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: February 28, 2003**

RESPONDENT BAYER CORPORATION'S OPPOSITION TO CVM'S MOTION TO ENTER EXHIBIT G-1799 INTO THE EVIDENTIARY RECORD

RESPONDENT Bayer Corporation hereby opposes the Center for Veterinary Medicine's Motion to Enter Exhibit G-1799 into the Evidentiary Record filed February 25, 2003.

Bayer has already moved to strike the Written Direct Testimony of CVM witness Kare Molbak (G-1468) on grounds that the testimony is unreliable and irrelevant. (*See*, Bayer Motion to Strike, p. 58-64). Exhibit G-1799, which is co-authored by Kare Molbak, Morton Helms and others, relates to the subject matter of Molbak's testimony and is itself similarly unreliable, irrelevant and does nothing to rectify the Molbak testimony's shortcomings. Pursuant to 21 C.F.R. § 12.94(c)(1)(i), Exhibit G-1799 should not be admitted into evidence.

It is noteworthy that even though the Helms/Molbak G-1799 article was published in a peer-reviewed journal, it has generated substantive critical comments from the medical community. (See attached comments.) These comments question the accuracy of the Helms/Molbak results for numerous reasons and should raise concerns for the reliability of the article. In the event that Exhibit G-1799 is admitted into evidence, Bayer hereby requests that the attached comments from the medical community, which includes a response from Helms and

Molbak to the comments, also be entered into the docket and into the evidentiary record as Exhibit B-1922. These comments, published on the *British Medical Journal* website, are recognized by the journal to "contribute substantially to the topic" and are eligible for publication in the paper version of *British Medical Journal*. (*See*, http://bmj.com/cgi/eletter-submit/326/7385/357). Because B-1922 contains responses to G-1799, which CVM acknowledges was unavailable and not reasonably known at the time of CVM's 21 CFR § 12.85 submissions and Written Direct Testimony submission, B-1922 also was not reasonably known or available to Bayer at the time that Bayer's 21 CFR § 12.85 submissions were made, or when Bayer's evidence was submitted.

Helms/Molbak Exhibit G-1799 Does Not Follow Generally Accepted Methods And Is Therefore Unreliable

The Helms/Molbak Exhibit G-1799 that CVM seeks to enter into evidence is unreliable because it fails to follow accepted epidemiological or statistical modeling methods, especially in constructing a representative sample for extrapolating to the general population.

The study method used in the Helms/Molbak article seeks to associate adverse health events to a previous *Campylobacter* infection by comparing a cohort of culture-proven *Campylobacter* cases one year after infection to the general population. The review was based on administrative medical registry data and not based on actual medical record review.

The Charlson co-morbidity index used by Helms/Molbak to attempt to adjust co-morbidity has not been validated for applications involving campylobacteriosis. Its validity has been questioned in the scientific literature and its predictive power has been shown to be limited or inadequate in many other applications. For example, in a recent review, Harboun M and Ankri J., 2001 state that "However, the Charlson index was found to be limited in recording the entirety of the old patients' pathologies, and in patients with cognitive deficits, only CIRS

appeared to be sufficiently trustworthy because it allows a comprehensive recording of all the comorbid disease from clinical examination and medical file data."

In addition, the co-morbidity index does not include the effects of unmeasured covariates, including aspects of diet, lifestyle, or immune system status that may predispose individuals to campylobacteriosis and to other illnesses. As with Dr. Molbak's testimony, G-1799 does not address the residual confounding due to factors (e.g., drinking contaminated water) that may not be adequately measured or accounted for in the index but that nonetheless predict both increased campylobacteriosis rates and increases in other adverse health effects.

The Helms/Molbak article's description of statistical methods on page 1 of 5 is virtually identical to Molbak's testimony paragraph 37, which Bayer moved to strike because the description of statistical methods was inadequate and calls into question Molbak's expertise in statistics. As with the testimony, the paper offers no reason why Helms/Molbak "excluded diagnostic groups with relative mortality rates less than 1.2." (G-1799, P. 1-2). Of course, one way to increase the apparent size of relative mortality rates is to omit all those that are small, but this should perhaps not be characterized as a "statistical method".

As is also pointed out in Bayer's Motion to Strike, Helms'/Molbak's method by which they "forced this index into the survival analyses, so that any difference between the relative mortality of patients and the general population quantified mortality beyond what is attributable to underlying illness" is unproven speculation. Helms/Molbak have not demonstrated that comparing sick, or even terminally sick, people (campylobacteriosis patients, disproportionately many of whom already had AIDS or cancer as shown in Table 1 of the Helms/Molbak paper) to well controls, and then attributing any differences in their future health to *Campylobacter* after

conditioning on the co-morbidity index, has any validity whatsoever. In the absence of such validation, the Helms/Molbak method remains purely speculative.

