzing possible statistical associations between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans? If yes, please specify the tests used and the results obtained.

ANSWER:

19. Has CVM used any generally accepted statistical methods to correct for the effects of possible confounders in analyzing possible statistical associations between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans? If yes, please specify the confounders considered, the methods used and the **difference** they made in CVM's risk assessment.

ANSWER:

20. In analyzing possible statistical associations between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans, did CVM use any generally accepted statistical methods to (a) test for and (b) correct for biases due to **the effects of model** specification errors and model selection? If yes, please specify the methods used and the difference they made in CVM's **risk** assessment.

ANSWER:

21. In analyzing possible statistical associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM use any generally accepted statistical methods to (a) test for and (b) correct for biases due to measurement errors in independent variables? If yes, please specify the methods used and the difference they made in CVM's risk assessment.

ANSWER:

22. What does CVM mean by "significant" in its Narrative Statement (p. 3-4) position that "fluoroquinolone-resistant *Campylobacter* spp. are transferred to humans and are a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans."

ANSWER:

23. Does CVM have any facts or data demonstrating any increase or decrease in overall *Campylobacter* loads in chickens (and separately for turkeys) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

24. Does CVM have any facts or data demonstrating any increase or decrease in overall *Campylobacter* loads in chickens (and separately for turkeys) at the point of sale since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

25. Does CVM have any facts or data demonstrating any increase or decrease in **fluoroquinolone-resistant *Campylobacter*** loads in chickens (and separately for turkeys) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

26. Does CVM have any facts or data demonstrating any increase or decrease in fluoroquinolone-resistant ***Campylobacter*** loads in chickens (and separately for turkeys) at the point of sale since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

27. Does **CVM** have any facts or data demonstrating any increase or decrease in **fluoroquinolone-resistant *Campylobacter*** loads in chickens (and separately for turkeys) at the point of consumption since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

28. Does CVM have any facts or data demonstrating **any increase or decrease** in incidence of campylobacteriosis in humans caused by *C. jejuni* (and separately for *C. coli*) since fluoroquinolone approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

29. Does **CVM** have any facts or data demonstrating **any increase or decrease** in **incidence of fluoroquinolone-resistant campylobacteriosis** in humans caused by *C.*

jejuni (and separately for *C. coli*) since **fluoroquinolone** approval for use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

30. Does CVM have any facts or data demonstrating any increase or decrease in incidence rates of **fluoroquinolone-resistant** campylobacteriosis in humans caused by fluoroquinolone use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

31. Does CVM have any facts or data that allow quantitation of the change in incidence rates of **fluoroquinolone-resistant** campylobacteriosis in humans caused by fluoroquinolone use in chickens and turkeys? If CVM does have such facts or data, please identify.

ANSWER:

32. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from the K. E. Smith studies "**Fluoroquinolone-Resistant *Campylobacter* Isolated From Humans and Poultry in Minnesota**" (G-588) and/or "**Quinolone-Resistant *Campylobacter Jejuni* Infections in Minnesota, 1992-1998**" (G-589) other than as published by the author in those studies; and, if so, what was the conclusion?

ANSWER:

33. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from H. Kassenborg's studies "Eating Chicken or Turkey Outside the Home Associated With Domestically Acquired **Fluoroquinolone-Resistant *Campylobacter* Infections: A FoodNet Case-Control Study**" (G-336) and/or "Domestically

Acquired **Fluoroquinolone-Resistant** *Campylobacter* Infections Associated With Eating Poultry Outside the Home” (G-337) other than **as** published by the author in those studies; and, if so, what was the conclusion?

ANSWER:

34. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from C. Friedman’s studies **“Risk** Factors For Sporadic *Campylobacter* Infections in the United States: A Case-Control Study on FoodNet Sites” (G-228) and/or **“Fluoroquinolone-resistant** *Campylobacter* Infections in the United States: A Pilot Case-Control Study in FoodNet Sites” (G-229) other than as published by the author in those studies; and, if so, what was the conclusion?

ANSWER:

35. Has CVM conducted, or is CVM aware of any, additional analysis of the raw data from N. Marano’s study **“Fluoroquinolone-Resistant** *Campylobacter* Causes Longer Duration of Diarrhea Than **Fluoroquinolone-Susceptible** *Campylobacter* Strains in FoodNet Sites” (G-394) other than **as** published by the author in that study; and, if so, what was the conclusion?

