



present or former directors, officers, employees, agents, and representatives, and any other person acting or purporting to act on behalf of Bayer.

- B. "Agent" or "agents" means any person employed by Bayer or working under Bayer's supervision, direction, or control, or acting on Bayer's behalf, including but not limited to employees, contract manufacturers and their employees, distributors, laboratories, consultants, independent contractors, trade associations, veterinarians, physicians, and attorneys.
- C. "And" and "or" shall be interpreted liberally, as conjunctive, disjunctive, or both, depending on the context, so that the fullest disclosure of information is achieved.
- D. "Breakpoint" means specific values, expressed relative to terms such as Minimum Inhibitory Concentrations (MICs) or zones of inhibitions (which can be correlated with MICs using appropriate statistical methods), which characterize bacteria as clinically susceptible, intermediate, or resistant.
- E. "Document" or "Documentation" means handwritten, typed, printed, or visually, electronically, or orally reproduced material of any kind in which information, facts, thoughts, or expressions of any kind are in any way preserved or recorded, whether or not privileged, in the possession, custody, or control of Bayer or Bayer's agent. "Document" includes every copy of every document where the copy is not identical in every respect to the original (e.g., because of any addition to, deletion from, alteration of, or notation on the copy).
- F. "Evidence" includes document as defined above.
- G. "~~Fluoroquinolone-resistant~~ Campylobacter" means *Campylobacter* isolates exhibiting ciprofloxacin MICs of 4  $\mu\text{g}/\text{mL}$  (micrograms per milliliter) or greater
- H. "Fluoroquinolone-susceptible Campylobacter" means *Campylobacter* isolates exhibiting ciprofloxacin MICs of less than 4  $\mu\text{g}/\text{mL}$  (micrograms per milliliter).
- I. "High level MIC" means *Campylobacter* isolates exhibiting ciprofloxacin MICs 16  $\mu\text{g}/\text{mL}$  (micrograms per milliliter) or greater.
- J. "Identify" means the following: With respect to a document, state the full name and address of the custodian of the document, the location of the document, and a general description of the document, including: (a) the type of document (e.g., letter, memorandum, notes, report); (b) the date of the document; (c) name and title of each author of the document; (d) the name and title of each person to whom the document is addressed; and (e) the general subject matter of the document. When identifying a document that is a published document, state the citation to the journal or series, volume number, issue number, page numbers, and date of publication.

- K. "Including" means "including without limitation."
- L. "Poultry" means both chickens and turkeys. When an interrogatory asks about "poultry," Bayer should provide responses to the interrogatory for chickens and turkeys separately, if such information is available.
- M. "Relating to" and "regarding" mean consisting, containing, embodying, reflecting, identifying, stating, dealing with, or in any way pertaining to, either directly or indirectly.
- N. Use of the singular includes the plural, as appropriate, and vice versa. Use of any tense of any verb includes within its meaning all other tenses of the verb.
- O. If Bayer asserts a claim of privilege (including work product) in responding or objecting to any interrogatory herein and does not provide information on the basis of such assertion, state in response or objection the nature of the privilege (including work product) that is being claimed. For any privilege claimed, indicate, as to the information requested, whether any such information exist.
- P. If Bayer believes there to be any ambiguity in construing an interrogatory, definition, or instruction, answer the interrogatory as completely as possible and state the matter deemed ambiguous and the construction selected in responding to the interrogatories.
- Q. If Bayer does not have information with the requested precision or specificity, so state and answer with the best available information.
- R. If Bayer objects to any interrogatory or any part of an interrogatory, state the reasons for the objection and respond to all parts of the interrogatory to which Bayer does not object.

### **INTERROGATORIES**

1. State the quantity (and state the units) of enrofloxacin sold (and if known, the quantity used) worldwide in poultry per month beginning the year before enrofloxacin was approved in each country to the present. Provide this information:
  - by country
  - by state, in the United States
  - by operation type (i.e., hatchery, breeder, grow-out)
  - by operation size
  - by species (chicken and turkey)
2. How many birds (chickens and turkeys) in the United States were given drinking water containing enrofloxacin in each year from 1995 – present? Provide your answer in actual

numbers of poultry, not a percentage of poultry produced in that year, breaking down the number of chickens and turkeys treated by state, if possible.

