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
New Animal Drug Application
NADA 140-828

FDA DOCKET: 00N-1571

Date: August 15, 2003

NON-PARTY PARTICIPANT ANIMAL HEALTH INSTITUTE'S REPLY TO CVM'S POST-HEARING BRIEF

Kent D. McClure, DVM, JD
Animal Health Institute
1325 G Street, NW Suite 700
Washington, DC 20005
(202) 637-2440 phone
(202) 637-1667 fax

Of Counsel:

Robert B. Nicholas
Gregory A. Krauss
M. Miller Baker
Jeffrey C. Bates
McDermott, Will & Emery
600 Thirteenth Street, N.W.
Washington, D.C. 20005
(202) 756-8000

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INTRODUCTION

This brief responds to CVM's Post-Hearing Brief ("CVM PHB") filed on July 18, 2003. The arguments in CVM's brief appear tailored to paint with a broad brush rather than to address in detail the substantive issues in this proceeding. CVM's brief first mischaracterizes CVM's burden by setting the bar too low and focusing on only a small portion of what CVM must actually prove. The remainder of the brief focuses on unreliable evidence that fails to satisfy CVM's burden, as well as on instances where CVM draws generalized conclusions from limited data, obscuring the weaknesses in CVM's evidence.

CVM estimates that out of 1.4 million cases of campylobacteriosis in the U.S. in 1999, only about 9,300, or about $^{2}/_{3}$ of 1 percent (0.0066), are chicken-related, FQ-resistant, and the cause for a visit to a physician at which a fluoroquinolone (FQ) is prescribed and, therefore, are potentially at risk of a treatment failure. [NOOH, 66 Fed. Reg. at 6623 (Jan. 22, 2001)]. This risk can be put into perspective once one understands that there are 8.6 billion chickens raised in the U.S. [RJS 43], which a quick but conservative calculation shows results in about 69 billion chicken meals consumed annually in the U.S.[1] These numbers illustrate a significant point: Most people eat chicken, but people rarely get campylobacteriosis. Even if one assumes that chicken is the source of all 1.4 million annual cases of campylobacteriosis (and none of the parties contends that it is), this represents 1 case of campylobacteriosis for approximately 49,000 chicken meals consumed. Using the same assumptions, a resistant case of campylobacteriosis would result in a potential for treatment failure only 1 in 455 *million* times (i.e., 69 billion multiplied by 0.0066) someone consumes a chicken meal—and, indeed, this is only a *potential*, as data demonstrate that most of these "potential" cases would actually respond to treatment with a FQ.

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[1] This calculation assumes that each chicken weighs only 4 four pounds on average and that a meal consists of ½ pound. These assumptions are very conservative. For example, if the average meal is only ¼ lb., the number of serving would be 137.6 billion servings.

I. CVM MISCHARACTERIZES ITS BURDEN OF PRODUCTION

As summarized below and discussed in Bayer's and AHI's Post-Hearing Briefs ("PHB"), CVM has failed to meet its burden of producing new evidence that provides a reasonable basis to raise a serious question about the safety of enrofloxacin.

A. A New Look at Old Evidence, Without More, Does Not Satisfy CVM's Burden

CVM initially argues that Section 512(e)(1)(B) does not require that wholly new information form the basis for a decision to withdraw approval of an NADA—a proposition that AHI and Bayer do not dispute. [CVM PHB P.5] As long as CVM has presented *some* new evidence, it may evaluate that evidence in connection with the old (i.e., pre-approval) evidence. This is made clear by the statute, which provides that the new evidence shall be "evaluated together with the evidence available to the Secretary when the application was approved." 21 U.S.C. § 360b(e)(1)(B).

CVM's brief, however, also suggests that it may be enough for CVM merely to re-analyze the "old" evidence, as CVM asserts that case law "suggests that a re-evaluation of evidence available before an NADA is approved could also meet the statutory requirement." [CVM PHB P.5] (citing *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966)). The *Bell* opinion does not support CVM's argument, however. Nowhere did the *Bell* court dispense with the requirement that the FDA produce "new" evidence in addition to what had been considered before. *Bell* turned on the court's holding that *an evaluation by new methods* (one of the categories of "new evidence" enumerated in the FFDCA) constituted "new evidence": "In this case an extensive re-evaluation which drew together clinical experience *in a manner not previously attempted* . . . provided the basis for the Commissioner's findings." *Bell*, 366 F.2d at 181 (emphasis supplied). The court also noted that "[t]he words 'clinical experience' must be held to include such experience *both prior and subsequent to* the effectiveness of the petitioner's application." *Id.* (emphasis supplied). The difference between *Bell* and CVM's argument is that in *Bell* there was something new—i.e., "tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved," 21 U.S.C. § 360b(e)(1)(B)—whereas CVM posits that it is enough for CVM simply to

go back and re-analyze what it knew before. What *Bell* actually says is what the FFDCA says—i.e., first the FDA must produce something new ("subsequent to the effectiveness"), and then, once it has done so, all of the evidence, old and new, may be evaluated together. Nothing in *Bell* supports the notion that CVM can satisfy its burden by simply recycling everything it knew pre-approval.

