A Partnership Including Professional Corporations
600 Thirteenth Street, N.W.
Washington, D.C. 20005-3096
202-756-8000
Facsimile 202-756-8087
www.mwe.com

Robert B. Nicholas
Attorney at Law
rnicholas@mwe.com
202-756-8170

Boston
Chicago
London
Los Angeles
Miami
Moscow
New York
Orange County
Silicon Valley
Vilnius
Washington, D.C

McDERMOTT, WILL & EMERY

Rec'd 3/31/03
4:03 p.m.

March 31, 2003

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, Maryland 20852

Re: In the Matter of Notice of Hearing: Proposal to Withdraw Approval of New Animal Drug Application for Enrofloxacin for Poultry ("Enrofloxacin Hearing)
FDA Docket: 00N-1571

Dear Sir/Madam:

Enclosed for filing please find an original and two copies of Bayer's and Animal Health Institute's Opposition to the Center for Veterinary Medicine's Supplemental Request to Submit Rebuttal Evidence.

Please call with any questions.

Sincerely,

Robert B. Nicholas

RBN:jeh
Enclosures
cc: Nadine Steinberg, Esquire (w/enclosure)
Kent McClure, Esquire (w/enclosure)

00N-1571

RMO 19

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

Rec'd 3/31/03
4:03 p.m.

In the Matter of:

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

FDA DOCKET: 00N-1571

Date: March 31, 2003

BAYER'S AND ANIMAL HEALTH INSTITUTE'S OPPOSITION TO THE CENTER FOR VETERINARY MEDICINE'S SUPPLEMENTAL REQUEST TO SUBMIT REBUTTAL EVIDENCE

By Order dated March 19, 2003, the Center for Veterinary Medicine (CVM) was directed to supplement its previously filed Request for Rebuttal, because CVM's initial request was inadequate in that it "d[id] not provide enough information." Specifically, the Order states; "CVM must show that it could not have reasonably anticipated the evidence that it seeks to rebut, and specify the nature of the rebuttal." In its March 24, 2003 Supplement, CVM requests to expand by over 50% the testimony of its witness Dr. Robert V. Tauxe (G-1475), by adding testimony seeking to rebut the written direct testimony of AHI witness Bradley DeGroot, Ph.D. CVM's request should be denied because the proposed rebuttal testimony covers points that CVM reasonably should have anticipated, since CVM had actual prior notice of Participant AHI's and Respondent Bayer's specific criticisms of NARMS that CVM now wishes permission to rebut. In fact, CVM did anticipate the need for such testimony and CVM's written direct testimony addresses the concerns it now seeks to file additional testimony to rebut. Additionally, CVM's proposed rebuttal testimony should not be allowed because the proposed rebuttal

00N-1571

RMO 19

testimony is repetitive of subject matter already contained in CVM's submitted written direct testimony. Finally, the rebuttal testimony subject matter proffered by CVM demonstrates a mere conflict of the evidence in the record. Cross-examination, rather than rebuttal testimony, is the appropriate mechanism for resolving such disputed evidence.

CVM seeks submission of rebuttal testimony on two issues: 1) "the effect of including ill people seeking medical care in the human NARMS surveillance program"; and 2) "the effect of not collecting data on prior antimicrobial use and foreign travel in the human NARMS surveillance program." (CVM Request P.1-2).

At their core, these two issues center on whether the human NARMS data are valid and can be *generalized* in any meaningful way, beyond the surveillance samples taken, to the broader United States population. CVM's summary of what it intends to show through rebuttal testimony concedes that these are the central issues:

> CVM intends to show through rebuttal testimony that ... including ill people seeking medical care in the human NARMS surveillance program is not a bias; ... estimates of the levels and trends of fluoroquinolone-resistant *Campylobacter* cases can be generalized beyond the samples tested in human NARMS even though human NARMS is based on ill people seeking medical care; ... not collecting data on prior antimicrobial use and foreign travel in the human NARMS surveillance program is not a bias; ... estimates of the levels and trends of fluoroquinolone-resistant *Campylobacter* cases can be generalized beyond the samples tested in human NARMS even though human NARMS does not collect data on prior antimicrobial use and foreign travel.
>
> (CVM Request P.2-3).

