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

In the Matter of:	**FDA DOCKET: 00N-1571**
	DATE: August 15, 2003
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	

Center for Veterinary Medicine's Reply to Animal Health Institute's Post-Hearing Brief in the Matter of Enrofloxacin for Poultry: Withdrawal of Approval of New Animal Drug Application (NADA) 140-828 (Baytril)

I. Introduction

On July 18, 2003, the parties, Center for Veterinary Medicine ("CVM" or "the Center") and Bayer Corporation ("Bayer"), and non-party participant Animal Health Institute ("AHI") submitted initial post-hearing briefs on the issues of hearing for the above-captioned case. This reply brief addresses AHI's initial post-hearing brief.

II. Legal Standards, Applicable Burdens, and Evidentiary Standards

A. CVM Presented "New" Evidence

As shown by the evidence presented by CVM, CVM has met its burden to present new evidence. CVM Br. P3-6, 9-11. Taken together with evidence available at the time enrofloxacin (or "Baytril") was approved, this new evidence presents a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred.

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In AHI's view "new" evidence must be: evidence that points to a different conclusion that was not contained in the original application; evidence that points to a different conclusion that was not available at the time of the original application; tests by methods that were developed since the time of the original application; or, tests by methods otherwise available at the time of the application but not deemed reasonably applicable at the time. AHI Br. P2-4.

CVM disagrees. AHI's interpretation of the first two statutory factors in 21 U.S.C. §360b(e)(1)(B) ("new evidence not contained in the application or not available to the Secretary until after such application was approved") as requiring the evidence to point to a different conclusion ignores that additional evidence confirming earlier data can assist in the re-examination of the previously available information and give regulators more confidence in the results of that information. In this way, the "new" evidence serves to add weight to the earlier evidence and allows a more informed determination to be made, based on the weight of all existing evidence.

AHI cites two cases, Upjohn Co. v. Finch, 422 F.2d 944 (6th Cir. 1970), and Hess & Clark v. FDA, 495 F.2d 975 (D.C. Cir. 1974) in support of its interpretation. A review of these decisions, however, does not support AHI's argument. Upjohn concerned a review of an order of the Commissioner of Food and Drugs that revoked certificates of safety and effectiveness previously issued for several fixed combination antibiotic drugs, and a denial of an evidentiary hearing request on this matter. Upjohn, 422 F.2d at 949. The Court never reached the issue here: i.e., that new evidence must point to a different conclusion than was available at the time an application was approved. Upjohn argued that "FDA could not . . . remove its products . . . because FDA had no new information or

evidence with respect to the drugs in question at the time the certifications were revoked." Upjohn, 422 F.2d at 951. The Court, however, found that the record demonstrated the contrary -- there was new information -- therefore it never reached this issue. Further, AHI's reliance on the Hess & Clark decision for the proposition that only evidence that would point to a different conclusion could be considered new is unwarranted. Nowhere does Hess & Clark state or imply this interpretation. Moreover, case law supports CVM's interpretation. See CVM Br. P5-6.

CVM also believes that it would have been well within its authority to look at data that only existed prior to the approval of Baytril if it determined that the chronologically "old" data could lead to a different conclusion today than was reached at the time the new animal drug application ("NADA") for Baytril was approved. See Bell v. Goddard, 366 F. 2d 177, 181 (7th Cir. 1966). This dispute in interpretation, however, is not now ripe for review because, in the case of Baytril, there is new evidence not contained in the Baytril application or available to CVM at the time of the Baytril approval, and tests by new methods, which do exist to present a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred. See CVM Br. P9-11; CVM's reply to Bayer Br. P2-5. Despite AHI's listing of articles published prior to the approval of Baytril (AHI Br. App. A), there can be no dispute about the "newness" of many significant studies and data that add to the scientific weight of CVM's re-evaluation of the safety of Baytril. These studies present either wholly new data or give additional weight to the results of earlier studies. A more detailed discussion of new evidence, as applied to the evidence on selection pressure, transfer of FQ-resistant

Campylobacter from poultry to humans, and human health impact of FQ-resistant *Campylobacter* from poultry, is included in CVM's reply to Bayer's brief.