Notably, other case law supports the requirement that CVM must produce something new. Indeed, the Sixth Circuit later cited *Bell* for precisely the proposition that the new and old evidence must be construed *together*. As in *Bell*, the drug manufacturer asserted that there was no new evidence in the record. The court disagreed, noting that "[a] number of . . . documents in the record, including some of the data submitted by Upjohn, reflect information which became available after these drugs had been certified by [the] FDA . . . ." *Upjohn Co. v. Finch*, 422 F.2d 944, 951 (6th Cir. 1970). The court then noted that "[i]n *Bell v. Goddard*, a case in which [the] FDA conducted an evidentiary hearing, the Court held that in suspending a drug [the] FDA can consider 'clinical experience' occurring both prior to and subsequent to the application." *Id.* (citation omitted). The court concluded that, because the FDA had new evidence not available to it when the drug was first approved some thirteen years earlier, it was proper for the FDA to proceed to re-examine the old evidence *together with the new*. *Id.*

Based on the foregoing, Paragraph 6 of CVM's proposed conclusions of law must be rejected, as it does not comport with the statutory requirement.

B. For Evidence Truly to Be "New" Under the FFDCA Standard, It Must Be Substantively New, Not Merely Chronologically New

CVM's burden is to produce new evidence that shows a conclusion *different* from the conclusion shown by the old evidence. *See Hess & Clark v. FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974) (stating that section 360b(e)(1)(B) places on the FDA "an initial burden to adduce the 'new evidence' *and what it shows in terms of undermining the previous conclusions as to safety*") (emphasis supplied). Evidence that is merely *chronologically* new, but fails to show a conclusion different from the pre-approval evidence, is not new within the meaning of the statute, because it cannot "undermine[ ] the previous conclusion as to safety." *Id.* In 1996, the evidence before the

agency showed that enrofloxacin was safe under the approved conditions of use. [RJS 39] If CVM's *chronologically* new evidence merely reiterates the same conclusions as the old evidence, CVM fails to undermine the previous conclusion and therefore to carry its burden of raising a serious question about enrofloxacin's safety.

Importantly, new evidence that shows that enrofloxacin use is *less* of a risk now than was understood in 1996 cannot satisfy CVM's burden, because such evidence *supports* the FDA's prior conclusion that enrofloxacin was safe (and, if anything, indicates that it is *safer* than expected). By definition, new evidence that supports the prior conclusion cannot "undermine[ ] the previous conclusion as to safety." It is not enough simply to take new evidence that *confirms* the prior conclusion and then to revisit the prior conclusion under the theory that CVM now believes that it might have been mistaken. If that were the rule, the statutory requirement of new evidence would be a sham.[2]

C. CVM's Evidence Must Be Reliable

Another point overlooked in CVM's PHB is that the new evidence it produces must be reliable. As is explained in AHI's PHB, the Administrative Procedure Act and the relevant FDA regulations require that the evidence on which any final decision in this proceeding is made must be reliable. [AHI PHB P.7–8] When these statutes are read together with the FFDCA, it is apparent that CVM's *new* evidence must be reliable (as opposed to simply the *old* evidence being reliable), because the only way that *all* of the evidence, viewed together, can raise "serious questions" about enrofloxacin's safety, or otherwise undermine the FDA's prior conclusions as to enrofloxacin's safety, is if the new evidence provides a basis for doubting the accuracy of the prior conclusions. If the new evidence is unreliable, then under the APA and the FDA regulations it cannot be considered. If it cannot be considered, all that is left is the old evidence, and if only the old evidence is considered, CVM cannot satisfy its burden. In addition, CVM's evidence must provide

[2] Accordingly, CVM's proposed conclusion of law #5 should be rejected.

a "reasonable basis" for questioning enrofloxacin's safety. It is unreasonable to rely on unreliable evidence.[3]

II. CVM HAS FAILED TO CARRY ITS INITIAL BURDEN

A. CVM's Evidence Is Not New

CVM's mistaken position on whether its evidence is "new" (an essential part of its burden) is summarized succinctly in two sentences in CVM's brief: "CVM has adduced a voluminous amount of evidence from which serious questions concerning the safety of Baytril may be inferred. Most of this evidence was not available to CVM at the time that Baytril was approved for use in poultry." [CVM PHB P.9 (emphasis in original).[4]] CVM then makes the following statement: "Most of the epidemiological studies, microbiological/molecular studies, and temporal data evidence is 'new,' that is, it was unavailable at the time [the] FDA approved the NADA for enrofloxacin. In addition, the evidence that was available at the time of approval has since been examined anew, in light of all of the new evidence that has emerged. The new evidence more than *confirms* the earlier evidence . . . ." [CVM PHB P.9–10 (emphasis supplied)]. This clearly illustrates the flaw in CVM's argument. In fact, *none* of CVM's evidence is new. As is explained above, CVM's burden is to produce new evidence that shows a conclusion *different* from the conclusion shown by the old evidence. *See Hess & Clark*, 495 F.2d at 992 (stating that section 360b(e)(1)(B) places on the FDA "an initial burden to adduce the 'new evidence' *and what it shows in terms of undermining the previous conclusions as to safety*") (emphasis supplied). CVM itself admits that its purported "new evidence" *confirms* what the FDA already knew in 1996. [*See, e.g.*, CVM PHB P.16] Obviously, where there is *confirmation* of previous conclusions that CVM considered as part of its initial