3. On average, how often is enrofloxacin used in each poultry house per year? Provide any data on treatment history by house.
4. For each country in which enrofloxacin is used in poultry (whether under a regulatory "approval" or not), how is enrofloxacin actually used (i.e., therapeutically, prophylactically, for growth promotion, etc.)?
5. State the quantity (and state the units) of ciprofloxacin used in humans for gastroenteritis and/or diarrhea in each year from 1985 – present in the United States. Also, provide prescription and marketing data for this time period.
6. On average, how often is the litter in poultry houses in the United States "scraped-out" and replaced with fresh litter?
9. What other quinolones/fluoroquinolones have been used in poultry in the United States from 1985 to the present, and what were they approved (if approved) for and actually used for?
10. Is it feasible to use enrofloxacin as an individual bird treatment in commercially grown poultry in the United States? If so, how? If not, why not?
11. How much money (gross and net) has Bayer made from the sale of enrofloxacin for use in poultry each year from the year before approval in each country through the present, by country?
12. How much money (gross and net) has Bayer made from the sale of ciprofloxacin for the treatment of gastroenteritis and/or diarrhea in humans each year from the year before approval in each country through the present, by country?
13. When, in what form, and for what indications, was enrofloxacin approved (or other equivalent regulatory mechanism) for use in poultry in each country where it is or was ever approved?
14. Was an approval to use enrofloxacin in poultry withdrawn (voluntarily or otherwise) in any country? If so, state the country(ies), dates of withdrawal, and reasons.
15. Has any country denied an application for approval (or that country's equivalent regulatory mechanism) to use enrofloxacin in poultry? If so, state the country(ies), dates of denial, and reasons?
16. When was ciprofloxacin approved (or other equivalent regulatory mechanism) for use in each country, and for what indications?

17. What is the "Harvard Risk Assessment" on *Campylobacter*? Who is conducting the Harvard Risk Assessment? Who financially supported the Harvard Risk Assessment?
18. How much money does Bayer provide to AHI annually? What are these figures each year from 1995 through the present? What percentage of AHI's budget does this represent for each year from 1995 through the present?
19. When Bayer alleges that fluoroquinolone-resistant campylobacteriosis in humans in the United States results from foreign travel, what is the actual source of the fluoroquinolone-resistant *Campylobacter*? What proportion of it may originate from poultry exposed to fluoroquinolones?
20. When was enrofloxacin first used for poultry in the United States? When was enrofloxacin first marketed in the United States for poultry?
21. When do Bayer's patent(s) for ciprofloxacin expire (in the United States)?
22. When do Bayer's patent(s) for enrofloxacin expire (in the United States)?
23. What constitutes a "flock" of poultry? What is the average chicken/turkey flock size in the United States? What is the average size of an enrofloxacin treated poultry flock in the United States?
24. On average, how many poultry flocks are raised per house per year in the United States?
25. What basis does Bayer have for alleging that sick poultry have more fragile intestines than healthy poultry?
26. Besides CVM's risk assessment, what other risk assessments have been done to study the impact of **fluoroquinolone-resistant** *Campylobacter* on human health?
27. What CDC data sets were made available to Dr. Cox in connection with his risk assessment on the impact of fluoroquinolone resistant *Campylobacter* on human health?
28. What is the basis for Dr. Cox's assumption that only 10% of human cases of campylobacteriosis are attributed to the consumption of chicken?
29. What is the basis for Dr. Cox's selection of the dose response model used in his *Campylobacter* risk assessment?
30. Does Bayer believe that a Beta Poisson model provides the best fit to the Black et al. data (Black, R.E, Levine, M.M., Clements, M.L., et al. Experimental *Campylobacter jejuni* Infection in Humans. J of Inf Dis. March, 1988. 157(3); 472-9.)? If so, why?
30. Does Bayer believe that an ingested dose by humans of *Campylobacter jejuni* less than 500 CFU has a zero possibility of producing illness in humans? Why or why not?