B. Serious Questions Exist From Which the Safety of Baytril May Be Inferred

In its initial brief, AHI argues that, in order to meet CVM's burden to present evidence from which serious questions about the safety of Baytril may be inferred, CVM must raise these safety questions about the drug under approved conditions of use. This, AHI claims, means foreign studies are irrelevant or are entitled to little weight "as CVM has not shown that the conditions of use (e.g., dosage and amount of administration) abroad are the same as in the U.S." AHI Br. P5. The studies conducted in Spain that AHI cites are indeed relevant. These studies are an excellent example of the selection for, and emergence and dissemination of, FQ-resistant *Campylobacter* from the use of enrofloxacin in poultry, and demonstrate clearly the direct relationship between the use of the drug in poultry and the high level of FQ resistance observed. The fact that Baytril is used more prudently in the United States and FQ resistance is still being observed in elevated levels in poultry, retail poultry meat, and humans, is itself a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred.

Moreover, AHI's argument that the results of foreign studies deserve little or no weight because they do not take into consideration other variables, such as contamination of the water supply, is speculative. Even if, as AHI speculates, *Campylobacter* contamination of the water supply in other countries is an issue (which has not been shown in the evidentiary record), there is no basis to believe any widespread FQ-resistant *Campylobacter* contamination could be present in the absence of the selection pressure of

enrofloxacin. WDT G-1465: P6, L9-11. Other so-called "variables" (which AHI does not even attempt to identify) are equally speculative.

It is also noteworthy that AHI's interpretation of CVM's burden in this hearing would effectively convert CVM's burden to adduce evidence into a burden of proof. The statute and regulations clearly provide that the burden of proof remains with the sponsor throughout the life of the drug, from application through any withdrawal proceeding. 21 U.S.C. §360b(e)(1)(B); 21 C.F.R. §12.87(d). CVM does not have to prove that the drug is unsafe. CVM's burden is only to present enough evidence to raise serious questions about the safety of Baytril's use in poultry. This view is not novel.

CVM's burden is clear: it need only present evidence from which serious questions may be inferred. There can be no question that CVM met this burden in this proceeding. CVM has presented an enormous amount of data and information, both pre- and post-approval, in the form of molecular and other microbiological studies and epidemiological studies, along with expert testimony, which serve as the basis to question the safety of Baytril.

C. The Risk to Humans of Baytril Use in Poultry Exceeds its Benefits

CVM has fully addressed the question of risk / benefit in its reply to Bayer's brief. See CVM's reply to Bayer Br. P36-43. In summary, Bayer has only offered evidence of one benefit from the use of Baytril and that evidence is not credible. The data upon which the benefit analysis is based are faulty. See CVM Br. P76-77; CVM's reply to Bayer Br. P36-37. Further, and fully addressed by CVM, Cox's mathematical model is designed to overstate the risks of withdrawal of Baytril. See CVM's reply to Bayer Br. P41-43.

As explained elsewhere, any benefit associated with the use of Baytril must be discounted by the availability of other alternatives to Baytril and to changes in the slaughter process which would reduce contamination of carcasses with fecal matter.

D. CVM's Evidence is Reliable

1. Daubert v. Merrell Dow Pharms., Inc.

The evidence presented by CVM during this process is reliable. AHI rehashes arguments which have already been briefed, citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993). However, as CVM stated in its Response to Bayer's Motion to Strike (February 9, 2003): P2-3:

> Bayer puts forward an argument that some of the data introduced by CVM is not reliable, citing Daubert, *infra*, and its progeny. However, it is clear from a reading of these cases that the evidence submitted by CVM meets the Daubert standards for relevance and reliability. The evidence will assist the Administrative Law Judge, as trier of fact, to understand or determine a fact in issue, and is relevant. The evidence is also reliable under a Daubert type evaluation of the evidence using some of the factors suggested by the Daubert Court along with other factors which the Administrative Law Judge should consider appropriate to evaluate in this case. The factors enumerated by Daubert are not binding or exclusive. "But, as the Court stated in *Daubert*, the test of reliability is "flexible," and *Dabuert's* list of specific factors neither necessarily or exclusively applies to all experts or in every case. Rather, the law grants a district court the same broad latitude when it decides *how* to determine reliability as it enjoys in respect to its ultimate reliability determination." Kumho Tire Co., v. Carmichael, 526 U.S. 143, at pp. 141-142 (1999) citing General Electric Co., v. Joiner, 522 U.S. 136 (1997).

