

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

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In the Matter of:

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

FDA DOCKET: 00N-1571

Date: April 28, 2003

**RESPONDENT BAYER'S MOTION TO SUPPLEMENT
DOCUMENT SUBMISSION UNDER 21 C.F.R. § 12.85 AND MOVE ADDITIONAL
DOCUMENTS INTO THE EVIDENTIARY RECORD**

Pursuant to 21 C.F.R. § 12.85(c) Respondent Bayer Corporation ("Bayer") moves to supplement its document submission under 21 C.F.R. § 12.85(a), and to add six documents, B-1923, B-1924, B-1925, B-1926, B-1927 and B-1928 into its evidentiary record under 21 C.F.R. § 12.94. The first document is a peer reviewed article entitled "Campylobacter and fluoroquinolones: a bias data set?" (the "Silley article") (B-1923).¹ The second document is a report from the Centers for Disease Control and Prevention (CDC), appearing in CDC's Morbidity and Mortality Weekly Report (MMWR), entitled "Preliminary FoodNet Data on the Incidence of Foodborne Illnesses – Selected Sites, United States, 2002" ("FoodNet Data 2002 report") (B-1924).² The third document is a peer reviewed article by N. J. Stern *et al.*, entitled

¹ The complete citation is Silley P. Opinion, *Campylobacter and fluoroquinolones: a bias data set?*. Environmental Microbiology 2003, 5(4): 219-230.

² The complete citation is CDC's *Preliminary FoodNet Data on the Incidence of Foodborne Illnesses – Selected Sites, United States, 2002*. Morbidity and Mortality Weekly Report (MMWR) 2003 April 19, 52(15): 340-343.

“*Campylobacter* spp. in Icelandic poultry operations and human disease” (B-1925).³ The fourth document is a published letter, entitled “Quinolone resistance in *Campylobacter*, which appeared in the peer reviewed Journal of Antimicrobial Chemotherapy (B-1926).⁴ The fifth document is a peer reviewed article by M. S. Nawaz *et al.*, entitled “Molecular Characterization of Fluoroquinolone-Resistant *Campylobacter* spp. Isolated from Poultry” (B-1927).⁵ The sixth document is a manuscript by Scott Russell, Ph.D., entitled “The Effect of Air Sacculitis on Bird Weights, Uniformity, Fecal Contamination, Processing Errors, and Populations of *Campylobacter* spp. and *Escherichia coli*”, that has now been accepted for publication by the peer reviewed Poultry Science (B-1928).⁶ The documents are submitted to the Dockets Management Branch along with this motion. Bayer also moves to enter Exhibits B-1923, B-1924, B-1925, B-1926, B-1927 and B-1928 into the evidentiary record.

21 C.F.R. § 12.85(a) requires Respondent to submit to the Dockets Management Branch documents in Respondent’s files containing factual information which relate to the issues (§ 12.85(a)(2)) as well as all other documentary data and information relied upon (§ 12.85(a)(3)). In accordance with 21 C.F.R § 12.85(c) and the July 17, 2002 Order entered in this matter, Bayer seeks to supplement its 12.85 document submission. 21 C.F.R. § 12.85(c) states:

Submissions required by ... this section may be supplemented later in the proceeding, with the approval of the presiding officer, upon a showing that the material contained in the supplement was not reasonably known or available when the submission was made or

³ The complete citation is Stern N.J. *et al.*, *Campylobacter* spp. Icelandic poultry operations in human disease. *Epidemiol. Infect.* 2003, 130: 23-32.

⁴ The complete citation is Greig J.R., *Quinolone resistance in Campylobacter*. *Journal of Antimicrobial Chemotherapy* 2003, 51(3): 740-41.

⁵ The complete citation is Nawaz M. S., *Molecular Characterization of Fluoroquinolone-Resistant Campylobacter* spp. *Isolated from Poultry*. *Poultry Science* 2003, 82: 251-258.

⁶ Russel S., *The Effect of Air Sacculitis on Bird Weights, Uniformity, Fecal Contamination, Processing Errors, and Populations of Campylobacter* spp. and *Escherichia coli*. *Poultry Science* (forthcoming).

that the relevance of the material contained in the supplement could not reasonably have been foreseen.

Furthermore, the July 17, 2002 Order in this matter states that:

21 C.F.R. § 12.85(c) indicates that the required submissions "... may be supplemented later in the proceeding, with the approval of the presiding officer, upon a showing that the material ... was not reasonably known or available ... or that the relevance of the material contained in the supplement could not reasonably [have] been foreseen." It appears that the use of the word "may" allows the submissions to be voluntary and that the parties may therefore voluntarily limit their Section 12.85 supplements to relevant material.

