

**Agriculture Division**

Animal Health

**John B. Payne**  
Senior Vice President

January 8, 2002

BY MESSENGER

Dr. Stephen F. Sundlof (HFV-1)  
Director, Center for Veterinary Medicine  
Food and Drug Administration  
Metro Park North 2, Room 482  
7500 Standish Place  
Rockville, MD 20855

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Dear Dr. Sundlof:

I refer you to the proposal by the Center for Veterinary Medicine ("CVM") to withdraw the approval of enrofloxacin for poultry (marketed under the tradename Baytril 3.23% Concentrate Antimicrobial Solution) by issuing a Notice of Opportunity for Hearing ("NOOH") on October 31, 2000. 65 Fed. Reg. 64,954 (October 31, 2000), (corrected by) 66 Fed. Reg. 6623 (January 22, 2001). I also refer you to Bayer's response to the NOOH in the form of a Submission of Facts, Information and Analysis submitted to Docket No. 00N-1571 (Enrofloxacin for Poultry; Opportunity for Hearing) on February 21, 2001 ("Bayer Submission"). The Bayer Submission contained a thorough analysis of all pertinent information available to Bayer at that time. Bayer concluded that the data do not support the Agency's conclusion that the use of enrofloxacin in poultry is leading to reduced effectiveness of fluoroquinolones in treating human *Campylobacter* infections. Based on our analysis, Bayer requested the Agency to withdraw the NOOH. Bayer Submission at 20.

In the 10 months that have ensued since the Bayer Submission, significant new data have become available from the Centers for Disease Control and Prevention ("CDC") which reinforce our conclusion. I am writing to you now to share this information with CVM for its consideration.

CVM's decision to issue the NOOH was based, for the most part, out of concern for a reported increase in fluoroquinolone resistant *Campylobacter jejuni* isolated from humans. See 65 Fed. Reg. at 64,954. This purported increase was observed in the National Antimicrobial Resistance Monitoring System ("NARMS") for 1999 which reported 17.6% resistance compared to 12.9% in 1997 and 13.1% in 1998. The implication drawn by the Agency was that this increase was related to the use of Baytril in poultry notwithstanding that NARMS also reported lower and stable levels of fluoroquinolone resistant *Campylobacter jejuni* for isolates from chickens for the same period of time (9.4% for 1998 and 9.3% for 1999). Ibid.

**00N-1571**

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Bayer Corporation  
P.O. Box 390  
Shawnee Mission, KS 66201-0390  
Phone: 913 268-2750  
Fax: 913 268-2855

This information, of course, is not new and was discussed in the Bayer Submission. Bayer Submission at 5-7. What is new, are the results for human isolates from the 2000 NARMS data set.<sup>1</sup> This information is important in determining if the 1999 data really did signal the beginning of an increasing trend in resistance or simply reflected a blip in the data. The 2000 data set, according to our calculations, shows a resistance level of 14.3% (43 resistant isolates out of a total of 300). A Chi-square analysis of the 2000 vs. the 1997 data shows no significant difference in the results between the two years with a p-value of 0.11. This provides strong evidence that results for 1999 do not represent a trend of increasing resistance and that during the first four years of Baytril use in poultry, there has been no impact on the *Campylobacter* resistance levels observed in humans (Baytril was approved for use in poultry in October of 1996).

I want to emphasize that a final report for the 2000 NARMS data is not yet available from CDC. What we have are preliminary data acquired on October 16, 2001, representing four quarters for NARMS 2000. Bayer obtained these data through a request made under FOIA. The data set is attached for your information and review. ("Exhibit 1.") The 2000 data were obtained after considerable effort involving many contacts with CDC in which we requested release of the data. Bayer filed a request for the final NARMS 2000 report some time ago, but have received no additional data from CDC since October 16, 2001.