It is noteworthy that virtually all of the data CVM presented in this hearing were generated apart from the hearing process (i.e., independent of the litigation), that the data in question have been developed in an open and transparent process, and that the methodologies used to generate these data have been generally accepted within the

relevant scientific community. CVM's Response to Bayer's Motion to Strike (Feb. 9, 2003): P3-4.

Likewise, AHI's claims regarding the reliability of the epidemiological studies relied upon by CVM are without merit. AHI Br. P8-11. Specific issues concerning the validity of the epidemiological studies have been fully briefed by CVM. See CVM's reply to Bayer Br. P10-26.

2. FDA Guidelines for Ensuring the Quality of Information Disseminated to the Public ("FDA Guidelines")

AHI's arguments (AHI Br. P11-13) based on the FDA Guidelines are again simply a rehash of its earlier arguments in its Motion to Strike. See Bayer's and AHI's Motion to Strike (Jan. 27, 2003). As shown below, CVM has met the requirements of the FDA Guidelines.

a. CVM's Risk Assessment Complies with FDA's Guidelines

AHI believes that CVM's risk assessment does not comply with the FDA Guidelines for four reasons. AHI Br. P14. AHI is mistaken.

First, AHI complains that CVM did not use the best available science and supporting studies (AHI Br. P14) and that CVM's risk assessment model has not been published in a peer review journal, AHI Br. P27. But CVM's risk assessment did in fact use the best available science and supporting studies. See WDT G-1480: P6, L40-42; WDT G-1454: P14, L25-26. As discussed in CVM's initial brief, the Harris and Deming case-control studies provided the best, supportable attributable fractions at the time CVM conducted its risk assessment. See CVM Br. P68. Contrary to AHI's assertions, CVM's risk assessment applied sound, objective scientific practices. Although CVM's risk assessment model has not been published in a peer reviewed journal, the studies that

CVM relied on in developing its risk assessment, and which form the basis for that assessment, were peer reviewed. This is all that the FDA Guidelines require. See FDA Guidelines, Sec. VII(C)(1)(a). Additionally, the CVM's risk assessment model went through a more rigorous review than the review that usually occurs during peer review for a journal. See WDT G-1480: P6, L25-34. CVM's risk assessment model was subject to scrutiny by the public and scientific experts, which is, after all, the goal of peer review. WDT G-1480: P6, L30-33; CVM Br. P69. Draft versions of CVM's risk assessment model were made public so that the anyone could comment on it. WDT G-1480: P6, L26-28; CVM Br. P69. CVM also invited several world experts to review its risk assessment and present their conclusions in a public forum. See WDT G-1480: P6, L30-33; CVM Br. P69, P74; Ex. G-1810. Additionally, at CVM's request , Dr. Cox reviewed CVM's risk assessment model and he initially agreed with the model. Tr. P871, L20 - P873, L10.

Second, AHI complains that CVM used data not collected by accepted methods. AHI Br. P14. But as discussed in CVM's initial brief, the data used in CVM's risk assessment were robust. CVM Br. P67-69. CVM's risk assessment used data compiled by federal agencies, such as CDC and USDA, and these were not compiled for the hearing, or any regulatory action with respect to specific drug products. CVM Br. P67-68. Ironically, AHI's and Bayer's experts use the same sources of data to form the bases of their opinions in this hearing. See AHI Br. P15; WDT B-1900: P2, L25-36, P25-40; WDT A-200: P22-23, P62; WDT B-1901: P57-60; Ex. B-1020: P17. Surely, AHI's concerns regarding the data CVM used in its risk assessment cannot be legitimate.

