

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

5832 02 SEP 20 9

In the Matter of:

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

FDA DOCKET: 00N-1571

JOINT STIPULATIONS

The parties and participants hereby stipulate to the following facts for use in the Administrative Hearing in this matter:

1. 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*.
2. In late 1993 or early 1994, before fluoroquinolones were approved for use in chickens and turkeys, CVM management understood and accepted that fluoroquinolone use in chickens and in turkeys could act as a selection pressure resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* in chickens and in turkeys.
3. In late 1993 or early 1994, before fluoroquinolones were approved for use in chickens and turkeys, CVM management understood and accepted that if fluoroquinolones were used in chickens and turkeys, the potential existed for fluoroquinolone-resistant *Campylobacter* to be transferred from chickens and turkeys to humans and contribute to the development of fluoroquinolone-resistant *Campylobacter* infections in humans.
4. In late 1993 or early 1994, before fluoroquinolones were approved for use in chickens and turkeys in the United States, CVM management understood and accepted that articles by Endtz and others posited a temporal association between the use of fluoroquinolones in chickens in Europe and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans in Europe.

5. In late 1993 or early 1994, before fluoroquinolones were approved for use in chickens and turkeys, CVM management understood and accepted that fluoroquinolone-resistant *Campylobacter* infections have the potential to adversely affect human health.
6. Fluoroquinolone use in humans can act as a selection pressure for fluoroquinolone-resistant bacteria in the human digestive tract.
7. Fluoroquinolone use in chickens and turkeys can act as a selection pressure for fluoroquinolone-resistant bacteria in the chicken and turkey digestive tract.
8. Human use of fluoroquinolones, including use for treatment of campylobacteriosis, can lead to the emergence of fluoroquinolone-resistant *Campylobacter* in the treated individual.
9. United States residents can acquire fluoroquinolone-resistant *Campylobacter* infections while traveling outside the United States.
10. The parties do not have any facts or data demonstrating horizontal gene transfer for fluoroquinolone resistance in *Campylobacter*.
11. 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.
12. NCCLS has established guidelines for susceptibility testing of certain bacteria to certain antimicrobial agents.
13. FDA is a member of the NCCLS and uses the NCCLS standards where feasible.
14. A NCCLS recognized breakpoint indicating loss of clinical effectiveness has not been established for fluoroquinolone drug use in *Campylobacter* infections in humans.
15. In the United States, enrofloxacin is approved for use only by prescription and only under veterinary supervision.
16. In the United States, enrofloxacin is approved for therapeutic use only and is not approved for growth promotion.
17. In the United States, extra-label use of enrofloxacin is prohibited by law for food producing animals.
18. 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.

19. Campylobacteriosis in humans can be a self-limiting disease, i.e., it may resolve without antibiotics or use of other drugs.
20. Many persons sick with gastroenteritis do not seek medical care.
21. In 1994, a Joint Advisory Committee comprised of FDA's Center for Veterinary Medicine's Veterinary Medicine Advisory Committee and the FDA's Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee was convened.
22. The 1994 Joint Advisory Committee was comprised of: **Veterinary Medicine Advisory Committee Members:** Dr. Debra K. Aaron, chair, Dr. Clarence B. Ammerman, Dr. Graham Purchase, Dr. Anthony J. Johnson, Dr. Gaylord D. Paulson, Dr. Bernard J. Curran, Dr. Stanley H. Kleven, Dr. Gary D. Koritz, Ms. Sue Hudson Duran; **Anti-Infective Drugs Advisory Committee Members:** Dr. Franklyn Judson, Dr. Joseph S. Bertino, Jr., Dr. Judith K. Dunn, Dr. Henry L. Francis, Dr. Barth Reller, Dr. Roselyn J. Rice, Dr. Edwin M. Thorpe; **Consultants:** Dr. Suzanne Fitzpatrick, Dr. Thomas O'Brien, Dr. Hans Reimann, and Dr. Robert Walker.
23. The following people testified before the Joint Advisory Committee: **FDA Invited Speakers:** Thomas R. Beam, Jr., M.D., Buffalo Veterans Hospital, Andrew Beaulieu, D.V.M., FDA Center for Veterinary Medicine, Gail Cassell, Ph.D., University of Alabama at Birmingham, David C. Hooper, M.D., Massachusetts General Hospital, Stuart Levy, M.D., Tufts University Medical School, James D. McKean, D.V.M., Iowa State University, Dik Mevius, Ph.D., Institute for Animal Science and Health, The Netherlands, Clyde Thornsberry, Ph.D., Daniel Upson, D.V.M., Kansas State University, Dennis Wages, D.V.M., North Carolina State University; **Sponsored Invited Speakers:** Dr. Peter Altreuther, Bayer AG, Mike Apley, D.V.M., Ph.D., Veterinary Research and Consulting Services, Jerry Boscia, M.D., SmithKline Beecham Animal Health, Dr. Peter Coloe, Royal Melbourne Institute of Technology, Mark A. Dekich, D.V.M., Perdue Farms, Diane Fagerberg, Ph.D., Colorado Agricultural Research Enterprises, Thomas Gootz, Ph.D., Pfizer Central Research, Richard Gustafson, Ph.D., Linda M. Hanna, Sciences International, Inc., Howard Hill, D.V.M., Iowa State University, Leon D. Sabath, M.D., University of Minnesota Hospital, Craig Tucker, Ph.D., Mississippi State University; **Public Speakers:** David Bossman, American Feed Industry Association, Dr. Janis Cleland, American Animal Hospital Association, Dr. Tom Holder, National Broiler Council, Joseph McCraren, National Aquaculture Association, Dr. Rod Noel, Association of American Feed Control Officials, Joseph Pocius, National Turkey Federation, Donna Reifschneider, National Pork Producers Council, Kay Richardson, Delmarva Poultry Industry, Louise Risk, Food Animal Concerns Trust, Dr. James Sears, Academy of Veterinary Consultants, Dr. Ran Smith, National Cattlemen's Association, Dr. Peter Theran, Massachusetts Society for the Prevention of

