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 Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	FDA DOCKET: 00N-1571 DATE: April 25, 2003

03 APR 25 P4:17

CVM's Motion to Supplement Document Submission under 21 C.F.R. §12.85 and Motion to Enter Exhibit G-1801 into the Evidentiary Record

The Center for Veterinary Medicine ("CVM" or "the Center") respectfully moves to supplement its document submission under 21 C.F.R. §12.85 with the accompanying document. The document has been numbered Government Exhibit G-1801, and has been submitted to Dockets Management Branch along with this Motion. The Center also moves to enter Exhibit G-1801 into the evidentiary record of this hearing.

21 C.F.R. §12.85(c) allows document submissions to be supplemented with the approval of the Administrative Law Judge under certain circumstances; namely, upon a showing that the material was not reasonably known or available at the time of the original submission, or the relevance of the information could not have reasonably been foreseen at the time of the original submission.[1]

[1] 21 C.F.R. §12.85(c) provides, "Submissions required by...of 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

00N-1571

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The document subject to this Motion is:

G-1801: A letter from Joseph A. Foster, of the Centers for Disease Control and Prevention to Robert Nicholas, counsel for Bayer, dated April 24, 2003. The letter, marked as Exhibit G-1801, responds to questions from Bayer counsel and describes the history of CDC's contact with Bayer Corporation's counsel with respect to the various datasets requested and received by Bayer's counsel from CDC. This document is relevant because it rebuts arguments made by Bayer to the Administrative Law Judge in earlier communications (see Attachment 1) and demonstrates that certain written direct testimony submitted by Bayer and/or AHI may be based on inappropriate evaluations and analyses of data, even after counsel was specifically warned about the possibility of data conversion problems if SAS files were not used.

Because G-1801 was sent to Bayer by CDC, and has come to the attention of CVM since its last document submission, and after its Motion to enter written direct testimony and other evidence into the evidentiary record was filed on December 9, 2002, the document falls under 21 C.F.R. §12.85(c), and the Center respectfully moves to add this exhibit to the docket and moves its entry into the evidentiary record of this hearing.

CVM believes that important information will be unavailable to the record if this document is not admitted onto the docket and into the evidentiary record.

Respectfully submitted,

Nadine Steinberg
Counsel for Veterinary Medicine

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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 forseen."

Enrofloxacin Hearing
Docket No: 00N-1571

CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of the foregoing Center for Veterinary Medicine's Motion to Add G-1801 to the Docket and into the Evidentiary Record was hand delivered this 25th day of April, 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 Center for Veterinary Medicine's Motion has been hand delivered and e-mailed, this 25th day of April, 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 Center for Veterinary Medicine's Motion was e-mailed and faxed (and a copy placed in outgoing mail, although after regular pickup hours) this 25th day of April, 2003, to:

Robert B. Nicholas
McDermott, Will & Emery
600 13th Street, NW
Washington, DC 20005

Kent D. McClure
Animal Health Institute
1325 G Street, NW, Suite 700
Washington, DC 20005

Dated: 4/25/03

Nadine Steinberg
Counsel for the Center for
Veterinary Medicine
5600 Fishers Lane (GCF-1)
Rockville, MD 20857
(301) 827-5050

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the General Counsel
1600 Clifton Road, N.E.
Atlanta Georgia 30333

April 24, 2003

Robert B. Nicholas
McDermott, Will, & Emery
600 13th Street, N.W.
Washington, DC 20005

Dear Mr. Nicholas:

In our recent telephone conversations, you have asked that CDC provide further clarification of the February 10, 2003 letter addressed to Nathan Beaver (Attachment A) in which Lynn Armstrong, the CDC/ATSDR Freedom of Information Act Officer, noted that inadvertent inaccuracies may have been introduced into the data when the previously provided data were converted from a SAS format to a Microsoft Excel format. The following is provided to illustrate how CDC personnel discovered the conversion problem that precipitated the February 10 letter.