Third, AHI argues that CVM did not identify, use, or explain why additional studies not used to produce the risk estimate were not used. AHI Br. P14. In particular, AHI argues that CVM relied on the Harris and Deming case-control studies instead of the Effler study or the CDC data analyzed by Friedman. AHI Br. P27. CVM's final risk assessment report was published in January 2001. CVM Br. P61. At the time CVM's risk assessment was conducted, Friedman's analysis of the CDC data had not been completed and Effler's data had not been published. To date, Friedman's analysis has not been published in a final form. Friedman's "preliminary" analysis was published by CDC in July 2000, Ex. G-228, and in "draft" form, Ex. G-1488. Effler's study was not published until February 2001, Ex. G-185, which is clearly after CVM's final risk assessment was published. Since neither Friedman's analysis of the CDC data, nor Effler's study, had been completed prior to CVM publishing its risk assessment report, CVM could not use those data in its report. AHI also argues that CVM should have modified its risk assessment based on the CDC data. AHI Br. P27. CVM's risk assessment acknowledged that a study of the CDC data was underway and that the data would provide updated risk factor information. Ex. G-953: P103. CVM reviewed the draft results produced by Friedman which found an attributable fraction of 28% for poultry meats consumed at a restaurant. Since CVM determined Friedman's results to be consistent with the estimates of attributable risk fractions from the Harris and Deming studies, there was no need to revise its model. See CVM's reply to Bayer Br. P33-35. CVM's risk assessment remains reliable.

Fourth, AHI contends that CVM did not follow the approach for quantitative risk assessment set forth in the Safe Drinking Water Act ("SDWA"). AHI Br. P14. AHI is

correct. CVM followed FDA's approach for quantitative risk assessment in accordance with FDA Guidelines. AHI mistakenly asserts that "the FDA Guidelines *adopt* as standards for quantitative risk assessment the approach set forth in the Safe Drinking Water Act." AHI Br. P13 (emphasis added). As noted by AHI, the Office of Management and Budget issued Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies ("OMB Guidelines"). See OMB Guidelines, 67 Fed. Reg. 8452 (Feb. 22, 2002); AHI Br. P11. The OMB Guidelines provide that "agencies shall either *adopt or adapt* the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996. The word 'adapt' is intended to provide agencies flexibility in applying these principles to various types of risk assessment." OMB Guidelines, 67 Fed. Reg. at 8458 (citations omitted) (emphasis added). In accordance with OMB Guidelines, and contrary to AHI's belief, FDA Guidelines *adapted* the general principles for risk assessment from the SDWA and set forth the principles FDA intends to apply for quantitative risk assessments. See http://www.hhs.gov/infoquality/fda.html; see also Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by HHS Agencies, 67 Fed. Reg. 61,343 (Sept. 30, 2002). As discussed above, CVM's risk assessment does indeed comply with FDA Guidelines.

b. The NAS/NRC Risk Assessment Guidelines are Not Required Or Appropriate

AHI contends that CVM's risk assessment is not scientifically reliable because it does not follow the National Academy of Sciences ("NAS") paradigm as produced by the National Research Council ("NRC"). AHI Br. P16-26. But CVM's risk assessment does

not have to follow the NRC guidelines because they are not necessary for developing a scientifically sound antimicrobial risk assessment. The NRC guidelines are just that – guidelines; they are not standards that must be followed. As noted by the NRC:

> The committee stresses to the readers of this report our conviction that *no set of guidelines or procedures can ever substitute for scientific rigor, fairness, and flexibility in coping with dynamic risk situations*. Yet we do hope our findings and recommendations will aid those of good will to make sounder decisions about risk.

http://books.nap.edu/books/030905396X/html/R12.html#pagetop (emphasis added). Although the NRC guidelines can aid in the development of a risk assessment, they are not essential to developing one. As discussed in CVM's initial brief, there is no single way to conduct a risk assessment. CVM Br. P63. Furthermore, the NRC also notes that: "Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing and analyzing scientific knowledge and information for potentially hazardous activities or for substances that might pose risks under specified conditions." http://books.nap.edu/books/030904894X/html/4.html#page_bottom. Notwithstanding this, to the extent that some aspects of the approach may have been relevant, CVM followed the NRC guidelines to aid in the development of CVM's risk assessment. See CVM's Response to Bayer's Interrog. 46-50 (June 24, 2002).