31. Identify the contributing genetic mechanisms underlying fluoroquinolone resistance in *Campylobacter*?
32. Is there evidence of horizontal gene transfer for fluoroquinolone resistance in *Campylobacter*?
33. Is *Campylobacter jejuni* a human pathogen?
34. Can antimicrobial-resistant *Campylobacter* be transmitted to humans via foods of animal origin including, specifically, poultry?
35. Is *Campylobacter* commonly (i.e., greater than 50%) found in live poultry in the United States?
36. Are chicken carcasses frequently (i.e., at least 40%) contaminated with *Campylobacter* in the United States?
37. Are retail poultry meats often (i.e., at least 20%) contaminated with fluoroquinolone-resistant *Campylobacter* in the United States?
38. Does the use of Baytril in *Campylobacter*-colonized poultry result in high-level ciprofloxacin MICs in *Campylobacter*?
39. Are poultry a source of sporadic *Campylobacter* infections for humans?
40. Is *Campylobacter* among the most frequently reported causes of bacterial enteritis in humans in the U.S.?
41. What are the established interpretive criteria for the use of ciprofloxacin in treating human *Campylobacter* infections?
42. Do most intestinal *Campylobacter* infections in humans caused by strains with ciprofloxacin MICs  $\geq 32\mu\text{g/mL}$  (micrograms per milliliter) respond to fluoroquinolone therapy?
43. What percentage of chickens suffering from *E. coli* (colibacillosis) consume adequate quantities of water to receive the proper dose of enrofloxacin? What percentage of turkeys suffering from *E. coli* (colibacillosis) or *P. multocida* (fowl cholera) consume adequate quantities of water to receive the proper dose of enrofloxacin?
44. What dosage of enrofloxacin is usually administered to sick poultry flocks?
45. In the United States, when an antibiotic is prescribed, is ciprofloxacin a drug of choice in treating gastroenteritis and/or diarrhea of unknown etiology in humans?

46. Are macrolides and fluoroquinolones the drugs of choice for treating human *Campylobacter* infections in the United States?
47. Why do an increasing number of studies indicate an increase in the occurrence of fluoroquinolone-resistant *Campylobacter* from food animals, in particular poultry, following the introduction of fluoroquinolones for the treatment of infections in animals?
48. Is there a link between the veterinary use of fluoroquinolones in poultry and the occurrence of fluoroquinolone-resistant *Campylobacter* among poultry and humans?
49. What was the level of fluoroquinolone-resistant *Campylobacter* in poultry in the United States in each year prior to introduction of enrofloxacin for use in poultry in the United States beginning in 1988? What is the basis for your answer?
50. What was the level (number and percent of infections) of fluoroquinolone-resistant *Campylobacter* infections in humans in the United States each year since 1980? What was the level (number and percent of infections) of fluoroquinolone-resistant *Campylobacter* infections in humans who had not taken a fluoroquinolone within 30 days of the onset of the fluoroquinolone-resistant *Campylobacter* infection?
51. Do agents other than fluoroquinolones select for high-level ciprofloxacin MICs in *Campylobacter* in humans and poultry? If so, what are these agents and what are the underlying mechanism(s) by which these other agents select for such resistance?
52. What is the relationship between the cessation of fluoroquinolone use in poultry and the subsequent decrease in prevalence of fluoroquinolone-resistant *Campylobacter* in live poultry? in retail poultry meat? in humans?
53. Are antimicrobials effective in limiting the duration of bacterial-associated gastroenteritis in humans when given early in the course of infection?
54. Are antimicrobials effective in limiting the duration of campylobacteriosis in humans when given early in the course of infection?
55. Are *Campylobacter* intrinsically less susceptible to fluoroquinolones than are other enteric pathogens (i.e., *Salmonella* or *E. coli*)? If so, why?
56. Do *Campylobacter* mutate more frequently to high-level fluoroquinolone MICs than do other enteric pathogens (i.e., *Salmonella* or *E. coli*)? Why or why not?
57. Do certain clones of *Campylobacter* persist in the environment (inside the poultry house or otherwise) during successive broiler flock rotations? If so, why?
58. Can litter function as a source of *Campylobacter* for successive poultry flocks within a given house? If yes, how long is the *Campylobacter* viable in the litter? Is this different for

fluoroquinolone-resistant *Campylobacter*s compared to fluoroquinolone-susceptible *Campylobacter*?