According to our records, at least three individuals from your firm, including yourself, have made at least twenty five (25) Freedom of Information Act requests related to this matter since July 21, 2000, many of them for large electronic datasets. According to CDC personnel, these datasets were requested by representatives from your firm in a Microsoft Excel format rather than the SAS format that is used by CDC.[1] Providing the datasets as Excel files requires an electronic conversion of the data in the SAS software into a format that can be read by Microsoft Excel. Since this conversion can result in inaccuracies, CDC program staff recommended to Nathan Beaver of your firm that he use the SAS format to avoid conversion problems and that the conversion into Excel may not be error free.[2] CDC staff provided the datasets in Excel format, and, on occasion, in SAS format.

Until January 13, 2003, CDC had not compared the SAS databases to the converted Excel files released to your firm. On that day, CDC program staff reviewed, pursuant to a request by FDA, witness testimony of Bradley D. DeGroot, D.V.M., Ph.D. CDC staff became confused by Dr. DeGroot's description of the National Antimicrobial Resistance Monitoring System (NARMS) data on page 37 of his testimony where he stated that "[t]wenty-one observations (6%) in 2000 have the specimen collection month in the CDC receipt date column, 249 (69%) observations have specimen collection month in the sensititre test date column, and only 92 observations (25%) have specimen collection month in the month column." Since the specimen collection month variable is not in the actual NARMS SAS database, this prompted the CDC staff to compare the NARMS SAS databases and Excel files that had been provided to the FOIA office. During this

[1] Indeed, there would be little reason to convert the data into Excel unless specifically requested to do so.
[2] See the attached July 26, 2001 email (Attachment B).

examination of the data, CDC staff determined that the original NARMS SAS database[3] had 362 observations in the specimen collection month (MONTH) variable field. When looking at the Excel file of the same data,[4] the MONTH variable was distributed across three variable fields: 21 observations had the MONTH variable in the CDC receipt data column, 249 had the MONTH variable in the sensititre test date column, and 92 had the MONTH variable in the specimen collection month column. This discovery led the CDC staff to believe that the conversions of this and perhaps other databases from SAS to Excel had generated "frameshifts" where one variable's value (e.g., MONTH) was shifted into the column of a second variable (e.g., sensititre test date). This conclusion led to the February 10 letter and the subsequent release of all previously requested CDC databases in SAS format or in hard copy, free of charge.

Although the logical inference from these "frameshifts" is that they may occur elsewhere in converted Excel files, CDC has not undertaken efforts to identify and document additional "frameshifts" or other inaccuracies that may have resulted from the conversion. CDC staff are confident, however, that any difference in the CDC databases when converted from the original SAS databases to Excel would not affect any manuscripts or abstracts prepared or presented by CDC personnel because all analyses performed by CDC personnel are done in SAS using the original SAS databases.

I hope you find this information helpful. Please feel free to contact me at 404.639.7209 if you would like to discuss this matter further.

Sincerely,

Joseph A. Foster

cc:

Lynn Armstrong

[3] Identified by CDC as filename "bayer5.sd2," and provided to Nathan Beaver on March 17, 2003.
[4] Identified by CDC as filename "bayer5.xls," and provided to Nathan Beaver on February 26, 2002.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

February 10, 2003

Nathan Beaver
McDermott, Will & Emery
600 13th Street, N.W.
Washington, D.C. 20005-3096

Dear Mr. Beaver:

This letter is an additional response to your Freedom of Information Act (FOIA) request number 02-0578 and other data-related requests.

In response to various FOIA requests, you were provided records that CDC maintains in SAS files. At your request, and in accordance with the Electronic FOIA Amendments of 1996, we converted SAS files to .xls format. It has come to our attention that the data may have converted incorrectly, or the conversion may have caused inaccuracies in the data. Thus, we have determined that the data are not readily reproducible in the .xls format. As a solution, we can provide all previously released data sets in SAS format, or we can provide hard copies for your use, at no additional cost. Just let my office know if you wish to receive these.