As is demonstrated below, CVM has already submitted evidence supporting its contentions that human NARMS data are not biased and are generalizable to the United States population. DeGroot's and other AHI and Bayer witness testimony disagrees with CVM's contentions, but such disagreements are appropriately resolved via cross-examination, not by

giving CVM an opportunity to submit repetitive testimony. As is also demonstrated below, by December 9, 2002 CVM reasonably should have anticipated (and in fact did anticipate) that AHI or Bayer would submit testimony and evidence questioning the validity and generalizability of the human NARMS *Campylobacter* resistance data, so rebuttal testimony is inappropriate.

CVM's Request For Rebuttal Should Be Denied Because CVM's Proposed Rebuttal Testimony Covers Points That Reasonably Should Have Been Anticipated By CVM

CVM claims that it "could not have reasonably anticipated the testimony that CVM seeks to rebut." (CVM Request P.2). This is not accurate, and in fact CVM and its witnesses had actual knowledge of the matters CVM now seeks to rebut.

Before CVM submitted its written direct testimony CVM was well aware of criticisms of the human NARMS program, including criticisms lodged by AHI and Bayer that the NARMS program data were not representative of the United States population, that the data were biased because the program selects its samples from persons who are ill and seeking medical care, and that the data are biased because the program does not collect data or information from patients to allow correction for those who acquired their resistant *Campylobacter* infections from foreign travel or whose resistance may be due to prior antibiotic treatment with fluoroquinolones.

As early as Bayer's February 21, 2001 response to the NOOH, Bayer pointed out that "in order to determine the amount of resistance potentially attributable to domestic chicken consumption, the [human NARMS] data must be corrected to account for other sources of resistance, most notably foreign travel and prior human use of fluoroquinolones." (Bayer's Submission of Facts, Information and Analyses in Response to the Notice of Opportunity for Hearing, P.6).

Even more importantly, all of the criticisms CVM now seeks to rebut were identified, publicly discussed and provided in written form to CVM and CVM witnesses a month before CVM's written direct testimony was to be submitted. In November 2002 the NARMS annual scientific meeting was held in Hilton Head, South Carolina ("NARMS 2002 Meeting"). It is Bayer's and AHI's understanding that chairmanship of the official NARMS meetings rotate between the three principals of NARMS, Dr. Paula Cray (USDA/ARS), Dr. Fred Angulo (CDC) and Dr. Linda Tollefson (G-1478, P.4. L.41-45), and that all three principals are involved in planning the annual NARMS meetings. Dr. Paula Cray, who was identified as a CVM witness (Center for Veterinary Medicine's Submission of Witness List; Full Curriculum Vitae of Witnesses and Prior Statements of Witnesses, FDA Docket 00N-1571, May 20, 2002) and who is referenced extensively in CVM's Deputy Director Linda Tollefson's written direct testimony (G-1478, P.7-12), was responsible for organizing the NARMS 2002 Meeting. Participant AHI's witness Dr. Richard A. Carnevale, Vice President for Regulatory, Scientific and International Affairs for AHI (listed on AHI's witness list since May 2002), was on the agenda to make a presentation at the NARMS 2002 Meeting. Prior to the meeting Carnevale submitted to the NARMS 2000 Meeting organizers a paper titled "The National Antimicrobial Resistance Monitoring System: A Quantitative Evaluation." The paper was prepared for hearing participant Animal Health Institute by Michael E. Ginevan and was distributed to all NARMS 2002 Meeting participants as part of the official meeting materials. (A version of this document is in evidence as A-199, P.44-76; *See also*, document A-52 and B-1879). AHI witness Dr. Richard A. Carnevale publicly presented the Ginevan paper at the NARMS 2002 meeting. In addition to the other NARMS principals, CVM's witnesses Dr. Fred Angulo (G-1452) Dr. Linda Tollefson (G-

1578), Dr. David White (G-1484) made presentations at and/or attended the NARMS 2002 Meeting

In light of the Ginevan report, as discussed below, it is clear that CVM not only could have reasonably anticipated, but was on actual notice of the need for testimony on the issue of whether collecting data on prior antimicrobial use and foreign travel in the human NARMS surveillance program creates a bias and whether estimates of the levels and trends of fluoroquinolone-resistant *Campylobacter* cases can be generalized beyond the samples tested in the human NARMS even though human NARMS does not collect data on prior antimicrobial use and foreign travel.