More importantly, the NRC guidelines that AHI argues should be followed by CVM pertain to chemical risk analysis rather than microbial risk analysis, to which CVM's risk assessment clearly relates. Had AHI read the paragraphs preceding its references to the NRC report, see AHI Br. P16, the inapplicability of the NRC guidelines to CVM's risk assessment would have been clear. The NRC provides the following context for its guidelines:

> *Chemical hazards* come in many forms. Some substances are radioactive, some explosive, some highly flammable. The particular hazard of concern here is *chemical toxicity*, including but not limited to *carcinogenicity*. Risk assessments can be carried out for any form of *chemical toxicity*. Risk assessment can be qualitative or quantitative. Many of the issues covered in this report concern quantitative expressions of risk.

http://books.nap.edu/books/030904894X/html/26.html#pagetop (emphasis added). The distinction between chemical risk analysis and microbial (or in this case antimicrobial resistance) risk analysis is extremely important. In chemical risk analysis, exposures are typically long-term via various routes (for example, skin exposure, inhalation, and ingestion). There can also be many sources of a chemical, or combinations of chemicals, that lead to the adverse health effect (usually cancer). In a chemical risk assessment, unlike microbial risk analysis, the exposure that caused the illness is almost never known. In CVM's antimicrobial resistance risk assessment, the source, however, of the exposure is known. For campylobacteriosis, the agent is, by definition, *Campylobacter*, and the agent for FQ-resistant campylobacteriosis is FQ-resistant *Campylobacter*. As discussed in CVM's initial brief, poultry is a significant risk factor for acquiring campylobacteriosis. See CVM Br. P24-52. FQ-resistant *Campylobacter* infections in humans stem from people eating poultry contaminated with FQ-resistant *Campylobacter*. Id.

E. AHI and Bayer Overstate the Importance of So-Called "Non-Controverted" Evidence

Throughout their respective post-hearing briefs, AHI and Bayer imply that, if CVM has not introduced any evidence to controvert Bayer or AHI sponsored testimony or exhibits, then that evidence should blindly be considered credible. However, there are many examples where there is no need to present conflicting evidence because the AHI

or Bayer sponsored testimony and/or exhibits controvert themselves. An excellent example of this is Patterson's written direct testimony. See CVM Br. P72-73. Another example is Russell's study, B-1912, Attach. 1. See CVM Br. P76-77. Other examples are abundant, including Dr. Glisson's study, referenced by Bayer Br. P81. Glisson only studied two other medications in addition to enrofloxacin, in one geographic location, during a limited (3 week) period of time. See WDT B-1903: P9, L3 - P11, L2; P15-16. A general conclusion from this study that Baytril is the only effective medication is inappropriate, not to mention immaterial to the issue of safety of Baytril. See CVM Br. P77.

Another example of so-called "uncontroverted" evidence is Dr. Burkhart's implication that Smith's case-comparison study is flawed because its analysis did not include 1998 data. WDT B-1903: P17, L18-22. However, as explained in Dr. Smith's published article, quinolone-susceptible cases (the comparison group) were matched with quinolone-resistant cases (the case group) for *Campylobacter jejuni* infections occurring during the period from 1996 through 1997. Ex. G-589: P2 Therefore, there was no comparison group for the quinolone-resistant cases in 1998 so including them in the case-comparison study was not possible. Further, Dr. Burkhart's questioning of the use of a 10-day window when asking about foreign travel in the Smith questionnaire is without merit. There is no evidence that the incubation period of *Campylobacter* is more than 10 days. See WDT G-1470: P2, L35-37; WDT G-1475: P3, L15-16. Thus, Dr. Burkhart's testimony actually calls into question his own knowledge and understanding of *Campylobacter*, rather than impeaching Dr. Smith's testimony or undermining the credibility of his study.