ANSWER:

36. ~~Has~~ CVM conducted, or is CVM aware of any, additional analysis of the raw data from J. McClellan presentation **“Prevalence and Consequences of Fluoroquinolone-Resistant** *Campylobacter* Infections: NARMS 1997 - 2000” other than as presented by the author in the presentation; and, if so, what was the conclusion?

ANSWER:

37. Identify when CVM first understood the existence of a temporal relationship between the use of fluoroquinolones in poultry (including separately chickens and turkeys) and an increase in resistance in *Campylobacter* (including separately *C. jejuni* and *C. coli*) isolates from humans.

ANSWER:

38. If CVM's answer to Interrogatory No. 37 is earlier than October 4, 1996, identify in what way, if any, CVM's current understanding of the temporal relationship between the use of fluoroquinolones in poultry and an increase in resistance in *Campylobacter* isolates from humans differs from CVM's understanding of the issue prior to October 4, 1996.

ANSWER:

39. In interpreting historical trends and data on associations between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans, did CVM control for internal and external threats to validity of causal inference (specifically including history) (Campbell and Stanley, 1963)? If yes, please specify the control procedures used and/or corrections made in the analysis, and their impacts on CVM's risk assessment.

ANSWER:

40. Has CVM applied any generally accepted methods of causal inference for interrupted time series and/or quasi-experimental designs to demonstrate a probable causal relation between fluoroquinolone use in chickens and fluoroquinolone-resistant *Campylobacter* infections in humans? If yes, please specify the data used, analyses performed, and results of these analyses.

ANSWER:

41. In interpreting historical trends and data on associations between fluoroquinolone use in chickens and **fluoroquinolone-resistant *Campylobacter*** infections in humans, did CVM control for the possibility of spurious regression? If yes, please specify the control procedures used and/or corrections **made in the analysis, and** their impacts on CVM's risk assessment.

ANSWER:

42. Does CVM acknowledge a **lack of** association between poultry use of fluoroquinolones and levels of resistance in ***Campylobacter*** isolates from humans in certain countries such as Canada, Sweden, Switzerland, Denmark and Turkey? If not, does CVM have an explanation of the poultry and human resistance data from these countries?

ANSWER:

43. Does CVM acknowledge the **existence of measurable levels of** fluoroquinolone resistant ***Campylobacter*** in humans prior to 1995 as demonstrated in Kiehlbauch (B-39); Smith (B-59) and Williams (B-67)? If not, does CVM have an explanation of the pre-1995 data in those references?

ANSWER:

44. Does **CVM** acknowledge the existence of fluoroquinolone resistance in bacteria other than ***Campylobacter*** in humans after the **introduction** of fluoroquinolones in human medicine but prior to 1995, e.g., as documented in Hooper D.C., Wolfson J.S., "Bacterial Resistance to the Quinolone Antimicrobial Agents"; *Am J Med.*

1989 Dec 29;87(6C):17S-23S? Does CVM have an explanation of the pre-1995 data in those references?

ANSWER:

45. Does CVM acknowledge 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” (Acar J.F., Goldstein F.W., “Trends In Bacterial Resistance to Fluoroquinolones”; *Clin Infect Dis* 1997 Jan;24 Suppl 1:S67-73)? Does CVM have an explanation of the international data on fluoroquinolone **resistance** emerging in bacteria in humans after clinical use started but before use in animals began?

ANSWER:

46. Does CVM acknowledge that the **CVM risk assessment** “Human Health Impact of Fluoroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken” (October 18, 2000) (G-111) does not follow National Academy of Sciences guidelines for risk assessments? If so, please explain if the Risk Assessment follows any other **risk assessment guidelines** or principles and identify them. If not, please explain why.

ANSWER:

47. Does CVM acknowledge that the **CVM risk assessment** “Human Health Impact of Fluoroquinolone-Resistant *Campylobacter* Attributed to the Consumption of Chicken” (October 18, 2000) does **not** follow National Academy of Sciences guidelines for hazard identification, specifically by failing to identify or specify

adverse human health effects that have been shown to be causally associated with exposures to *Campylobacter*?