59. What other antimicrobials (other than fluoroquinolones) are or were legally available to treat *E. coli* (colibacillosis) in chickens and turkeys and *P. multocida* (fowl cholera) in turkeys in each country where enrofloxacin is or has been used in poultry?
60. How often (percentage of flocks treated) are culture and susceptibility tests performed on isolates from infected poultry flocks prior to initiating antimicrobial therapy? specifically prior to enrofloxacin treatment?
61. How often (percentage of patients prescribed antimicrobials) are culture and susceptibility tests performed on bacterial isolates from humans associated with gastroenteritis/diarrhea prior to initiating antimicrobial therapy? specifically prior to ciprofloxacin treatment?
62. How does the veterinarian arrive at a decision to use enrofloxacin in poultry? Is enrofloxacin only used when infections do not respond to other therapies?
63. What is the preferred genotypic method for typing of *Campylobacter*? Why?
64. Are pulsed-field gel electrophoresis (PFGE), amplified fragment length polymorphisms (AFLP), flagella gene restriction fragment length polymorphisms (fla-RFLP), multi-locus sequence typing (MLST), random amplification of polymorphic DNA (RAPD), and ribotyping, suitable methods for evaluating genetic relatedness of *Campylobacter* for epidemiological purposes? For each, why or why not?
65. How many distinct mutations are necessary for induction of fluoroquinolone-resistant strains of *Campylobacter*?
66. How many distinct mutations are necessary for induction of fluoroquinolone-resistant strains of most other enteric pathogens (i.e., *Salmonella* or *E. coli*)?
67. In actual practice, what percentage of enrofloxacin administration is accompanied by chlorination of drinking water for the poultry involved?
68. What side effects to the poultry are associated with the use of enrofloxacin in poultry? What percentage of birds experience each such side effect?
69. Is there any difference in the manner of colonization or spread of infection between live poultry colonized with fluoroquinolone-susceptible *Campylobacter* and fluoroquinolone-resistant *Campylobacter*? If so, please describe.
70. Explain the meaning of seasonality of *Campylobacter* infection of live poultry and of campylobacteriosis in humans.

71. How does genomic instability in *Campylobacter* effect the reliability and interpretation of genetic typing materials?
72. Do mixed cultures of *Campylobacter* play a part in antimicrobial susceptibility testing? If so, describe how.
73. In *Campylobacter*-colonized poultry, will enrofloxacin (used according to labeling) eliminate the majority of susceptible *Campylobacter* isolates?
74. Is it Bayer's position that the only valid risk assessment paradigm for modeling the impact of fluoroquinolone-resistant *Campylobacter* on human health is a farm-to-fork model? If so, why? If not, what other models could be appropriate?
75. After ending treatment with enrofloxacin in poultry, how long are fluoroquinolone-resistant *Campylobacter* shed in the feces of the treated birds?

Submitted this 24th day of June, 2002, by:



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Enrofloxacin Hearing  
Docket No: OON-1571

**CERTIFICATE OF SERVICE**

I hereby certify that an original and one copy of the foregoing Center for Veterinary Medicine's Interrogatories to Bayer Corporation was hand delivered this 24th day of June, 2002, 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 Interrogatories has been hand delivered and e-mailed, this 24th day of June, 2002, to:

The Office of the Administrative Law Judge (ddavidso@oc.fda.gov)  
Food and Drug Administration  
Room 9-57. HF-3  
5600 Fishers Lane  
Rockville, MD 20857

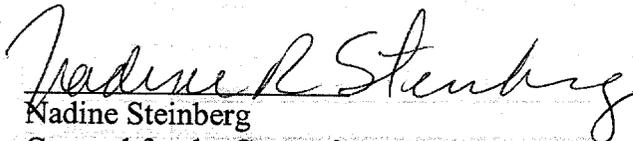
I also certify that a copy of the Interrogatories was e-mailed and sent by U.S. mail, postage prepaid, this 24th day of June, 2002, to:

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