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: January 14, 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 two documents, B-1920 and B-1921, into its evidentiary record under 21 C.F.R. § 12.94. The first document is entitled "An Observational Clinic-Based Study Of Diarrheal Illness In Deployed United States Military Personnel In Thailand: Presentation And Outcome Of Campylobacter Infection," ("The Sanders Article").[1] The second document is a symposium published by the International Journal of Infectious Diseases entitled "The Therapeutic Use of Fluoroquinolones in Poultry: the Effect on *Campylobacter* and the Potential Human Health Consequences," (the "Symposium Article").[2] The documents are submitted herewith. These documents only became publicly available in

[1] The complete citation is, Sanders JW, Isenbarger DW, Walz SE, Pang LW, Scott DA, Tamminga C, Oyofo BA, Hewitson WC, Sanchez JL, Pitarangsi C, Echeverria P, Tribble DR. *An Observational Clinic-Based Study Of Diarrheal Illness In Deployed United States Military Personnel In Thailand: Presentation And Outcome Of Campylobacter Infection.* Am J Trop Med Hyg 2002 Nov; 67(5):533-8.

[2] The complete citation is Symposium, *The Therapeutic Use of Fluoroquinolones in Poultry: the Effect on Campylobacter and the Potential Human Health Consequences*, Int'l J of Inf Dis, Vol. 6, Supp. 3, (December 2002).

December 2002, and provide important relevant information to this administrative hearing. The Sanders Article only very recently came to Bayer's attention, while a pre-print of the Symposium Article was known by Bayer, the article itself was only very recently published, and thus publicly available.

Regulatory Requirements To Supplement Documents

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 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. Bayer 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).[3]

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[3] 21 C.F.R. § 12.70(h) grants the ALJ authority to "[r]ule on, admit, exclude, or limit evidence."

The Sanders Article Was Unknown To Bayer When Bayer Submitted Its Written Direct Testimony and Its Last 12.85 Submission

The Sanders Article did not come to Bayer's attention until after Bayer's written direct testimony was submitted on December 13, 2002, and its last 12.85 submission, submitted on December 20, 2002. The Sanders Article was published in the November 2002 volume of the American Journal of Tropical Medicine Hygiene. According to the publisher, this volume was "drop-shipped" on November 26, 2002 by Sheridian Press for delivery to subscribers and library recipients.[4] Thus, the volume was not first publicly available until sometime in December 2002. In fact, Bayer did not become aware of this article until January 2003, after the submission of its written direct testimony and last 12.85 submission.

The Sanders Article Contains Important Relevant Information

The Sanders Article contains important information that is relevant to this administrative hearing. The article provides several important observations regarding the course and response to therapy of fluoroquinolone-resistant Campylobacteriosis. The authors of the article report on the management and outcomes of acute diarrheal illness in 169 U.S. military personnel in Thailand studied during April-June, 1998. This population is noteworthy for the high risk of acquisition of fluoroquinolone-resistant *Campylobacter* infection (in this study, the rate of fluoroquinolone resistance among *Campylobacter* isolates was 96%), and for the ready availability of expert clinical care with excellent microbiology support; patients were evaluated after one day of symptomatic illness.

The key observations may be summarized as follows:

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[4] "Drop-shipped" means dropped at a post office for bulk mail delivery.

1) The presenting signs and symptoms of individuals infected with *Campylobacter* (*C. jejuni or C. coli,* not speciated in this study) tended to be more severe than those seen in individuals determined to have non-*Campylobacter* illnesses (primarily Salmonellosis, enterotoxigenic E. coli, and attaching and effacing E. coli). *Campylobacter*-infected individuals had a significantly higher rate of systemic complaints such as fever (65% vs. 22%), myalgias (53% vs. 20%), and arthralgias (47% vs. 11%), had more severe diarrhea, and had greater limitation of normal activities. Thus, although it was not possible to identify prospectively all *Campylobacter*-infected individually, it was possible to develop a heightened suspicion of this diagnosis in many of the infected individuals. Heightened clinical suspicion of *Campylobacter* infection facilitates targeted antibiotic therapy based on known antibiotic susceptibilities, rather than a rigid empirical regimen for all patients with acute diarrheal illness.

2) Overall, 79% of the patients were treated with antibiotics, and 82% of these individuals recovered within 72 hours of treatment. However, among the 21% of individuals who did not receive antimicrobial therapy, the 72 hour response rate was 75%. Although this was an observational study, where therapeutic decisions were made clinically, (and presumably therapy was biased toward more symptomatic individuals), these outcomes underscore the concept that acute bacterial enteritis is largely a self-limited illness. Antibiotic therapy offers only slight incremental benefit when compared to supportive care alone, even when administered after an average of only 24 hours of symptoms.

3) With specific regard to *Campylobacter* infection, 2 of 3 patients with fluoroquinolone-resistant *Campylobacter* infection recovered within 72 hours of presentation without

antimicrobial therapy. Of 19 patients with *Campylobacter* infection treated with ciprofloxacin, 5 patients (26%) had suboptimal responses (3 patients were lost to followup and presumably had resolution of their symptoms). Thus, despite a 96% rate of fluoroquinolone resistance among the *Campylobacter* strains recovered during the study, 74% of patients had a satisfactory response to fluoroquinolone therapy. Moreover, the authors obtained quantitative data regarding ciprofloxacin resistance. Mean inhibitory concentrations (MICs) ranged between 4 and 64 μg/ml, but there was no correlation between therapeutic response and MIC. This supports the concept that currently utilized ciprofloxacin MIC data against *Campylobacter* are not helpful for predicting the clinical response of ciprofloxacin therapy, since intestinal intraluminal antibiotic concentrations greatly exceed these MICs.