[3] CVM relies on (i) written direct testimony that was previously "stricken from the evidentiary record in this proceeding as irrelevant, immaterial, unreliable or unduly repetitive," *see* Order at 2 (March 3, 2003) (footnote citation omitted); as well as (ii) exhibits that were not moved into the evidentiary record in this proceeding. *See* Order at 2, ¶ 10 (April 10, 2002). Specifically, CVM cites to stricken testimony of Smith (B-1914) P.19 L.5–7 and L.21 (CVM PHB P.77). CVM also cites to the following exhibits not in evidence at the referenced pages: G-200 (P.32); G-300 (P.25, 31); G-1788 (P.66); G-1800 (P.16–19); B-927 (P.72, 73); and John Last, A Dictionary of Epidemiology (4th ed. 2001) (page 48).

[4] Notably, CVM also simply says that "serious questions" may be inferred from this evidence, perhaps recognizing that this evidence does not provide a *reasonable basis* for inferring any such questions.

decision that enrofloxacin usage is safe, the evidence cannot and does not "undermine the previous conclusions" in any way.

CVM's PHB makes it clear that CVM does not have, and has not offered, any evidence that is *substantively new*. Notably, CVM repeatedly states that its evidence "confirms the earlier evidence" or "more than confirms the earlier evidence" [*e.g.*, CVM PHB P.9-10], or that a study "supports the earlier findings of" a pre-approval study [CVM PHB P.17] (arguing that the Zhang study—which is not even in evidence—confirms the 1994 Jacobs-Reitsma findings), or that a study "has provided confirmation" of old evidence [CVM PHB P.37] (discussing genetic typing).[5] Cumulative studies simply do not constitute anything "new" because they do not provide any basis for undermining the previous conclusions. While CVM protests that it has produced a large volume of material that was not available in 1996 [CVM PHB P.9], this contention is irrelevant if the material merely reiterates pre-1996 knowledge.

CVM acknowledges that if an epidemiology "study reveals that poultry is associated with campylobacteriosis, the study's findings relate to campylobacteriosis, whether FQ-resistant or FQ-susceptible. There is *no plausible scientific reason* that transmission of FQ-resistant *Campylobacter* from poultry to humans is different from transmission of FQ-susceptible *Campylobacter* from poultry to humans." [CVM PHB P.26] (emphasis supplied). That being the case, CVM has an uphill burden to demonstrate that there is *any* new evidence, let alone new evidence raising a serious question about the safety of enrofloxacin used in chickens or turkeys. Unquestionably, CVM believed and considered prior to approval of enrofloxacin that poultry was the primary source of campylobacteriosis, including FQ-resistant campylobacteriosis. Chronologically new evidence, whether on selection pressure or poultry as a source, whether by new techniques or otherwise, cannot therefore add to CVM's pre-approval certainty on these questions. CVM's efforts to declare its evidence as new are simply unavailing, and, as AHI and Bayer demonstrate, what new evidence

[5] As is discussed elsewhere herein and in Bayer's briefs, CVM's evidence, including but not limited to that cited here, is unreliable for other reasons such that, even if it *were* new, it would still fail to satisfy CVM's burden of production. Be that as it may, AHI respectfully submits that it is unnecessary even to reach the question of the reliability of CVM's evidence, because CVM has failed to clear the initial "new evidence" hurdle.

there is, particularly U.S. data, raises significant doubt about how much of a role poultry actually has in campylobacteriosis. In fact, the more recent U.S. and other data suggest that poultry's role may be fairly small or minimal, but in any case certainly substantially less that what CVM concluded pre-approval. [*See* Bayer PHB P.21–25]

This leaves open only the questions of (1) whether there is any new evidence supporting an adverse human impact that differentiates resistant from susceptible campylobacteriosis, *i.e.*, complications or extended illness, and (2) if so, whether the benefits to human health outweigh the risks.

Regarding the former point—whether the evidence supports a differential adverse human health impact between resistant and susceptible campylobacteriosis—CVM's evidence in this regard is not new and does not provide a reasonable basis to raise a serious question about enrofloxacin use in poultry. It is difficult to understand how CVM's evidence could be new, because CVM believed pre-approval that resistance could compromise treatment [RJS 5], yet nevertheless concluded that enrofloxacin was safe. [RJS 39] This evidence is not new—rather, it is exactly what CVM knew and considered pre-approval.

Moreover, it is remarkable, given CVM's assertion that it has "voluminous" amounts of new evidence [CVM PHB P.9], that CVM's brief makes no mention of "new evidence" anywhere between pages 18 and 77 of its brief—i.e., the most substantive portion. CVM's silence is truly deafening.