These are just a few of many examples where Bayer and/or AHI witnesses effectively rebut their own testimony. It would have been superfluous to present even more evidence for each of these pieces of evidence, as each is easily rebutted by reference to other information on the evidentiary record. Most importantly, however, is that AHI's and Bayer's incorrect assumption of absolute credibility would usurp the authority of the Administrative Law Judge, whose role is to evaluate the evidence, and the credibility of that evidence, in deciding its weight.

F. SDWA Maximum Contaminant Level Guidelines and the Risk Identified by CVM's Risk Assessment Are Not Comparable

AHI's argument that the risk identified by CVM's risk assessment is lower than that allowed for bottled drinking water is immaterial. The question here is not the safety of bottled drinking water but the safety of a new animal drug, i.e., whether there is a reasonable certainty of no harm from the use of the drug. With respect to the regulation of bottled drinking water, FDA effectively "borrows" the maximum contaminant level ("MCL") limits set out in the national primary drinking water standards by the Environmental Protection Agency ("EPA"). In short, if EPA sets a MCL, FDA must either accept that MCL (or treatment technique if no specific limit is set) or set a more stringent standard. If FDA fails to promulgate such a regulation, EPA's MCL (or level of protection achieved by a treatment technique) is deemed required as a bottled water standard. See 21 U.S.C. §349.

Although both the SDWA and the Federal Food, Drug, and Cosmetic Act ("Act") are public health statutes, they have different statutory authority and standards. Under the SDWA, EPA sets unenforceable goals called Maximum Contaminant Level Goals (MCLGs). 42 U.S.C. §300g-1(a)(3). Then, EPA looks at these goals when it sets its

MCLs, which are enforceable limits for contaminants in drinking water. The MCL is supposed to be as close to the MCLG as feasible. 42 U.S.C. §300g-1(b)(4)(B). EPA defines feasible, in this respect, to include both costs and technological feasibility. 42 U.S.C. §300g-1(b)(4)(D). There is no similar requirement in the Act to consider costs in evaluating the safety of a new animal drug. See 21 U.S.C. §360b. In fact, as fully briefed in CVM's initial brief, costs of the regulation (in this case withdrawal) are not appropriately considered in a new animal drug withdrawal proceeding under the Act. See CVM Br. P8-9.

It is also inappropriate to compare naturally occurring bacteria -- which public drinking water facilities are required to reduce to a certain degree based not only on health but on economic factors as well -- to antimicrobial-resistant bacteria, in this case caused by the use of antimicrobials and that do not appear to any large degree without that selection pressure.

Finally, it should be stressed that Cox's analysis is incorrect with respect to the risks associated with FQ-resistant *Campylobacter,* and, therefore, the comparison AHI seeks to make between the risks associated with microbial contamination in bottled water and the risks associated with FQ-resistant campylobacteriosis from poultry is invalid. For example, Cox's utilization of a treatment failure range taken from Ex. B-50 and Ex. B-1920 (Piddock and Sanders, respectively) is inappropriate, see CVM's reply to Bayer Br. P28, and unfairly skews the results of the calculation in Table 1 of AHI's initial brief to fit an argument of relative risk.