ANSWER:

48. Does CVM acknowledge that the CVM risk assessment “Human Health Impact of **Fluoroquinolone-Resistant** *Campylobacter* Attributed to the Consumption of Chicken” (October 18, 2000) does not follow National Academy of Sciences guidelines for exposure assessment, specifically by failing to quantify or characterize probable levels (or frequency distributions) of individual exposures to *Campylobacter*?

ANSWER:

49. Does CVM acknowledge that the **CVM** risk assessment “Human Health Impact of **Fluoroquinolone-Resistant** *Campylobacter* Attributed to the Consumption of Chicken” (October 18, 2000) does not follow National Academy of Sciences guidelines for risk assessment, specifically by failing to quantify or characterize an exposure-responder relation for *Campylobacter* and campylobacteriosis?

ANSWER:

50. Does CVM acknowledge that the CVM risk assessment “Human Health Impact of **Fluoroquinolone-Resistant** *Campylobacter* Attributed to the Consumption of Chicken” (October 18, 2000) does not follow National Academy of Sciences guidelines for uncertainty characterization in its risk assessment?

ANSWER:

51. Identify all facts and data on which CVM relies for its position that **fluoroquinolone-resistant *Campylobacter*** infections (caused by *C. jejuni*, and separately, *C. coli*) have the potential to adversely affect human health.

ANSWER:

52. Identify when CVM first understood that fluoroquinolone-resistant ***Campylobacter*** infections (caused by *C. jejuni*, and separately, *C. coli*) have the potential to adversely effect human health.

ANSWER:

53. If CVM's answer to Interrogatory No. 52 is earlier than October 4, 1996, identify in what way, if any, CVM's current understanding that fluoroquinolone-resistant ***Campylobacter*** infections (caused by *C. jejuni*, and separately, *C. coli*) have the potential to adversely effect human health differs from its understanding of the potential prior to October 4, 1996.

ANSWER:

54. Does CVM contend that infections caused by **fluoroquinolone-resistant *Campylobacter*** (caused by *C. jejuni*, and separately, *C. coli*) have a greater adverse affect on human health than infections caused by fluoroquinolone-susceptible ***Campylobacter***?

ANSWER:

55. If CVM's answer to Interrogatory No. 54 is anything other than an unqualified "no," please identify all facts and data upon which CVM relies to supports its contention.

ANSWER:

56. Does CVM have any facts or data demonstrating any increase in severity of infections caused by **fluoroquinolone-resistant** *Campylobacter* (*C. jejuni*, and separately, *C. coli*) as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter* (*C. jejuni*, and separately, *C. coli*)? If CVM does have such facts or data, please identify the increase in severity, identify all facts and data on which **CVM** relies, and identify when CVM first learned of such facts or data.

ANSWER:

57. Does CVM have any facts or data demonstrating any increase in duration of illness from infections caused by fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) as compared to infections caused by fluoroquinolone-susceptible (non-resistant) *Campylobacter* (*C. jejuni*, and separately, *C. coli*)? If **CVM** does have such facts or data, please identify the increase in duration of illness, identify all facts and data on which **CVM** relies and identify when CVM first learned of such facts or data.

ANSWER:

58. Does **CVM** have any facts or data demonstrating any other adverse human health consequences from infections caused by fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) as compared to infections caused by **fluoroquinolone-susceptible** (non-resistant) *Campylobacter* (*C. jejuni*, and separately, *C. coli*)? If **CVM** does have such facts or data, please identify the other adverse consequences, identify the facts and data on which CVM relies and identify when CVM first learned of such facts or data.

ANSWER:

59. Identify all complications CVM is aware of that are associated with infections caused by **fluoroquinolone-resistant** *Campylobacter* that are not associated with infections caused by **fluoroquinolone-susceptible** (non-resistant) *Campylobacter*? If CVM is aware of any such complications, please identify all facts or data in support and identify when CVM first learned of such facts or data.

ANSWER:

60. Does CVM have any facts or data demonstrating any increase in the rate or extent of complications (including but not limited to Guillian-Barre syndrome) from infections caused by **fluoroquinolone-resistant** *Campylobacter* as compared to infections caused by **fluoroquinolone-susceptible** (non-resistant) *Campylobacter*? If CVM has such facts or data, please identify the increase in the rate or extent of complications, identify the facts and data on which CVM relies and identify when CVM first learned of such facts or data.