CVM attempts to circumvent the requirement of substantive "newness" by asserting that its evidence "serve[s] to add to the scientific body of knowledge and give[s] substantial scientific weight to the findings of the early studies. This new evidence sheds light on the meaning of studies that existed before the NADA for Baytril was approved." [CVM PHB P.11] It appears that even CVM is acknowledging, albeit subtly, that its evidence is not "new." Once again, evidence that merely "sheds light on" an earlier study is not "new evidence" if the conclusion brought about by the "light" does not lead to a conclusion that substantively differs from that of the older study.

B. CVM's Scientific Evidence Is Not Reliable

AHI's post-hearing brief contains a substantial discussion of what constitutes "reliability" for purposes of assessing scientific evidence. As is explained more fully there, scientific evidence must employ proper scientific methods, adhere to the standards that govern whether any conclusions may legitimately be drawn from scientific evidence, and (in FDA proceedings) comply with the FDA Guidelines for Ensuring the Quality of Information Disseminated to the Public. [*See* AHI PHB P.7–15]

CVM's brief cites extensively to scientific analyses that have already been shown to be unreliable for the purposes for which CVM relies upon them. For example, CVM refers to Nelson's analysis of data from the 1998-1999 CDC *Campylobacter* (*CP*) Case-Control study [G-1489]. [*See* CVM PHB P.55–57] However, as has been amply shown in Bayer's brief, her analysis is unreliable. [Bayer PHB P.51, 59; *see also* Feldman (B-1902) P.36 L.12-21; Burkhart (B-1900) P.33-40]. CVM states that in Nelson's more recent analysis [G-1489] "persons with an FQ-resistant *Campylobacter* infection are likely to have diarrhea for a longer duration." [CVM PHB P.56] However, Nelson's conclusion that there was a longer duration of illness in the resistant cohort vs. the susceptible one is <u>not</u> statistically significant (8 days vs. 7 day, p=0.1), since a finding is said to be statistically significant only if the "P" value is less than 0.05. [Tr. P.60 L.13–15]. As noted by CVM's witness Smith, if a finding is not statistically significant, it cannot be stated that there is a difference. [Tr. P.544 L.15–21] Nevertheless, CVM does not address this issue and impliedly asserts this evidence is reliable.

CVM asserts that the Smith analysis "made an even more striking finding by molecularly linking domestically-acquired quinolone-resistant *Campylobacter* illness with quinolone-resistant *Campylobacter* from poultry." [CVM PHB P.37-38] Smith set out "to analyze . . . risk factors for infection with resistant organisms, and poultry as a potential source of resistant organisms." [G-589 P.1] Despite CVM's claims, Smith's case-comparison epidemiology (both interim and final analysis) did *not* show poultry as a source of FQ-resistant *CP* infections. [Tr. P.522 L.3–16; P.534 L.13–20] Because of this, Smith relied on genetic typing to try to establish the link, but it is

undisputed that genetic typing does not provide proof of causation of disease.[6] [Tr. P.518 L.20–P.521 L.4] Thus, CVM's assertion that "[i]nvestigation of strains of *Campylobacter* from animals, food, and humans by genetic fingerprinting and other sensitive methods for tracing sources of human infection has provided confirmation for the assertion that poultry, particularly chicken, is a source of human *Campylobacter* infections, specifically FQ-resistant *Campylobacter* infections" [CVM PHB P.37], is incorrect. The genetic evidence cannot "confirm" anything, as there was nothing for it to "confirm." Indeed, CVM itself can offer no baseline evidence for the genetic evidence to "confirm" and instead relies upon "common sense" and "logic." [*See* CVM PHB P.41] ("In my opinion, it's not likely at all that there's a common third source. You have to kind of use common sense and go by what's logical—that resistant *Campylobacter* is on the chicken and people are eating the chicken.") (quoting Tr. P.557 L.15–P.558 L.1). However, "common sense" and "logic" do not equate to scientific reliability, especially when they are based purely on what simply "sounds right."

CVM's efforts to quantify the impact of resistant campylobacteriosis are also unreliable. The parties are essentially in agreement that campylobacteriosis, while unpleasant and sometimes painful, is generally not severe. [RJS 19] It is mostly self-limiting, can be asymptomatic, and the vast majority of people do not even see a physician. [RJS 19, 20; G-953 P.5] Most at risk for more severe disease are those with weaker immune systems such as children, the elderly, and HIV-AIDS and transplant patients. [RJS 42; Ohl (G-1485) P.7 L.8–16] Children, who comprise a significant group of campylobacteriosis patients, are not prescribed FQs. [RJS 25; Iannini (B-1905) P.4 L.8–9; Bayer PHB P.3] For the small number of patients who are prescribed an antibiotic, whether empirically or based on a stool culture, there are options for treatment, including one of several FQs, macrolides such as erythromycin and azithromycin, rifaximin (which is available in Europe and appears likely soon to be approved by the FDA), and combination therapy. [Pasternack (B-1909) P.7 L.17–P.8 L.16, P.13 L.9–P.14 L.18] Those patients most at risk for all types of infections are frequently under the ongoing care of a physician and are likely to receive combination therapy.