Sincerely yours,

Lynn Armstrong

Lynn Armstrong
CDC/ATSDR FOIA Officer
Office of Communication
(404) 639-7270
Fax: (404) 639-7395

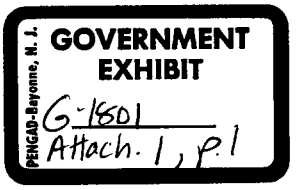
From: Kennedy, Malinda
Sent: Thursday, July 26, 2001 10:08 AM
To: 'nbeaver@mwe.com'
Cc: Armstrong, Lynn
Subject: zipped dbf file for FOIA of FoodNet campylobacter case control study

campdatdbf.zip

Attached is the zipped DBF version of the zipped SAS Campylobacter case-control study dataset sent yesterday. I would recommend trying to use the SAS file if at all possible to avoid the possibility of conversion problems. I can not guarantee that the dbf file converted properly and is error free. Most statistical analysis packages will allow you to import a SAS file into the software package you use most frequently.

Zuckerman, Claudia

From: rnicholas@MWE.com
Sent: Tuesday, February 25, 2003 7:11 PM
To: ddavidso@oc.fda.gov; Steinberg, Nadine; Kent D. McClure
Cc: Spiller, Robert; CZuckerm@oc.fda.gov
Subject: Correspondence Requesting A Meeting Regarding Docket No. 00N-1571



Your Honor and Counsel

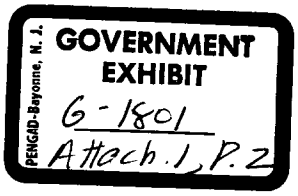
Attached please find a courtesy copy of a request for a meeting pursuant to 21 CFR §12.94(e). I have also sent the original by facsimile since the attached letter is in Word format and therefore does not contain a signature or the referenced attachments.

As explained in the attached letter, this request is being made based on a letter Bayer's counsel recently received from CDC. The CDC letter questions the accuracy of data provided to Bayer's counsel by CDC under the Freedom of Information Act and by CVM during discovery. These data have been relied on by various Bayer witnesses and perhaps by CVM as well.

Sincerely

Robert B. Nicholas

Robert B. Nicholas
McDermott, Will, & Emery
600 13th St. NW
Washington, DC 20005
202-756-8170 Phone
202-756-8087 Fax



February 25, 2003

VIA FACSIMILE AND EMAIL

Honorable Daniel J. Davidson
Administrative Law Judge
Food and Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, Maryland 20857

Re: Enrofloxacin Hearing
FDA Docket: 00N-1571
Request for Conference Pursuant to 21 CFR §12.94(e)

Dear Judge Davidson:

Respondent Bayer Corporation hereby requests an immediate conference pursuant to 21 CFR 12.94(e) to discuss a critical issue regarding the development of evidence in this matter. As described below, Bayer has recently become aware of potential inaccuracies in data that could adversely affect a substantial portion of the Written Direct Testimony submitted by all parties in this administrative proceeding and impact the Motions to Strike pending before Your Honor.

CVM produced to Bayer certain Centers for Disease Control and Prevention (CDC) data in .xls (Microsoft Excel) format pursuant to Bayer's discovery requests. Bayer and AHI relied on that and other CDC data in preparing their Written Direct Testimony in this matter. CDC recently disclosed to Bayer's counsel that relevant data CDC provided to Bayer pursuant to the Freedom of Information Act, and relied on by Bayer and AHI witnesses, may be incorrect and inaccurate. Specifically, certain CDC data was converted by CDC from SAS format to .xls (Microsoft Excel) format; CDC now discloses that in the process, "the data may have converted incorrectly, or the conversion may have caused inaccuracies in the data."[1] The conversion concerns disclosed by CDC apply equally to CDC-generated data produced in .xls format by CVM to Bayer during discovery.

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[1] CDC's letter (attached), received by Bayer's counsel on February 14, 2003. See also Bayer counsel's reply to CDC.