ANSWER:

61. CVM's Notice of Opportunity for Hearing states "The current level of resistance among human *Campylobacter* isolates attributed to the use of fluoroquinolones in poultry represents a harm to human health." 65 FR 64955. Does CVM accept some level of resistance among human *Campylobacter* isolates attributed to the use of fluoroquinolones in poultry greater than zero that would **not** constitute a harm to human health. If so, what is that level?

ANSWER:

62. CVM's Narrative Statement (p. 5) states "The magnitude of the benefit of antibiotic treatment is directly related to the early initiation of therapy." Identify specifically, by number of days after symptoms commence, what CVM means by "early initiation of therapy". Identify at what point **CVM** believes therapy is no longer effective.

ANSWER:

63. How does **CVM** define *in vitro* *Campylobacter* resistance (i.e. at what minimum inhibitory concentration) for *C.jejuni* (and separately for *C. coli*)? To the extent that CVM defines resistance as an MIC of > 4 µg/ml, identify all facts or data **CVM** relies on to support that infection with *Campylobacter* having an *in vitro* MIC of > 4 µg/ml would result in an adverse impact on treatment if the patient was prescribed a fluoroquinolone.

ANSWER:

64. Is CVM aware of any analysis of NARMS *Campylobacter* resistance data examining year-to-year patterns of change of susceptibility of isolates over the entire range of MICs tested?

ANSWER:

65. Does **CVM** have knowledge of the portion of fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that were acquired outside the United States? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

ANSWER:

66. Does CVM have knowledge of the portion of fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that were acquired inside the United States? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

ANSWER:

67. Does CVM have knowledge of the portion of fluoroquinolone-resistant *Campylobacter* infections in humans reported by NARMS that were acquired inside the United States, where the patient had a history of prior fluoroquinolone use within the previous 30 days? If so, identify the portion for the years 1997, 1998, 1999, and 2000.

ANSWER:

68. Other than as specifically referenced in the Notice of Opportunity for Hearing, Notice of Hearing and Risk Assessment, identify any additional basis for CVM's assertion that severe enteric diseases are treated empirically.

ANSWER:

69. Identify any populations in the United States of which CVM is aware for which severe enteric disease are and are *not* treated empirically.

ANSWER:

70. In light of antibiotic resistance issues, the risk of the hemolytic-uremic syndrome (HUS) after antibiotic treatment of severe enteric infections caused by *Escherichia coli* 0157:H7, and other issues, does CVM believe there is a trend toward less empiric treatment of severe enteric disease?

ANSWER:

71. Identify all facts and data, of which CVM is aware, if any, to demonstrate that *Campylobacter coli* is a human pathogen or human health hazard.

ANSWER:

72. Identify all facts and data on which CVM relies to demonstrate that there is a reasonable basis from which serious questions may be inferred about the safety of enrofloxacin for the control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms. If none, please state CVM's basis for the belief.

ANSWER:

73. Identify all data in CVM's possession showing levels of fluoroquinolone-resistant *Campylobacter spp.* in turkeys.

ANSWER:

74. Identify all epidemiological studies that CVM contends demonstrate a strong association between eating chickens (and separately for turkeys) and acquiring human *Campylobacter* infections as well as all epidemiological studies demonstrating a strong association between eating chickens (and separately for turkeys) and acquiring fluoroquinolone-resistant *Campylobacter* infections.

ANSWER:

75. Does CVM acknowledge that multiple epidemiological studies demonstrate a significant negative association between handling, cooking, and eating chickens at home and acquiring human *Campylobacter* infections?

ANSWER:

76. Identify all studies CVM believes link the genetic make-up of *Campylobacter* isolates from chickens (and separately for turkeys) and humans.

ANSWER:

77. Explain why CVM believes that it is biologically implausible that the level of fluoroquinolone-resistant human *Campylobacter* infections in the United States is due to fluoroquinolone use in humans or the spread of resistant *Campylobacter* infections from one human to another.

ANSWER:

78. Does CVM acknowledge that human *Campylobacter* infections in the United States have sometimes been caused by the spread of *Campylobacter* infections from one human to another?

ANSWER:

79. Does CVM believe that fluoroquinolone-resistant *Campylobacter* infections in humans existed in the United States prior to 1995?