[6] This issue is discussed in greater detail in Bayer's PHB § I.B.2.c.

[Pasternack (B-1909) P.8 L.21–P.9 L.3; Iannini (B-1905) P.5 L.6–8; B-273 P.7; B-742 P.5] The FDA's recent approval of a *Campylobacter* diagnosis test facilitates quick and accurate diagnosis, lessening the need for empiric treatment of campylobacteriosis generally, and particularly with FQs. [Iannini (B-1905) P.6 L.1–7; B-1143 P.3] Finally, widespread concern about resistance, particularly in traveler's diarrhea, makes FQs less of a drug of choice for empiric treatment. [Pasternack (B-1909) P.4 L.10–12; G-705 P.1] All these factors, together with CVM's proffered evidence as analyzed by Bayer's and AHI's experts, demonstrate that CVM's pre-approval concerns about treatment failure, concerns it found acceptable even though it believed they were demonstrated, are now less of a concern.

Because CVM's evidence is unreliable, it is insufficient to carry CVM's burden in this matter, as it cannot raise "reasonable questions" about the safety of enrofloxacin usage as previously approved, and it cannot undermine the FDA's previous conclusion that enrofloxacin is safe. Accordingly, this evidence should be rejected, and all of CVM's proposed findings of fact that rely on it (numbers 59, 72, 78, 86, 87, 88, 89, 91, 92, 93, 94, and 95) likewise should be rejected.

C. CVM's Other Evidence Is Not Reliable

1. NARMS and Temporal Data Are Unreliable

CVM's PHB contains a long discussion arguing that the NARMS data are supposedly reliable. CVM's argument, however, consists of little more than an attempt to justify data solely by the *ipse dixit* of CVM's own witnesses—an approach that is erroneous and should be rejected. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (stating that there must be something substantive linking the data and the conclusion); *Redland Genstar, Inc. v. United States*, 39 Fed. Cl. 220, 232 (1997) ("An expert who supplies nothing but a bottom line supplies nothing of value to the judicial process."). CVM completely fails to rebut the point that NARMS data are not reliably collected and cannot be reliably used to support any sort of temporal trend argument.[7] CVM's brief nowhere

[7] It is undisputed that susceptibility testing of *CP* isolates from poultry was not added to the animal arm of NARMS until 1998 [Tollefson (G-1478) P.9 L.4–5] and that because 2001 Poultry NARMS data have not been released in a final report [Tr. P.105 L.19–P.106 L.10], there are essentially only 3 years of Poultry NARMS data—1998, 1999, and 2000—on which to base any trend. For those years, assuming the reported data to be valid, the reported resistance results of 9.4%, 9.3%, and 10.4% [Tollefson (G-1478) P.12 L.6–7] do not constitute an upward trend. CVM has

acknowledges the fact that the Poultry NARMS protocol has changed repeatedly over the years to the point where it is impossible accurately to compare data from one year with data from another year. [*See* Bayer PHB P.36–37] CVM states that Human NARMS data are generalizable to the U.S. population as a whole and that "[a]ny seasonal variation in FQ-resistant *Campylobacter* is not believed to skew the approximation of NARMS data to the national prevalence of FQ resistance in *Campylobacter*." [CVM PHB P.71] What CVM's brief fails to address, however, is the arbitrary nature of the NARMS sampling procedure, which even CVM's own witness described as "artificial." [Carnevale (A-199) P.13 L.25–28, P.89] The NARMS sampling program for *CP* only requires one sample per week *regardless of the number of incoming samples*. Thus, it becomes wholly impossible for the arbitrary number of samples to be representative of the national population, in which the number of cases fluctuates. [*Id.* P.14 L.1–18] Again, this was admitted by CVM's own witness when Dr. Angulo stated that the NARMS *Campylobacter* numbers are not estimates of the national prevalence. [*Id.* P.13 L.25–28, P.89] The arbitrary and artificial sampling procedure was clearly illustrated when Minnesota reported 11% resistance for all isolates tested in that state in 2000, but NARMS reported 24.5% resistance for the 49 isolates received from Minnesota during the same period. [Bayer PHB P.38–39] One of CVM's expert witnesses stated that even though the FoodNet data provide the most detailed information available for these infections, the data do not reflect the entire U.S. population. [Molbak (G-1468) P.5 L.20–21] Since the NARMS data are generated from these same FoodNet sites, it stands to reason that the NARMS findings likewise do not reflect the entire U.S. population. The fact that individual laboratories are following the NARMS procedures when they submit their one sample per week does not make the NARMS data reliable. Obviously, mere adherence to the protocol is not enough to establish reliability when the protocol itself is flawed.