According to Ginevan's final report, "AHI requested this review to 'deconstruct' the human... NARMS program[s] in order to better understand how the data was being collected and interpreted by the FDA, CDC, USDA, and others interested in tracking antibiotic resistance in food-borne pathogens." (Ginevan final report B-1879, P.3)

The Ginevan report identified specific issues with the human NARMS program that are relevant to this discussion, including: (1) that reporting of culture confirmed human cases of food-borne illness is seriously incomplete; (2) the sampling protocol produces biased results; (3) there is a lack of meta-data (the data about the data); and (4) that there is a lack of study design. [A-199, P.46-47]

The Ginevan report provides specific suggestions to remedy the criticisms regarding the human NARMS program, including (1) to develop sampling plans that will yield true national resistance prevalence data; and (2) to collect appropriate meta-data. [A-199, P.47]

The Ginevan report asserts that NARMS reporting of culture confirmed human cases of foodborne illness is seriously incomplete because of NARMS' reliance on collecting isolates

from ill persons who must have symptoms severe enough to seek medical care and the possibility that "there may be a built in bias toward isolation of resistant organisms" as a result. [A-199, P.56]. The Ginevan report lays out a schematic at Figure 2 showing how human bacterial isolates are generated and how the result of the process is that isolation of resistant organisms is more likely under certain scenarios. [A-199, P.56-58]

In light of this, it is difficult to accord any credibility to CVM's contention that it could not anticipate the need for testimony on the issue of whether "including ill people seeking medical care in the human NARMS surveillance program is a bias" and whether "estimates of the levels and trends of fluoroquinolone-resistant *Campylobacter* cases can be generalized beyond the samples tested in the human NARMS program, even though human NARMS is based on ill people seeking medical care." (CVM Request P.2)

Additionally, the Ginevan report specifically criticizes the lack of collection of "meta-data" on whether NARMS resistant isolates might arise from prior fluoroquinolone use or foreign travel stating:

> Meta-data is literally the data about the data, and is of great importance in the interpretation of any large body of data like that generated by the NARMS program. For human illness we have mentioned that foreign travel is a risk factor repeatedly identified for both enteric infections in general and infections involving resistant organisms. However, the NARMS program does not collect information on whether or not a given isolate is from an individual who recently engaged in foreign travel. Likewise, one can speculate that some resistant infections are identified as a result of an isolate being ordered after the patient has failed to respond to treatment with antibiotics. It would be most useful to know if the person who is the source of a given isolate was treated with antibiotics in the month prior to when the isolate was obtained.
>
> [A-199, P.61]

The Ginevan report's suggestions on improving the human NARMS program, including developing sampling plans that will yield true national resistance prevalence data, also raises the issues CVM now seeks to rebut. The report states:

> For the Human NARMS data three clear problems are: state compliance with study protocols, likely variations in the procedures by which cultures are isolated, and the possibility that the failure of a given antibiotic in treating a person is a reason for ordering an attempt to isolate an organism. There is also a question of how representative the populations sample really are. The large catchment area of the Human NARMS program may be an advantage, but there could still be significant issues like wealthy areas yielding disproportionate numbers of cultures because there is medical insurance to pay for their isolation.
>
> [A-199, P.65]

Additionally, at the November 2002 NARMS meeting, an attendee clearly identifying himself as a Bayer employee questioned CVM witness Angulo about the validity, representativeness and generalizability of the human NARMS data in light of the sample scheme and other issues. [Carnevale (A-199), P.13 L.2-28; P.14 L.19 – P.15 L.15; P.18 L.12-23; A-199, Attachment 3]

In light of the concerns publicly raised in the Ginevan report and Carnevale presentation, as well as the questions asked at the November 2002 NARMS meeting regarding the representativeness and generalizability of the human NARMS data and the potential biases in the NARMS surveillance program, CVM should have anticipated the need for addressing the validity and generalizability of the NARMS program data. In fact, CVM did anticipate the need for such testimony and did in fact submit testimony on the validity, representativeness and generalizability of the human NARMS data. CVM's request for rebuttal should also therefore be denied because the testimony it seeks in repetitive.