Order at 1. Respondent also seeks to add these documents to its evidentiary record under 21 C.F.R. § 12.94, and pursuant to the Administrative Law Judge's authority under 12.70(h).⁷

The Silley article (B-1923) was published in April, 2003, in the peer reviewed journal, Environmental Microbiology. It relates to other exhibits on the docket and placed into evidence, particularly the written direct testimony of Peter Silley, Ph.D. (B-1913). Specifically, the Silley article is a published, peer reviewed version of pages 14-18 of Peter Silley's written direct testimony, Silley (B-1913), P.14 L.5 through P.18 L.15, as well as portions of Attachment #1 to Exhibit B-1913 ("Review of Literature Data Relating to Isolation and Susceptibility Testing of *Campylobacter jejuni* and *Campylobacter coli* with Special Reference to Fluoroquinolone Susceptible and Fluoroquinolone Resistant Strains"), also by Peter Silley. It, therefore, contains important information that is relevant to this hearing, including (but not limited to) the following findings:

- (a) The diversity of *Campylobacter* spp. in samples from poultry and from man is far greater than that initially considered to be the case.
- (b) Isolation methods from poultry usually involve enrichment techniques which will favour the isolation of the faster growing strains.
- (c) Isolation procedures will tend to overestimate the numbers of *C. jejuni*, particularly from human and companion animal cases, as strains such as *C. upsaliensis* tend to be missed because of their sensitivity to the antimicrobials

⁷ 21 C.F.R. § 12.70(h) grants the ALJ authority to "[r]ule on, admit, exclude, or limit evidence."

used in culture medium. *C. upsaliensis* has been shown to be present in more than 10% of cases of human infection.

(d) Sampling bias suggests that the test populations of *Campylobacter* spp. are not representative of the sources from which they were sampled be they poultry, man or the environment.

(e) Samples whether they are from poultry or man are commonly known to support multiple species of *Campylobacter* and indeed multiple strains of the same species. It is therefore not always possible to isolate a single strain from a human faecal sample and attribute it as the disease causing strain.

(f) It is crucial that improved and standardized methodologies be utilised to clarify the role of campylobacters in human disease and that consensus is reached with regard to working definitions of resistant and susceptible. In order to achieve these objectives there must be greater collaboration between the laboratory and the clinician.⁸

Currently, this information is unavailable to the docket and evidentiary record in published form in a peer reviewed journal.

The FoodNet Data 2002 report (B-1924) was published by CDC on April 18, 2003, in Volume 52, No. 15 of the MMWR. It contains preliminary survey data for 2002 and also a comparison with the 1996-2001 data, making it the most current data and analysis of trends in foodborne infections, utilizing laboratory-based surveillance for culture illness caused by several enteric pathogens commonly transmitted through food. Importantly, “[t]he data indicate a sustained decrease in major bacterial foodborne illnesses such as *Campylobacter* and *Listeria*, indicating progress toward meeting the national health objectives of reducing the incidence of foodborne infections...”⁹

In addition, the FoodNet Data 2002 report relates to exhibits and written direct testimony on the docket and placed into evidence, such as the written direct testimony of Angulo (G-1452), Kassenborg (G-1460) and Molback (G-1468), among others. It further contains updated information since the most recent FoodNet data in the record was produced during 2001 (B-

⁸ Silley article at 227.

⁹ FoodNet Data 2002 report at 340. However, “the data do not indicate a sustained decline in other major foodborne infections such as *Escherichia coli* O157 and *Salmonella*...” *Id.*

1042).¹⁰ Accordingly, important information will be unavailable to the record if this document is not admitted onto the docket and into the evidentiary record.

The third document is a peer reviewed article by N. J. Stern *et al.*, entitled “*Campylobacter* spp. in Icelandic poultry operations and human disease” (B-1925) (the “Stern article”). The Stern article was also recently published. It relates to other exhibits on the docket and placed into evidence, including the written direct testimony of Dr. Kare Molback, M.D., D.M.Sc. (G-1468), Henrik C. Wegener, Ph.D., M.Sc. (G-1483) and Robert V. Tauxe, M.D., M.P.H. (G-1475), in that it “describes the observed relationship of campylobacter in poultry operations to human cases in a closed environment.”¹¹ In particular, the Stern article focuses on the documented decrease in *Campylobacter* infection in Iceland from 1999 to 2000, and offers theories to explain this reduction, including “that public education, enhanced on-farm biological security measures, carcass freezing and other unidentified factors, such as variations in weather, contributed to the large reduction in poultry-borne campylobacteriosis.”¹² Currently, the Stern article and its findings are unavailable to the docket and evidentiary record in this hearing in published form.

The fourth document is a published letter by J.R. Greig, entitled “Quinolone resistance in *Campylobacter*, that appeared in the peer reviewed Journal of Antimicrobial Chemotherapy (B-1926) (the “Greig letter”). The Greig letter was published in 2003. It relates to other exhibits on the docket and placed into evidence in this hearing, including the written direct testimony of Diane G. Newell, Ph.D. (B-1908). Among other things, the Greig letter presents pertinent

¹⁰ CDC’s *Preliminary FoodNet Data on the Incidence of Foodborne Illnesses – Selected Sites, United States, 2001*. Morbidity and Mortality Weekly Report (MMWR) 2002 April 19, 51(15): 325-29.