Cruelty to Animals, Richard Vulliet, Ph.D., D.V.M., University of California at Davis.

24. Freezing chicken (and turkey) products may reduce the population of *Campylobacter*.
25. Other than for inhalational anthrax exposure (approved August 30, 2000), fluoroquinolones are not approved for use in children.
26. At the time enrofloxacin was approved in 1996, CVM determined that use of enrofloxacin to treat broiler chickens and turkeys was safe under the approved labeled conditions of use.
27. The risk that a given meal will cause campylobacteriosis depends at least in part on the number of CFUs of *Campylobacter* ingested.
28. FDA is committed to following well recognized principles of epidemiology.
29. A NCCLS approved method for animal-origin *Campylobacter* susceptibility testing was not available until May 2002 when NCCLS published M31-A2, "Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals."
30. The "agar dilution" method is the only NCCLS-approved method for testing susceptibility in *Campylobacter* isolates.
31. Under the normal conditions of food storage, freezing chicken products may reduce the population of *Campylobacter*.
32. Sources of *Campylobacter* infection other than poultry, such as domestic pets, are known.
33. Many *Campylobacter* isolation and enrichment broths contain antimicrobial agents.
34. Efflux mechanisms are not necessarily specific to antibiotic class.
35. The 1994 Joint Advisory Committee meeting was held to discuss the use of fluoroquinolones in food animal medicine. The Joint Advisory Committee discussed the relative benefits and risks to animals and humans of the use of fluoroquinolones in food animals in light of possible concerns about microbial resistance to fluoroquinolones.
36. 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.

37. In the United States, a broiler grow-out house typically contains on the order of 20,000 to 25,000 broilers.
38. In the United States, a turkey grow-out house typically contains on the order of 10,000 to 20,000 turkeys.
39. 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.
40. The horizontal transfer of genes conferring fluoroquinolone resistance in *Campylobacter* has not been demonstrated.
41. *Campylobacter jejuni* and *Campylobacter coli* can be human pathogens.
42. 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.
43. In 2001, there were 8.6 billion broilers (chickens) raised for slaughter in the United States.
44. In 2000, there were 270 million turkeys raised for slaughter in the United States.
45. The use of enrofloxacin in chickens and turkeys can exert a selection pressure that can lead to fluoroquinolone resistance.
46. Extra-label use of enrofloxacin is prohibited in the United States.
47. 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.
48. 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.
49. Any stipulation relating to the registration date of Bayer's ciprofloxacin products or Bayer's enrofloxacin products contains no representation regarding the approval date or date of first use of non-Bayer ciprofloxacin products, enrofloxacin products or fluoroquinolones.