CVM's Request For Rebuttal Should Be Denied Because CVM's Proposed Rebuttal Testimony Is Repetitive Of Subject Matter Already Contained In CVM's Written Direct Testimony

CVM's request for rebuttal testimony is nothing more than an attempt to get the proverbial two bites at the apple by submitting additional testimony in support of its contention that human NARMS data are valid, unbiased and generalizable to the broader United States population. CVM has already submitted testimony on these points.

CVM witness Frederick J. Angulo, Chief of the FoodNet/NARMS Unit of the Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, and one of the principal architects of NARMS, testified at length that the NARMS/FoodNet data is representative of the United States population and concludes that "data support the generalizability of FoodNet [NARMS] data to the United States population for the purpose of understanding the epidemiology of foodborne illness." [Angulo (G-1452) P.3 L.45 – P.4 L.26]

Similarly, CVM witness Mary Bartholomew has already testified that "human isolates sent to the CDC for susceptibility testing constituted a statistically valid subset of the culture-confirmed cases reported to FoodNet." [Bartholomew (G-1454) P.6 L.13-14].

CVM witness Kare Molbak testified regarding the national prevalence of fluoroquinolone-resistant *Campylobacter* in the United States from 1997 to 2001 based on the NARMS data set. His testimony includes a discussion of the adjustments that are made which he believes permit the NARMS data to be generalized to the United States population. [Molbak (G-1468) P.8 L.1-35]. In particular, Molbak testifies "to adjust for the differences in sites, the site- and age-adjusted prevalence ratio was determined in a generalized linear model with binomial variability and a logarithmic link function." [Molbak (G-1468) P.8 L.18-20]

CVM witness Linda Tollefson testified that for most of the period relevant to the hearing on fluoroquinolones, "27 state and local public health departments representing 63% of the United States population submitted isolates to the CDC for inclusion in NARMS." [Tollefson (G-1478) P.7 L.17-23]. Tollefson goes on to testify that she and the other designers of the NARMS system "designed the system to allow us to track changes over time in both [animal and human] populations and thus be able to draw comparisons between the two populations. [Tollefson (G-1478) P.14 L.39-43]

Both CVM witness Bartholomew and CVM witness Curtis Travis submitted testimony relating to the fact that the human NARMS resistance data does not distinguish resistance that might have been derived through foreign travel or that might have been derived through having received a fluoroquinolone prior to stool culture. [See, *e.g.* Bartholomew (G-1454) P.9 L.18-33; Travis (G-1479) P.19 L.16-24]

While Bayer and AHI disagree with the substance of the above testimony claiming that the human NARMS data are unbiased and generalizable to the United States population, it is clear that CVM has already submitted evidence on the point. Additional testimony on whether the human NARMS data are unbiased and generalizable would clearly be repetitive. Repetitive testimony such as the rebuttal proposed by CVM is inadmissible. 21 CFR § 12.94(c)(1)(i).

CVM's Request For Rebuttal Should Be Denied Because Cross-Examination Is The Appropriate Mechanism For Resolving Disputes Of Evidence

The overriding purpose of CVM's request to submit the written rebuttal testimony of Dr. Tauxe is to attack the credibility and knowledge of AHI witness Dr. Bradley DeGroot. Specifically, by submitting the written rebuttal testimony of Dr. Tauxe, CVM's hope is to show that the "specific criticisms of the human NARMS surveillance program in Dr. Bradley

DeGroot's testimony (Exhibit A-200) are *inapplicable, immaterial, or misinformed* and that *those criticisms provide no basis for undermining the utility of the human NARMS surveillance program, data from human NARMS, or analyses conducted on those data.*" (CVM Request P.1, emphasis added). Because the center's primary aim in introducing the written rebuttal testimony of Dr. Tauxe is to show that Dr. DeGroot's testimony as it relates to the human NARMS surveillance program is "inapplicable, immaterial, or misinformed", the appropriate vehicle for resolving CVM's concerns regarding Dr. DeGroot's testimony is *via* cross-examination rather than through rebuttal evidence.