The Helms/Molbak article G-1799 inverts the medically obvious causal logic to conclude that *Campylobacter* causes AIDS-related and cancer-related deaths rather than recognizing that AIDS and cancer compromise immunity and lead to increased campylobacteriosis as well as to increased mortality. The study does not offer any evidence of a causal relation between campylobacteriosis illness and increased mortality or morbidity rates.

The Helms/Molbak article states that they use a conditional proportional hazards regression. (G-1799, P. 2). However, no justification has been given for this model. The proportional hazards model can give incorrect and biased results in the presence of missing data, errors in the recorded values of the explanatory variables, missing confounders and covariates, and other realistic conditions. Helms/Molbak do not discuss these issues or offer any justification for ignoring them. The extent to which the results of the proportional hazards model have been biased by not accounting for missing covariates (e.g., immune status indicators, cooking habits) and other limitations in the data cannot be estimated.

Helms/Molbak use administrative data rather than medical record review; this is not an accurate substitute for an actual medical record review. Medical records give a more complete view of the patients' medical conditions to allow for a better adjustment of co-morbidity. Moreover, comparing patients to the general population may involve many uncontrolled confounders (e.g., cases may have been more likely to have had compromised immunity, unhealthy lifestyles or other risk factors predisposing them to both increased risk of campylobacteriosis and increased risks of other illnesses). The analysis of morbidity and mortality also did not identify specific endpoints. Additionally, and significantly, Helms/Molbak

do not establish a clear definition of a "case" at the outset, so as to ensure that the endpoints selected were meaningful.

The Helms/Molbak Cohort May Include Non-poultry Infections Such As Serious *C. Fetus* Infections

Helms/Molbak Exhibit G-1799 refers to the genus *Campylobacter* broadly but does not examine the species of *Campylobacter* at the root of the morbidity or mortality. To the extent that the relationship between *Campylobacter* infections and increased mortality that Helms/Molbak claim to see relates to non-*C. jejuni* or non-*C. coli Campylobacter* infections, the article is irrelevant. The name *Campylobacter* refers to *Campylobacter* of all species and would necessarily include not only *C. jejuni* and *C. coli* but also *C. fetus*. *C. fetus* causes serious systemic and septicemic disease in humans but is not a zoonatic pathogen from poultry. The fact that the Helms/Molbak research does not correct for diseases that may be caused by the far more serious enteric pathogen *Campylobacter fetus*, which does not come from poultry, but can impact morbidity and mortality, underscores the article's unreliability and irrelevance.

Helms/Molbak Exhibit G-1799 Is Not Relevant

The Helms/Molbak Exhibit G-1799 refers to morbidity and mortality in patients infected with all species of *Campylobacter*, from all sources, in *Denmark*. The focus of this hearing, on the other hand, is fluoroquinolone-resistant *Campylobacter jejuni* or *coli* from chickens or turkeys that may be causing infections in the *United States*. As such, Exhibit G-1799 is not relevant. Molbak's patients very well may have had non-poultry and non *C. jejuni* or *C. coli* infections which render his study irrelevant to the issues here. Moreover, there is no evidence in the Helms/Molbak article that the strains of *Campylobacter* in Denmark are the same as in the U.S. Finally, the Helms/Molbak article has nothing to do with health effects from fluoroquinolone-resistant *Campylobacter*.

CONCLUSION

The Helms/Molbak Exhibit G-1799 does not meet the standards for admissibility in this proceeding. Comments from the medical community (acknowledged by the authors) question the reliability of the effect between campylobacteriosis and increased mortality purportedly shown by Helms/Molbak. The differences between the Helms/Molbak parameters (Danish citizens ill with all species of *Campylobacter* from all sources) and the issues of this hearing (U.S. citizens ill with *Campylobacter jejuni* or *coli* from poultry) are such that the Helms/Molbak article is not relevant. If, however, G-1799 is admitted into evidence, the comments to G-1799 as set forth in B-1922 should also be entered into the Docket and evidentiary record.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of Bayer's Opposition to CVM's Motion to Enter Exhibit G-1799 into the Evidentiary Record was sent via Federal Express this 28th day of February, 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 sent via Federal Express and e-mailed this 28th day of February, 2003 to:

The Office of the Administrative Law Judge
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I also certify that a copy of the foregoing Opposition was sent via Federal Express and e-mailed this 28th day of February, 2003 to:

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