ANSWER

80. If CVM's response to Interrogatory No. 79 is "no," identify all facts and data supporting CVM's belief.

ANSWER:

81. Does CVM believe that fluoroquinolone-resistant *Campylobacter* (*C. jejuni*, and separately, *C. coli*) bacteria existed in chickens (and separately for turkeys) in the United States prior to 1995?

ANSWER

82. If CVM's response to Interrogatory No. 81 is "no," identify all facts and data supporting CVM's belief.

ANSWER:

83. Identify all human health risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

ANSWER:

84. Identify all animal health risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

ANSWER:

85. Identify all environmental risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

ANSWER:

86. Identify all economic risks and benefits of enrofloxacin use in chickens (and separately for turkeys) that FDA/CVM considered in making the decision to withdraw the NADA for enrofloxacin. If none, please explain why none were considered.

ANSWER:

87. If the NADA for enrofloxacin is withdrawn, what drugs, if any, does CVM believe are available for the control of mortality in chickens associated with *E. coli*

organisms, and available for the control of mortality in **turkeys** associated with *E. coli* and *Pasteurella multocida* organisms?

ANSWER:

88. With regard to each **drug identified in response to Interrogatory No. 87**, identify specifically, all studies which assess: the **human health impact** of each drug when used in chickens or turkeys, the **animal health impact** of each drug when used in chickens or turkeys, the **impact of the drug on chicken and turkey pathogen loads**, and the **potential for residues on chicken and turkey carcasses**.

ANSWER:

89. Identify all pending studies including protocols and requests for proposals, that are being conducting by **CVM** or otherwise known by **CVM** that address the **emergence and dissemination of fluoroquinolone-resistant *Campylobacter* spp. in chickens and/or turkeys**.

ANSWER:

90. Identify all pending studies including protocols and requests for proposals, that are being conducting by **CVM** or otherwise known by **CVM** that address the **transfer of fluoroquinolone-resistant *Campylobacter* from chickens and/or turkeys to humans**.

ANSWER:

91. Identify all pending studies including protocols and requests for proposals, that are being conducting by **CVM** or otherwise known by **CVM** that address whether **fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely effect human health**.

ANSWER:

Respectfully submitted,

Robert B. Nicholas / RBN

Robert B. Nicholas

James H. Sneed

Gregory A. Krauss

M. Miller Baker

McDERMOTT, WILL & EMERY

600 Thirteenth Street, N.W.

Washington, D.C. 20005

(202) 756-8000

Attorneys for Bayer

CERTIFICATE OF SERVICE

I hereby certify that a copy of Respondent Bayer Corporation's First Set of Interrogatories to CVM was sent via e-mail and mailed this 24th day of June 2002, via first-class mail, postage pre-paid to:

Nadine R. Steinberg, Esquire
Food and Drug Administration
Office of General Counsel (CGF-1)
5600 Fischers Lane, Room 7-77
Rockville, MD 20857

Kent D. McClure
Animal Health Institute
1325 G Street, N.W., Suite 700
Washington, D.C. 20005

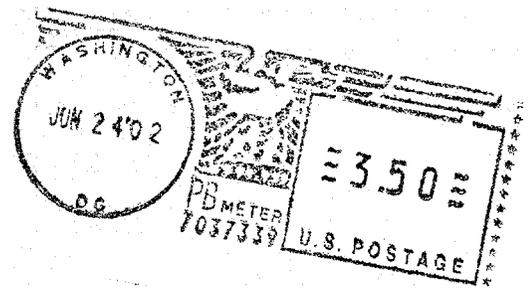
and was sent via facsimile and mailed this 24th day of June 2002, via first-class mail, postage pre-paid to:

Honorable Daniel J. Davidson
Administrative Law Judge
Food and Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, Maryland 20857

and was mailed this 24th day of June 2002, via first-class mail, postage pre-paid to:

Dockets Management Branch (HFA - 305) - FDA
5630 Fishers Lane
Room 1061
Rockville, Maryland 20857


Robert B. Nicholas



600 13th Street N.W.
Washington, D.C. 20005-3096

McDERMOTT, WILL & EMERY

**Dockets Management Branch (HFA - 305) - FDA
5630 Fishers Lane
Room 1061
Rockville, Maryland 20857**