In contrast to cross-examination, which typically involves attacks on a witness' credibility and/or knowledge, the purpose of rebuttal evidence is very narrow. Its purpose is simply to meet and reply (or rebut) any new evidence offered by an opponent; it is not to attack the credibility and/or knowledge of a particular witness. *La Esperanza De P.R. v. Perez Y Cia. De P.R.*, 124 F.3d 10, 31 (1st. Cir. 1997); *U.S. v. Tejada*, 956 F.2d 1256, 1266-67 (2d Cir. 1992). Again, the parties' dispute concerning the value of the human NARMS data is not a "new" dispute, or one in which CVM did not have previous knowledge and/or notice.

Although the specific purpose of a cross-examination may vary, counsel generally conduct cross-examinations in order to achieve one (or more) of the following objectives:

> (1) attempt to elicit disputed facts from the witness favorable to his case, (2) have the witness repeat those facts testified to on direct favorable to the cross-examiner, (3) have the witness testify to nondisputed facts essential to presentation of his theory of the case, (4) attempt to have the witness qualify, modify, or otherwise shed light upon his testimony with respect to unfavorable versions of disputed facts given on direct examination, (5) establish that the witness' testimony is not harmful to the advocate's case on the critical points under dispute and/or (6) ask questions of the witness designed primarily to keep the cross-examiners' theory of the case before the trier of fact.

Graham, Handbook of Federal Evidence § 611.10 (5th ed. 2001).

Rule 611 of the Federal Rules of Evidence circumscribes the scope of cross-examination "to the subject matter of the direct examination and matters affecting the credibility of the witness." FRE Rule 611. Courts in applying this limited scope, however, tend to construe liberally what falls within the subject matter of direct examination. *U.S. v. Arnott*, 704 F.2d 322, 324 (6th Cir.), *cert. denied*, 464 U.S. 948, 104 S.Ct. 364 (1983); *U.S. v. Lara*, 181 F.3d 183, 199 (1st Cir. 1999), *cert. denied*, 528 U.S. 1127, 120 S.Ct. 960 (2000); *U.S. v. Vasquez*, 858 F.2d 1387, 1392 (9th Cir. 1988), *cert. denied*, 488 U.S. 1034, 109 S.Ct. 847 (1989). Importantly, inquiry affecting the credibility of the witness is generally perceived to extend to include whatever tends to explain, modify, qualify, discredit or otherwise shed light upon the testimony given on direct without regard to whether such matters are also supportive of the adversary's case in chief. *U.S. v. Lara*, 181 F.3d at 199; *U.S. v. Garcia*, 936 F.2d 648, 653-54 (2d Cir. 1991), *cert. denied*, 502 U.S. 986, 112 S.Ct. 595 (1991).

In the present matter, CVM's avowed purpose in introducing the written rebuttal testimony of Dr. Tauxe is undisputed. It is: (1) to overcome, qualify, or explain Dr. DeGroot's testimony given on direct examination; as well as (2) to challenge his knowledge and credibility by exposing alleged inaccuracies in the direct examination. Therefore, based on the foregoing, the appropriate vehicle for resolving CVM's concerns regarding Dr. DeGroot's testimony is *via* cross-examination rather than through rebuttal evidence.

In conclusion, CVM's motion to submit rebuttal testimony should be denied because CVM reasonably should have anticipated the need for such testimony, and did in fact anticipate the need for such testimony. In addition, CVM's proposed rebuttal testimony is repetitive and the matters presented for rebuttal testimony are more appropriately address by cross-examination.

Respectfully submitted,

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
Counsel for Bayer

Kent D. McClure
Animal Health Institute
1325 G Street, N.W, Suite 700
Washington, D.C. 20005
(202) 637-2440
Counsel for AHI

CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of Bayer's and Animal Health Institute's Opposition to the Center for Veterinary Medicine's Supplemental Request to Submit Rebuttal Evidence was hand-delivered this 31st day of March, 2003 to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

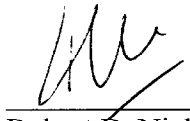
I also certify that a copy of the foregoing Opposition was e-mailed this 31st day of March 2003 to:

The Office of the Administrative Law Judge
Food And Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, MD 20857

I also certify that a copy of the foregoing Opposition was e-mailed and mailed via first-class mail, postage pre-paid, 31st day of March 2003 to:

Nadine Steinberg
Counsel for the Center for
Veterinary Medicine
5600 Fishers Lane (GCF-1)
Rockville, MD 20857

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



Robert B. Nicholas
Counsel for Bayer