As important as these new data might be, the more significant issue is the risk of people becoming infected with a resistant *Campylobacter* and the potential impact on public health. Additional CDC data are now available on the incidence of diagnosed infections with *Campylobacter* (for both resistant and susceptible isolates) for the year 2000. CDC, "Morbidity and Mortality Weekly Report," April 6, 2001/V.50/13. ("Exhibit 2.") The incidence rate reported was 15.7 people infected with *Campylobacter* per 100,000 population. This is down from 24.7 people per 100,000 in 1997. CDC, "Morbidity and Mortality Weekly Report," September 25, 1998/ 47 (37); 782. ("Exhibit 3.") This represents a reduction of 36% and confirms the trend reported in the Bayer Submission. Bayer Submission at 12-13. If, one then takes the NARMS data for those same years, it is easy to calculate the risk for resistant *Campylobacter* infections ( $12.9\% \times 24.7 = 3.2$  people per 100,000 in 1997 vs.  $14.3\% \times 15.7 = 2.2$  people per 100,000 in 2000, a 30% reduction). In other words, these data indicate that from 1997-2000, the period of time when the vast majority of Baytril use in poultry occurred, the risk to Americans of acquiring a fluoroquinolone resistant *Campylobacter* infection has actually decreased by 30%. CVM's risk assessment did not project this 30 % reduction in the population at risk of *Campylobacter* infections with fluoroquinolone resistant isolates, but instead postulated an increase. This further calls into question the validity of the assumptions that drive the model's risk estimates.

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<sup>1</sup> The Bayer Submission contained preliminary data for the first two quarters from NARMS 2000. Bayer Submission at 5-6. Those data, obtained by Bayer from CDC under the Freedom of Information Act ("FOIA"), "suggest that the human fluoroquinolone rate is not increasing compared to 1999." Bayer Submission at 5. The "new" data presented in this letter represent the preliminary data set for the four quarters of NARMS 2000.

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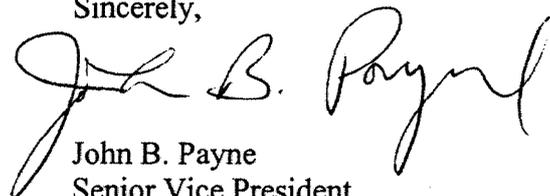
Unfortunately, data on human *Campylobacter* isolates were not collected by the NARMS program prior to 1997, therefore, a valid baseline for comparison of resistance levels before the approval of fluoroquinolones, does not exist. However, as presented in the Bayer Submission, resistance levels of 12% were reported as early as 1992-1995 in Wisconsin (Kiehlbauch, 1996) and 6% resistance was observed in Minnesota in 1995 (Smith, 1999). Bayer Submission at 8.

These resistance levels, prior to the commercial use of fluoroquinolones in poultry, are not surprising since it has been well known for many years that resistant *Campylobacter* emerge rapidly following exposure to fluoroquinolones. Reports began to appear as early as 1987 of resistance in isolates from humans receiving fluoroquinolone therapy. This phenomenon was attributed to a one step mutation leading directly to resistance. About a dozen reports on this issue appeared in the literature between 1987 and 1995. For example, *see*, M. Altwegg et. al, "Problems in Identification of *Campylobacter jejuni* Associated with Acquisition of Resistance to Nalidixic Acid, Journal of Clinical Microbiology, Sept, 1987, p. 1807-808." ("Exhibit 4.") The same observation was also made by Jacobs-Reitsma in chickens artificially infected with *Campylobacter*. 65 Fed. Reg. at 64,957. She was able to induce 100% resistance with fluoroquinolone therapy and reported these findings in 1994. The Jacobs-Reitsma paper was reported to CVM prior to the approval of Baytril for poultry. (A copy of Bayer's 1996 submission to the Baytril INAD is attached for your convenience. "Exhibit 5.")

In addition to the extensive domestic use of fluoroquinolones in human medicine for more than a decade, it is important to consider reports suggesting that the majority of the resistant *Campylobacter* infections observed in the U.S. are associated with foreign travel. Minnesota has reported 70% of the resistance they observed was associated with foreign travel, primarily travel to Mexico, or prior fluoroquinolone use (Smith, 1999). Bayer Submission at 12-13. Knowledge of these facts needs to be considered when CVM evaluates the levels of resistance observed in the data collected by NARMS, as the NARMS reports do not segregate domestically acquired resistance from that associated with foreign travel.

When consideration is given to these new findings, and this information is incorporated with the assessment in the Bayer Submission, we can only come to one conclusion. The concerns expressed in the NOOH are not supported by available data and removal of the product from the market would have no measurable impact on resistant *Campylobacter* infections in humans. Bayer therefore respectfully renews its request that the NOOH be withdrawn.

Sincerely,



John B. Payne  
Senior Vice President  
Bayer Corporation  
Animal Health

cc: Docket No. 00N-1571  
Bernard A. Schwetz, Acting Principal Deputy Commissioner (FDA)  
Daniel Troy, General Counsel (FDA)  
Robert B. Nicholas, Outside Regulatory Counsel/Bayer (McDermott, Will & Emery)