Several of Bayer's and AHI's witnesses relied on the data that CDC and CVM provided in .xls format in preparing their Written Direct Testimony submitted on December 13, 2002. CDC's recent disclosure raises serious concerns about the accuracy of the data on which Bayer's, AHI's and CVM's witnesses relied in drawing their conclusions in this matter. Moreover, Bayer's ability to prepare and put on its case may have been prejudiced to the extent that CVM and its witnesses (many of whom work for CDC) had access to the original SAS formatted data while Bayer's and AHI's witnesses had available to them only the inaccurately converted .xls formatted data.

Bayer has reason to suspect that the following data it received from CDC and CVM are subject to the problems disclosed by CDC:

- **Sentinel County Survey Data** (Bayer11.2.xls received from CVM and Bayer11.4(FOIA 02-0578).xls received from CDC);

- **NARMS data from 2001** (Bayer12.xls received from CDC; G1503.xls received from CVM), **NARMS data from 2000** (Bayer5.xls received from CDC), **NARMS data from 1998** (Bayer14.xls received from CDC), and **NARMS data from 1997** (Bayer10.xls received from CVM and Bayer13.xls received from CVM);

- **FoodNet data from 1997-1998** (CampyFN.xls received from CDC).

Bayer requests a conference as soon as possible to determine an appropriate resolution to these issues.

To demonstrate the gravity of the situation, below are examples of how this situation impacts this administrative hearing. These examples are non-exhaustive and Bayer does not waive any rights to raise additional concerns it may have.

Issues Related to the Sentinel County Survey Data

The Sentinel County Survey data is critical to this case because CVM relies on it to claim that the pre-approval baseline of *Campylobacter* resistance to fluoroquinolones (i.e., prior to approval of enrofloxacin) was "at most, very low in the United States in 1989 and 1990." (See, e.g., Angulo (G-1452) P. 13 L. 28; Barrett (G-1453) P. 3 L.13-20). Realizing the import of the Sentinel County Survey, Bayer sought the data and other information from the study from CDC through a FOIA request submitted May 7, 2002. Bayer also sought similar information from CVM through discovery in this case. Bayer received a Sentinel County Survey dataset from CVM in August 2002 but did not receive the Sentinel County Survey dataset directly from CDC until November 6, 2002 (despite the fact that the data was provided to CVM in July 2002). CDC did not provide the protocol, questionnaire, or other information that would have permitted Bayer to thoroughly analyze the dataset (and CVM disclaimed having them in their possession).

Despite certain unanswered issues, Bayer's witnesses nevertheless interpreted the dataset to the best of their medical and scientific ability, and provided relevant testimony on the basis of this interpretation. (*See e.g.,* Burkhart (B-1900) P. 42 L 3-36). Significantly, Dr. Burkhart believed based on his interpretation of the November 6, 2002 dataset provided by CDC that there was a demonstrable level of pre-approval *Campylobacter* fluoroquinolone resistance in isolates from humans. Two months after this testimony was submitted, CDC now discloses that the data may be inaccurate. Worse, because of CDC's disclosure, Bayer compared the CDC-provided dataset (Bayer11.4(FOIA 02-0578).xls) with the one provided by CVM (Bayer11.2.xls). It now appears that Dr. Burkhart's testimony on the level of pre-approval resistance is low by a factor of 2; the CVM dataset has 8 samples in the "CIPROFL" column with MIC (apparently minimum inhibitory concentrations) greater than 4 μg/ml whereas Dr. Burkhart found only 4 such samples in the CDC dataset.

Further, upon comparison of the CDC-provided dataset (Bayer11.4(FOIA 02-0578).xls) with the one provided by CVM (Bayer11.2.xls) it became clear that identical isolates, identified by their case number, show different values in the column labeled CIPROFL (apparently minimum inhibitory concentrations). As the table below shows, isolates with the same CASENUM identification have different CIPROFL values listed.