NARMS has no value as a tool for monitoring domestically-acquired infections because isolates are included from cases where infections were acquired in foreign countries. NARMS is

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acknowledged that the 2001 data are not comparable, and have not yet been officially released. [Tollefson (G-1478) P.11 L.5–38; Tr. P.80 L.9–P.81 L.10; Tr. P.106 L.1–10]

unable to distinguish which cases these are and the extent to which they occur. [Tr. P.113 L.12–P.114 L.17] This case, however, is about the human health impact attributed to the use of enrofloxacin *in the U.S.* Infections acquired in foreign countries cannot be connected in any way to the domestic use of enrofloxacin, and such infections therefore are immaterial to the issue of whether or not the use of enrofloxacin in the U.S. is safe.

CVM's brief also focuses on various temporal evidence that purports to show that resistance has increased (or, as CVM put it in one instance, "skyrocketed") after approval of enrofloxacin. [CVM PHB P.47] CVM's brief never acknowledges a number of fundamental problems with the data on which CVM relies. First, CVM concedes that a temporal relationship is not the same as a causal relationship. [Tr. P.649 L.10–13] Second, the bulk of CVM's data come from foreign countries, and CVM simply treats such data as though they were automatically imputable to the U.S. experience, but CVM fails to account for the significant differences in the way enrofloxacin is used in other countries and other factors influencing *CP* and resistance. For example, CVM states that "[b]efore 1990, the prevalence of FQ-resistant *Campylobacter* in humans was between zero and three percent. Since approval of enrofloxacin, the level of FQ resistance in Spain skyrocketed in the presence of widespread use." [CVM PHB P.47 (citation omitted)]. Data from Spain cannot be generalized to the U.S., however, because Spanish FQ use has been characterized as "indiscriminate" [B-655 P.3; G-530 P.2] and not strictly regulated [Tr. P.675 L.22–P.676 L.1] In the U.S., by comparison, the FDA imposed strict limitations upon the use of enrofloxacin, such that its use in this country could hardly be considered "indiscriminate," and the foreign data from countries in which enrofloxacin use was strictly regulated (such as Denmark, *see* Bayer PHB P.43) show minimal increases in resistance. Further, for the U.S., according to CVM's Deputy Director, the incidence of FQ-resistant *Campylobacter* infections has decreased from 1997 through 2001, the year for which the most recent data are available. [Tr. P.143 L.15–P.144 L.3] CVM's temporal evidence is unreliable because it fails to account for, separate, or explain any of these divergences. Thus, it cannot be said to support the proposition in support of which CVM has offered it, and it is

insufficient to satisfy CVM's burden because it does not provide a "reasonable basis" to question enrofloxacin's safety.[8]

2. CVM's Risk Assessment Is Unreliable

CVM asserts that "[t]here is no single process for conducting a risk assessment" and that "all risk assessments do not need to follow a rigid formula." [CVM PHB P.63] AHI has never asserted that there is one rigid process that *all* risk assessments must follow. However, it is undisputed that risk assessments must at least follow accepted *guidelines* and *standards*, in particular including elements of the paradigm set forth by the National Academy of Sciences in two documents produced by the National Research Council, *viz.* Risk Assessment in the Federal Government (1983) and Science and Judgment in Risk Assessment (1994). [AHI PHB P.16] Indeed, the FDA's CFSAN has described these elements as the generally accepted methodology. [*Id.* at 16–17] Of course the *actual process used* in the course of the risk assessment will vary depending on what is being studied. The point is that a risk assessment that does not adhere to *minimal baseline standards* is unreliable.

CVM's brief actually explains quite succinctly the central flaw in CVM's risk assessment when CVM states that the risk assessment is "appropriate for [CVM's] needs." [CVM PHB P.63] Indeed, while this statement may be true on the surface, it hardly proves the risk assessment's validity. The risk assessment is based upon a variety of assumptions made by CVM that were never tested, never verified, and never objectively examined. CVM's entire process was therefore compromised from the beginning by unreliable and extraneous material. CVM then selectively chose the data it wanted to include in its analysis (which served CVM's purposes) while failing to consider other relevant data (that *did not* support CVM's position) *from the same studies from which CVM drew the data it used.* [*See* Bayer PHB P.50–52] CVM also failed to consider all sorts of data that raise serious questions about the accuracy of the data on which CVM chose to rely (or that, at the least, when balanced together with CVM's data, essentially create a proverbial wash). [*See* Bayer PHB P.53–57]

[8] Accordingly, CVM's proposed findings of fact # 42, 111, 112, 113, 116, and 117 should be rejected.