50. Any stipulation relating to the registration date of Bayer's ciprofloxacin products or Bayer's enrofloxacin products contains no representation regarding the dates of sale or use, if any, of Bayer's ciprofloxacin products or Bayer's enrofloxacin products in any country, or whether such registrations are currently in effect.
51. Bayer's ciprofloxacin product was first registered in Austria on June 26, 1987; Bayer's enrofloxacin product was first registered in Austria on May 3, 1988.
52. Bayer's ciprofloxacin product was first registered in Belgium on January 20, 1989; Bayer's enrofloxacin product was first registered in Belgium on January 19, 1988.
53. Bayer's ciprofloxacin product was first registered in Denmark on March 3, 1989; Bayer's enrofloxacin product was first registered in Denmark on December 27, 1991.
54. Bayer's ciprofloxacin product was first registered in Finland on January 10, 1990.
55. Bayer's ciprofloxacin product was first registered in France on October 30, 1987; Bayer's enrofloxacin product was first registered in France on December 31, 1991.
56. Bayer's ciprofloxacin product was first registered in Germany on January 30, 1987; Bayer's enrofloxacin product was first registered in Germany on January 17, 1990.
57. Bayer's ciprofloxacin product was first registered in Greece on April 6, 1988; Bayer's enrofloxacin product was first registered in Greece on January 22, 1990.
58. Bayer's ciprofloxacin product was first registered in Ireland on December 20, 1988; Bayer's enrofloxacin product was first registered in Ireland on October 1, 1988.
59. Bayer's ciprofloxacin product was first registered in Italy on March 3, 1992; Bayer's enrofloxacin product was first registered in Italy on March 4, 1997.
60. Bayer's ciprofloxacin product was first registered in Luxembourg on June 16, 1987; Bayer's enrofloxacin product was first registered in Luxembourg on February 23, 1990.
61. Bayer's ciprofloxacin product was first registered in The Netherlands on August 15, 1988; Bayer's enrofloxacin product was first registered in The Netherlands on October 13, 1992.

62. Bayer's ciprofloxacin product was first registered in Portugal on March 19, 1990; Bayer's enrofloxacin product was first registered in Portugal on June 20, 1994.
63. Bayer's ciprofloxacin product was first registered in Spain on June 27, 1990; Bayer's enrofloxacin product was first registered in Spain on October 1, 1990.
64. Bayer's ciprofloxacin product was first registered in Sweden on September 16, 1988; Bayer's enrofloxacin product was first registered in Sweden on September 8, 1989.
65. Bayer's ciprofloxacin product was first registered in the United Kingdom on February 2, 1987; Bayer's enrofloxacin product was first registered in the United Kingdom on November 11, 1993.
66. Bayer's ciprofloxacin product was first registered in Australia on December 21, 1993.
67. Bayer's ciprofloxacin product was first registered in New Zealand on August 7, 1991.
68. Bayer's ciprofloxacin product was first registered in Thailand on May 23, 1988; Bayer's enrofloxacin product was first registered in Thailand on November 30, 1988.
69. Bayer's ciprofloxacin product was first registered in Taiwan on July 3, 1990; Bayer's enrofloxacin product was first registered in Taiwan on November 1, 1990.
70. Bayer's ciprofloxacin product was first registered in Japan on September 22, 2000; Bayer's enrofloxacin product was first registered in Japan on November 15, 1991.
71. Bayer's ciprofloxacin product was first registered in Vietnam on July 16, 1994.
72. Bayer's ciprofloxacin product was first registered in Israel on September 1, 1988; Bayer's enrofloxacin product was first registered in Israel on June 1, 1996.
73. Bayer's ciprofloxacin product was first registered in Turkey on March 16, 1989; Bayer's enrofloxacin product was first registered in Turkey on March 20, 1989.
74. Bayer's ciprofloxacin product was first registered in the Russian Federation on September 26, 1996; Bayer's enrofloxacin product was first registered in the Russian Federation on October 25, 1989.
75. Bayer's ciprofloxacin product was first registered in Norway on March 11, 1993.

76. Bayer's ciprofloxacin product was first registered in Canada on October 15, 1991; Bayer's enrofloxacin product was first registered as a turkey egg dip in Canada on December 5, 1988.
77. Bayer's ciprofloxacin product was first registered in Mexico on March 2, 1990; Bayer's enrofloxacin product was first registered in Mexico on September 18, 1992.
78. Bayer's ciprofloxacin product was first registered in Switzerland on May 21, 1987; Bayer's enrofloxacin product was first registered in Switzerland on October 10, 1991.

Respectfully submitted,



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CERTIFICATE OF FILING

I hereby certify that a copy of the foregoing Joint Stipulations was filed with the Dockets Management Branch, FDA Docket No.: 00N-1571 on this 20th day of September, 2002.

I also certify that a copy of the Joint Stipulations was sent via e-mail and via facsimile to:

Honorable Daniel J. Davidson
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