III. There is a Reasonable Basis From Which Serious Questions About the Safety of Baytril Use In Turkeys May Be Inferred

AHI claims that CVM has not presented new evidence that raises a reasonable basis from which serious questions about the safety of enrofloxacin use in turkeys may be inferred. See AHI Br. P31-40. Notwithstanding AHI's faulty interpretation of "new," CVM has offered new evidence on turkeys which, when taken together with existing information available at the time of Baytril approval, presents a reasonable basis from which the safety of Baytril use in turkeys may be inferred. In the late 1990's, after Baytril was approved for use in turkeys, Dr. Logue conducted a large study at two turkey slaughterhouses in the mid-west in order to determine the prevalence of foodborne pathogens, including *Campylobacter* at slaughter. WDT G-1464: P2, L26-29. Dr. Logue also studied the antimicrobial susceptibility of these bacteria. WDT G-1464: P2, L29-30. These data must be considered "new" information. Further, Friedman's analysis of the 1998-1999 FoodNet case-control study contains new epidemiological findings with respect to turkeys. Ex. G-1488. Additionally, Fitzgerald's molecular typing study showing an association between *Campylobacter* strains from turkeys and humans is also new evidence, Ex. B-318, as are the data from the retail meat studies showing FQ-resistant *Campylobacter* on retail turkey, Ex. G-763.

If Baytril is withdrawn for use in chickens, it must also be withdrawn for use in turkeys. Both chickens and turkeys are colonized with *Campylobacter*, WDT G-1459: P2, L28-29, with some studies showing almost 100% of turkeys colonized with *Campylobacter*, Ex. G-686; WDT G-1459: P4, L9-11.

Further, there is no biological reason that Baytril's effect on *Campylobacter* in *Campylobacter*-colonized turkeys is any different than its effect on *Campylobacter* in

Campylobacter-colonized chickens. Although AHI argues that there is no evidence of selective pressure of Baytril in turkeys, a leading expert in the field of antimicrobial resistance disagrees. Dr. Levy testified:

> The emergence, selection, and mechanism of fluoroquinolone resistance in bacteria is characteristic of the bacterium and not the host animal in which resistance is selected. No one has demonstrated that the selection of a particular resistance mechanism depends on a particular host animal of the bacteria. What we observe in the selection of fluoroquinolone resistance in *Campylobacter* from chickens is what we would expect to see emerge in *Campylobacter* associated with people, turkey, cattle, pigs, and other animals when given fluoroquinolones.

WDT G-1463: P4, L9-16. Moreover, Bayer admits that Baytril is used in turkeys. Approximately 10,800,000 turkeys are directly treated with Baytril each year. See CVM Br. P15.

Although AHI argues that the processing of turkeys is different than that of chickens, and that most turkeys are further processed, AHI Br. P34, this does not explain away Dr. Logue's findings of *Campylobacter* and FQ-resistant *Campylobacter* in turkeys at the slaughterhouse, WDT G-1464: P5, L22- P6, L23, or the retail meat studies that show that FQ-resistant *Campylobacter* remain on turkeys after the slaughter process (see Ex. G-727; Ex. G-763). Although it is true that retail meat studies find a lower prevalence of *Campylobacter* in retail turkey than in retail chicken (i.e., Meng's finding that 70.7% of chicken contaminated with *Campylobacter* but only 14.5% of turkeys contaminated with *Campylobacter*, WDT G-1466: P2, L32-35), what AHI fails to acknowledge is that the prevalence of *Campylobacter* contamination in turkey is much higher than in other retail meat except chicken. Meng found only 1.7% of pork and 0.5% of beef contaminated with *Campylobacter*. WDT G-1484: P3, L13-15. Results from the

Iowa state study show only 1% of pork and no beef samples positive for *Campylobacter.* WDT G-1484: P7, L31-33. Further, preliminary data from the 2002 retail food arm of NARMS shows only 3% of ground beef and only 2% of pork chops positive for *Campylobacter.* WDT G-1484: P4, L13-15. Thus, it appears from these studies that turkey is second only to chicken in prevalence of *Campylobacter* on retail meat.

Additionally, epidemiological studies have shown that eating turkey is a risk factor for acquiring FQ-resistant *Campylobacter* infection. See Ex. G-1488: P10-11, P20-23; Ex. G-228: P1; Ex. G-337: P9-10. Interestingly, AHI does not even attempt to deny that turkey is a source of campylobacteriosis, but argues only that it is a "minor source."[1] AHI Br. P38. This argument is meaningless, however, because there is no requirement that CVM show that turkey is the only source of FQ-resistant *Campylobacter* or even a major source. The fact remains that turkey is a source of concern for FQ-resistant campylobacteriosis, and CVM has the authority and responsibility to address this source, which stems from the use of Baytril in turkeys.