¹¹ Stern article at 23.

¹² *Id.*

information that complements that of the Campylobacter Sentinel Surveillance Scheme Collaborators (“CSSSC”), and “shows the importance of knowing the country of acquisition of *Campylobacter* infection and hence the likelihood of quinolone resistance.”¹³ In addition, “[l]ocally one should be aware of the travel habits and destinations of the local population as the likelihood of antibiotic-resistant *Campylobacter* gastroenteritis in returning travellers will be dictated by the rates of resistance in the country where they return from.”¹⁴ Currently, the Greig letter is unavailable to the docket and evidentiary record in this hearing in published form.

The fifth document is a peer reviewed article by M. S. Nawaz *et al.*, entitled “Molecular Characterization of Fluoroquinolone-Resistant *Campylobacter* spp. Isolated from Poultry” (B-1927) (the “Nawaz article”). The Nawaz article was published in 2003 in Poultry Science. Its findings, which include the study of 21 fluoroquinolone-resistant campylobacters isolated from poultry samples, relate to other exhibits on the docket and placed into evidence, including the written direct testimony of Kirk Smith, Ph.D., D.V.M. (G-1473), John Besser, B.S., M.S. (G-1455) and Diane G. Newell, Ph.D. (B-1908), in that it discusses genetic typing of poultry. In addition,

The 21 fluoroquinolone-resistant strains of bacteria could only be classified into four distinct groups by PCR-RFLP of the *flaA* gene. However, PFGE of campylobacters may be invaluable for epidemiological studies because of the high discriminatory power of the technique. *SalI* or *SmaI* PFGE indicated 10 to 12 different strain profiles within the 17 typable strains of campylobacters. However, a combination of restriction enzymes digestion resulted in distinguishing the 17 strains into 13 different unique profiles. The *SmaI* or *SalI-SmaI* combination PFGE may be better than *SalI* PFGE in epidemiological studies because of the ability to better discriminate the strains.¹⁵

¹³ Greig letter at 741.

¹⁴ *Id.*

The Nawaz article is currently unavailable to the docket and evidentiary record in this hearing in published form.

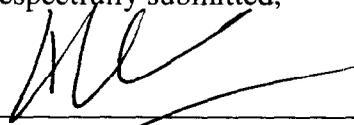
The sixth document is a manuscript by Scott Russell, Ph.D., entitled “The Effect of Air Sacculitis on Bird Weights, Uniformity, Fecal Contamination, Processing Errors, and Populations of *Campylobacter* spp. and *Escherichia coli*”, that was recently accepted for publication by the peer reviewed Poultry Science (B-1928) (the “Russell article”). The Russell article describes a study that was discussed at length in Russell’s written direct testimony (B-1912) to determine if the presence of air sacculitis in broiler contributes to loss of saleable yield, lack of uniformity, fecal contamination, processing errors and increases populations of pathogenic and indicator bacteria. In sum, the results of the study show that, because flocks of chickens showing signs of air sacculitis have lower weights, more fecal contamination, more processing errors, and higher levels of *Campylobacter* spp., broiler companies should emphasize control of air sacculitis in the flocks as a means of preventing subsequent food-borne bacterial infection.

The Russell article relates to other exhibits on the docket and placed into evidence. However, it is currently is unavailable to the docket and evidentiary record in this hearing in manuscript form, as accepted for publication in Poultry Science.

In conclusion, because all six of these documents are related to the issues of the hearing, and have only been published, released, acquired, and/or come to the attention of Bayer very recently, and the documents fall under 21 C.F.R. § 12.85(c), and Bayer respectfully moves to add these exhibits to the docket and moves their entry into the evidentiary record of this hearing.

¹⁵ Nawaz article at 257.

Respectfully submitted,



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CERTIFICATE OF SERVICE

I hereby certify that a copy of Respondent Bayer's Motion To Supplement Document Submission Under 21 C.F.R. § 12.85 and Move Additional Documents into the Evidentiary Record was e-mailed and also mailed, postage pre-paid, this 28 day of April, 2003 to:

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ORDER

By motion filed April 28, 2003, Respondent Bayer Corporation seeks to supplement its documentary submission pursuant to 21 C.F.R. § 12.85(c) and move additional documents into its evidentiary record under 21 C.F.R § 12.94.

Bayer states that the documents are related to the issues of the hearing, and have only been published, released, acquired, and/or come to the attention of Bayer since its last § 12.85 submission on January 14, 2003.

Accordingly, Respondent's Motion To Supplement Document Submission Under 21 C.F.R. § 12.85 and Move Additional Documents into the Evidentiary Record is GRANTED and documents B-1923, B-1924, B-1925, B-1926, B-1927 and B-1928 are entered into the § 12.85 docket and into the evidentiary record.

DATED this the ___ day of April , 2003.

Daniel J. Davidson
Administrative Law Judge

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