CVM's brief does not defend CVM's risk assessment. CVM simply says that (1) there is no single process to follow (which is true, but irrelevant), (2) CVM made reasonable assumptions (an assertion belied by the uncontested fact that CVM never tested its assumptions to *verify* that they were reasonable, but instead simply said that they are—a classic *ipse dixit*), and (3) the data relied upon by CVM are "robust" (which they emphatically are *not* when one considers the host of other data that CVM failed to include). [CVM PHB P.63–69]

There are several fundamental flaws in CVM's risk assessment [G-953], none adequately addressed in CVM's testimony. The first is that CVM only estimates persons with FQ-resistant campylobacteriosis who received FQs, and assumes harm, *i.e.*, treatment failure. [AHI PHB P.19] The clinical and other data show that treatment failure is not a frequent outcome. The second fundamental flaw in CVM's risk assessment is that its chicken attributable risk fraction is derived from non-representative and old studies that do not reflect post-approval risks. Indeed, it attributes risk to chicken consumed at home, when such consumption is actually protective against acquiring campylobacteriosis. Consequently, CVM's attribution to chicken greatly overestimates the potential contribution of chicken to campylobacteriosis. [Bayer PHB P.53–58] A third fundamental flaw is that CVM only attempts to exclude foreign travel acquired FQ-resistant campylobacteriosis and those attributable to prior treatment use of FQs (thus implicitly recognizing that they are confounders). CVM attributes all other cases of FQ-resistant campylobacteriosis to domestic chicken consumption. The available data do not support CVM's assumptions. *Id.* CVM's failure to use a dose response variable in its risk assessment model is perhaps one of the most fundamental flaws. This failure ignores the very basic principle, essential to any microbial assessment, that "the dose makes the poison," i.e., the number of bacteria ingested is critical to determining that illness will occur. [Bayer PHB P.47] Other microbial risk assessments on *Campylobacter* and other enteric pathogens utilize such information to inform the risk estimates. [AHI PHB P.20–22; Bayer PHB P.62–64]. While CVM tries to explain this failure, CVM has not received support for its model in the scientific community, making it all the more problematic since CVM's model deviates from the generally accepted scientific methodologies. [AHI PHB P.15–28]

The flaws in CVM's risk assessment are fundamental and undercut the scientific reliability of CVM's estimates of persons affected by use of enrofloxacin in chickens. Additionally, when appropriate data are used, even assuming CVM's model is appropriate, it is clear that CVM's estimate of risk is off by at least an order of magnitude.

Another fundamental deficiency in the CVM model is that CVM does not consider the benefits to human health by use of enrofloxacin or, stated another way, the risks to human health of withdrawal of enrofloxacin. CVM did not consider the benefits when it published the NOOH or the NOH, though it has acknowledged it is required to do so. [CVM's Opp. to Bayer's Mot. to Reformulate Issues for Hearing at 12.] Bayer's and AHI's evidence is uncontroverted by CVM's testimony or articles in evidence and clearly demonstrates that, with Baytril use, healthier poultry go to market, meaning fewer cases of chicken-associated food-borne illness. [*See, e.g.,* Bayer PHB P.77–89] Since CVM's treatment failure argument largely assumes two or more additional days of diarrhea, even one additional case of campylobacteriosis prevented by enrofloxacin results in a public health "savings" of 3 to 10 days of illness. Since CVM's ratio of resistant to susceptible campylobacteriosis is about 20 percent versus 80 percent, respectively, [CVM PHB P.50] one could expect far greater benefit to public health by a reduction in susceptible cases (each with 3–10 days of diarrhea) than by prevention of resistant cases (assumed by CVM to be 2–3 additional days of diarrhea).

Because CVM's risk assessment is replete with defects, it cannot be considered reliable, and therefore it is insufficient to carry CVM's burden because it cannot be said to raise "reasonable questions" about the safety of enrofloxacin.[9]

D. CVM's Evidence Does Not Show Any Potential Harm

CVM's brief utilizes the phrase "potential harm" on occasion in attempting to recast CVM's burden. [*E.g.*, CVM PHB P.4] ("[I]n order to meet its burden CVM need only present enough information to show how FQ-resistant *Campylobacter* in poultry is related to the use of FQs in poultry . . . and that the FQ-resistant *Campylobacter* presents some potential harm to the public

[9] Accordingly, CVM's proposed findings of fact # 141–162 should be rejected.

health."). It is unclear what CVM means by "some potential harm." It is clear that the fact that the use of a drug might result in "some potential harm" is not justification for removing it from the marketplace (or for initially refusing to approve it), for it is undisputed that a drug may be allowed (or kept) on the marketplace even though its use entails certain risks. *E.g.*, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000) (stating that whether a product is "safe" under the FFDCA is determined by whether a "product's probable therapeutic benefits . . . outweigh its risk of harm"). The word "risk" is defined as, *inter alia*, "[d]anger; (exposure to) the possibility of loss, injury, or other adverse circumstance," and also as "[a] chance or possibility of danger, commercial loss, or other risk." *Shorter Oxford English Dictionary* 2593 (5th ed. 2002). Thus, "risk" and "potential harm" essentially mean the same thing, and CVM is attempting to make a distinction without a difference.

Even if there were some relevance to the notion that CVM could carry its burden simply by showing "some potential harm," however, CVM would still have failed to satisfy its burden, because, as is discussed more fully in Bayer's briefs, CVM has failed to show that the use of enrofloxacin leads to any "potential harm" beyond any risks that were already known when its use was approved in 1996.