4) The *Campylobacter* isolates were uniformly susceptible to azithromycin (a macrolide and a non-fluoroquinolone) in vitro. Of 6 *Campylobacter*-infected individuals given azithromycin after supportive therapy alone (1 patient) or ciprofloxacin (5 patients), a suboptimal response was observed in only 1 patient (4 cures, 1 lost to followup, presumably improved, and 1 with a suboptimal response). This confirms that azithromycin has retained its efficacy for the treatment of *Campylobacter* enteritis in Thailand over a decade where fluoroquinolone resistance has grown from zero to 96% in an eight year interval (1990-1998). Azithromycin is an efficacious and broad-spectrum alternative to ciprofloxacin for the empiric treatment of bacterial enteritis as well as for specific therapy for the minority (~25%) of individuals with fluoroquinolone-resistant *Campylobacter* infection who fail initial therapy with ciprofloxacin.

The Sanders Article, describing the course and response to therapy of fluoroquinolone-resistant Campylobacteriosis, is consistent with testimony provided by Dr. Mark Pasternack, (see Pasternack testimony at 14-17), but provides additional relevant data and information on the treatment and satisfactory resolution of "fluoroquinolone-resistant" *Campylobacter* infections. Therefore, the document is relevant to the hearing.

The Symposium Article Was Not Available When Bayer Submitted Its Written Direct Testimony and Its Last 12.85 Submission

The Symposium Article appears in the December 2002 volume of the International Journal of Infectious Diseases.[5] This volume was not published and mailed to subscribers until the third week of December 2002, after Bayer had submitted its written direct testimony and 12.85 submission. In fact, Bayer did not receive its copy of the Symposium Article until January 2003. Thus, the Symposium Article was not available at the time of Bayer's written direct testimony or its last 12.85 submission.

The Symposium Article Contains Important Relevant Information

The Symposium Article contains important information that is relevant to this hearing. The symposium entitled," The Therapeutic Use of Fluoroquinolones in Poultry: the Effect on *Campylobacter* and the Potential Human Health Consequences" includes papers and discussions from experts in the field of animal and human medicine, some of whom have submitted testimony in this case. The meeting was co-chaired by a veterinarian specializing in food animal medicine, Professor Otto Radostits, and a physician and infectious disease

[5] An earlier pre-publication (i.e., galley proof) version of the Symposium Article was submitted to the docket as B-1562, however, this version was not final and the published version of the Symposium Article differs from the previous version.

expert, Professor Ethan Rubinstein. The article consists of papers and discussions which reflect the proceedings of the symposium.

Case Law Demonstrates That Supplementing the Evidentiary Record in an Administrative Hearing is Permitted Under Certain Circumstances, Like Those Presented Above

Bayer recognizes and respects the need for closure of the record if proceedings are to be conducted in an expeditious and efficient manner. Bayer submits, however, that in limited circumstances, fairness to the parties and the interests of justice require allowing for supplementation of the evidentiary record. This instance is a classic example of such a situation, because the articles in question did not even exist until just prior (the Sanders Article) or just after (the Symposium Article) the date on which the parties were to submit their evidence, and thus Bayer could not submit them with its evidence. Thus, this is not a situation where a party should have known of a piece of evidence but simply failed to discover it, or forgot to include it in the record—rather, it is a situation where the article *could not have been* included in the record in a more expeditious manner.

Other administrative agencies have recognized that supplementation of the record is appropriate in such situations. *E.g.*, *Ohio Dep't of Human Servs.*, DAB No. 900, 1987 HHSDAB LEXIS 837, at *21 n.9 (HHS Dep't Grant Appeals Bd., 1987) (granting motion to supplement to include document where document was relevant and where party had not had previous access to it); *Wash. Heights Nurs. & Rehab. Ctr. v. Health Care Fin. Admin.*, CR No. 703, 2001 HHSDAB LEXIS 75, at **6-7 (HHS Dep't Appeals Bd., Civil Remedies Div., 2001) (granting motion to supplement record to include a relevant decision handed down in another matter subsequent to the briefing deadline); ("There are, of course, circumstances where the admission of additional

evidence into the record should be permitted on notice and a proper showing such as when the evidence is newly discovered.") *Industrial Contractors*, 86-1 B.C.A. (CCH) P18,600, 1985 AGBCA LEXIS 92, at *4 (U.S. Dep't of Agric. Bd. of Contract Appeals, 1985) (analyzing motion to supplement filed after hearing had taken place). In these instances, and in the instance at issue, it is appropriate to allow the addition of newly discovered evidence.

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In conclusion, the Sanders and Symposium Articles were either not available or not known to Bayer at the time of submission of its written direct testimony or of its 12.85 submission, are relevant to the issues of the hearing, and should be permitted to be added as part of Bayer's 12.85 submission and Bayer's evidentiary record.

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 14th day of January, 2003 to:

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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**

ORDER

By motion filed January 14, 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 were either not known or not available to Bayer when it submitted its written direct testimony on December 13, 2002, and its 12.85 submission on December 20, 2002.

Accordingly, Respondent's Motion To Supplement Document Submission Under 21 CFR § 12.85 and Move Additional Documents into the Evidentiary Record is GRANTED and documents B-1920 and B-1921 are entered into the 12.85 docket and into the evidentiary record.

DATED this the ___ day of January , 2003.

Daniel J. Davidson
Administrative Law Judge