AHI also argues that the risk assessment measures only the human health impact of FQ-resistant *Campylobacter* from chicken and not from turkey and that there is no support for CVM's proposal to withdraw the approval of Baytril use for turkeys. AHI Br. P40-41. This argument, too, lacks merit. CVM's risk assessment is simply a way to quantify the potential human health impact of FQ-resistant *Campylobacter* acquired from chicken. Even without the risk assessment, CVM has presented evidence that FQ-resistant *Campylobacter* infections in humans have the potential to adversely affect

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[1] CVM notes that AHI's characterization of the attributable risk associated with turkey consumption as "at most 4%" is incorrect. A more reasonable interpretation is that the attributable risk associated with turkey is at least 4% since this figure does not include other turkey-related sources, such as cross-contamination of other foods with *Campylobacter* from turkeys.

human health. The evidence presented in the hearing and summarized in CVM's initial brief provide a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry (both chickens and turkeys) may be inferred, apart from any risk assessment model results.

Finally, neither AHI nor Bayer has offered any human health benefit from the use of Baytril in turkeys. AHI's entire "benefit" argument with respect to turkeys is:

> Assuming only for the sake of argument that FDA's paradigm is correct, and that turkeys are identical to chickens with respect to the transfer of *Campylobacter*, then Bayer's evidence on the benefits of enrofloxacin use with respect to chickens would be equally applicable to turkeys, and this benefit would outweigh any potential harms. However, taking into account the significant differences between chickens and turkeys, it is apparent that the human health risks from turkey consumption are so de minimis as not to require any weighing of the benefits in order to conclude that enrofloxacin use in turkeys is safe.

AHI Br. P42-43.

CVM has already refuted Bayer's evidence on benefit, and therefore there is nothing left on which AHI can base its benefits argument with respect to turkeys. See CVM's reply to Bayer Br. P36-43. However, even if Bayer's argument with respect to benefits had any merit, Bayer and AHI witnesses have already disproved its applicability to turkeys since the claimed excess fecal contamination in the non-uniformly sized chickens is claimed to be a result of automated evisceration during slaughter. AHI Br. P34. As the evidence shows, and as AHI admits in its initial brief, the evisceration of turkeys is more frequently done manually. Id. Therefore, AHI effectively rebuts its own benefits argument. Furthermore, AHI's argument that the risks of Baytril use in turkeys are de minimis is without merit.

Although CVM has presented sufficient evidence from which the safety of Baytril use specifically in turkeys may be inferred, there is, nonetheless, precedent for withdrawing the approval of the drug in multiple species, even when the existing evidence is mainly from one species. In an evidentiary hearing held on the proposal to withdraw the NADA for DES, most of the evidence presented was with respect to DES in cattle. The Commissioner, however, ordered withdrawal of the NADA in both cattle and sheep, and the Court of Appeals upheld the Commissioner on this point. Rhone-Poulenc v. FDA, 636 F.2d 750, 753 (D.C. Cir. 1980).

IV. Conclusion

The evidentiary record of this hearing provides a reasonable basis from which serious questions about the safety of Baytril use in poultry can be inferred. CVM has met its burden to adduce this evidence and what it shows, shifting to Bayer the burden to demonstrate that the use of Baytril under the approved conditions of use in poultry has been shown to be safe. Bayer has not met its burden to show that the use of Baytril, under approved conditions of use in poultry, is safe.

Respectfully submitted:

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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 Reply to the Animal Health Institute's Post Hearing Brief was hand delivered this 15th day of August, 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 Reply Brief was hand delivered and e-mailed this 15th day of August, 2003, to:

The Office of the Administrative Law Judge
Food and Drug Administration
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I also certify that a copy of the Center for Veterinary Medicine's Reply Brief was mailed and e-mailed this 15th day of August, 2003, to:

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