(Bayer11.2.xls) (CVM Dataset)	
CASENUM	CIPROFL
0313	129
0501	16
0912	33
1418	4
1438	8
1625	17
1627	9
1730	8

Bayer11.4(FOIA 02-0578).xls (CDC Dataset)	
CASENUM	CIPROFL
0313	8
0501	[cell empty]
0912	0.5
1418	1
1438	128
1625	8
1627	0.5
1730	64

The existence of two different datasets, each purporting to be the dataset from the Sentinel County Survey calls into question the validity of all CDC and CVM data, especially in light of CDC's recent disclosure to Bayer. A clock that strikes "13" is not only wrong on its face but calls into question all that went before.

Issues Related to the NARMS Data

As part of its evidence gathering in preparation for the hearing, Bayer also made numerous FOIA requests to CDC for human NARMS data. This included requests for the datasets for NARMS years 1997 through 2001, each of which CVM has relied upon in its

witness testimony. (See e.g., Angulo (G-1452) at P. 7 L. 26 - P. 9 L. 7; Tollefson (G-1478) P.14 L.26 - P.15 L.12). Bayer received each of these datasets in the .xls format and analyzed and drafted its testimony on the basis of the data received from CDC. Bayer also received some NARMS data from CVM in .xls format pursuant to discovery requests. Bayer's and AHI's witnesses testified about problems found in the Human NARMS data from CDC and moved to strike all testimony relating to the CDC Human NARMS data on the grounds that the CDC Human NARMS data was unreliable. Meanwhile, CVM's own Motion to Strike sought to exclude Dr. DeGroot's testimony critical of NARMS, stating:

> DeGroot testifies to the numbers of samples submitted to human NARMS and concludes there is "potential data corruption" in human NARMS. This portion of his testimony is unreliable and immaterial. This testimony, which is based on Dr. DeGroot's version of the data set, is pure speculation. Without more information (and none has been offered by Dr. DeGroot), there is no way to know whether any data manipulation or data transfer between software packages that was done by Dr. DeGroot, or by anyone on his behalf, corrupted the data set and is responsible for any data discrepancies alleged by Dr. DeGroot.

CVM's Motion to Strike P. 72-73

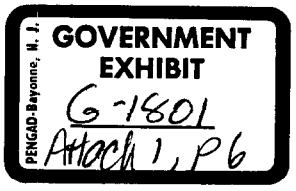
Now, after Bayer has reviewed and analyzed this data, submitted testimony on the basis of this analysis, and with pending motions where the reliability of the Human NARMS data is at issue, CDC has acknowledged that the data it provided may be inaccurate. An immediate conference is required to sort through this important issue.

Issues Relating to FoodNet Data

Finally, on September 4, 2002 Bayer also received FoodNet data from the years 1997-1998. This data is discussed in Dr. Angulo's testimony as well. See Angulo (G-1452) at P. 4 L. 37 - P. 5 L. 33. Bayer received this dataset in .xls format as well, and now has reason to believe that the data it received may not be accurate.

Conclusion

In conclusion, Bayer, AHI and CVM have all materially relied on CDC data in formulating their conclusions and Written Direct Testimony in this administrative hearing. Now, over a year into the hearing process and two months after Written Direct Testimony was submitted, this data has been called into question by the agency that generated it. If CVM and its witnesses relied on the .xls formatted data (as Bayer and AHI have), then CVM also has an interest in confirming the accuracy of the data. On the other hand, if CVM and its witnesses relied on the original SAS formatted data, then Bayer and AHI have been prejudiced in preparing their Written Direct Testimony. Bayer and AHI were given one set of data, the accuracy of which is now called into question by the responsible agency, while CVM and its witnesses had



access to the original SAS formatted data, the accuracy of which is not questioned by the responsible agency. Either way a conference is necessary and appropriate to discuss this problem.

Bayer thus requests an immediate conference pursuant to 21 CFR 12.94(e) to discuss this critical issue regarding the development of evidence in this matter. Bayer is available to meet at the Your Honor's and CVM counsel's earliest convenience.

Sincerely,

Robert B. Nicholas

RBN:jeh
Enclosures
cc: Nadine Steinberg, Esquire
Kent McClure, Esquire