III. SAFETY IS DETERMINED BY A HUMAN HEALTH RISK/BENEFIT ANALYSIS

CVM's brief asserts that the term "safe," as used in the FFDCA, means "reasonable certainty of no harm." [CVM PHB P.6–8] It is not entirely clear what CVM means when it uses this phrase because CVM's explanation that "reasonable certainty of no harm" does not mean "zero risk" but instead "means that there is a 'reasonable certainty' that any risk will not manifest itself as harm," CVM PHB P.7, is convoluted at best. CVM's brief states that the phrase "reasonable certainty of no harm" originated in the context of human food safety. [CVM PHB P.6] Yet "[the] FDA has long maintained that there is no provision for consideration of benefits under the safety standards for food." [A-99 P.23] At the Risk Assessment and the Establishment of Resistance Thresholds Workshop in 1999, the Director of CSFAN's Office of Food Additive Safety confirmed

this view, explaining that the "reasonable certainty of no harm" standard "does not weigh risks and benefits." [A-121 P.15]

CVM apparently concedes that the determination of whether Baytril is "safe" under the FFDCA standard requires an analysis of the risks and benefits of its use. [*E.g.*, CVM PHB P.9] ("In this case, the proper analysis would compare the risks to humans of keeping this drug on the market for use in poultry, to the benefits to humans of keeping this drug on the market for use in poultry."). AHI and Bayer both agree that an assessment of risks and benefits is required,[10] [AHI PHB P.6–7, Bayer PHB P.1] and the Administrative Law Judge's ruling confirms the parties' views. [March 3, 2003, Order at 1]

Thus, it is clear that, regardless of the terminology one uses to describe the analysis of "safety," the standard used must include a risk/benefit analysis. It is therefore equally clear that, if a proposed standard does not include a risk/benefit analysis, that standard cannot apply. If the FDA believes that its "reasonable certainty of no harm" standard has no room for a risk/benefit analysis, that standard could not apply here. Even accepting CVM's statement that "reasonable certainty of no harm" does not mean zero risk, the entire notion of a risk/benefit analysis inherently recognizes, and accepts, the reality that some risks may be acceptable if sufficiently outweighed by a drug's benefits. Inherent in accepting risks is the possibility that, however unlikely, a risk might manifest itself as an actual harm. Given this fact, and given that all of the parties are in agreement that a risk/benefit analysis is an integral part of the analysis of "safety," it would better serve the interests of clarity and consistency if the phrase "reasonable certainty of no harm" were dropped from the discussion, since it only serves to confuse the issue.[11] CVM's proposed conclusions of law nos. 7

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[10] AHI and Bayer do not waive their argument that the risk/benefit analysis also extends to economic and environmental considerations, but for purposes of this submission assume that the risk/benefit analysis is limited to direct human health considerations. In addition, in view of the Administrative Law Judge's prior ruling excluding economic and environmental considerations, including health effects from environmental considerations, Paragraph 10 of CVM's proposed conclusions of law should be rejected as moot.

[11] To the extent, however, that CVM may argue that "reasonable certainty of no harm" does not include a risk/benefit analysis, CVM is incorrect. It is settled law that an assessment of "safety" under the FFDCA requires a risk/benefit analysis. *Hess & Clark*, 495 F.2d at 993–94; *Rhone-Poulenc v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980); *Brown & Williamson*, 529 U.S. at 140. Notably, the *Rhone-Poulenc* court flat-out rejected the FDA's contention that the "risk/benefit" requirement is not binding on the FDA. *Rhone-Poulenc*, 636 F.2d at 754. CVM's arguments as to the historical evolution of the statute are irrelevant in view of this controlling precedent, and AHI will not address them here, but reserves the right to do so on appeal if necessary. Suffice it to say that CVM's statements about "reasonable

and 13 should therefore be rejected, or, alternatively, modified to clarify that "reasonable certainty of no harm" requires an analysis of the risks and benefits of the use of enrofloxacin.

IV. ENROFLOXACIN IS SAFE FOR USE BECAUSE ITS BENEFITS OUTWEIGH ITS RISKS

AHI's and Bayer's evidence demonstrates that there are no significant adverse human health consequences differentiating so-called "resistant" from "susceptible" *Campylobacter* infections. [*See, e.g.*, Bayer PHB P.69–74] However, even if CVM's evidence is credible, the risk of treatment failure is largely characterized by CVM as two or so additional days of diarrhea. [CVM PHB P.8, 52–60] *It is important to note that under CVM's analysis, removing Baytril from the market will not prevent one single case of human campylobacteriosis.* As discussed above, AHI's and Bayer's evidence, largely uncontroverted during this proceeding, and not considered by CVM before it commenced this proceeding, demonstrates that the benefits to human health from use of enrofloxacin greatly outweigh any potential risks. [Bayer PHB P.77–89; AHI PHB P.42–43][12]

V. COX'S ANALYSIS IS RELIABLE AND SHOWS LOW RISKS FROM ENROFLOXACIN USE IN POULTRY

CVM's *ad hominem* attack on Dr. Cox and his analysis is unwarranted. CVM's statement that "testimony should be truthful, accurate and non-misleading" [CVM PHB P.74] applies equally to briefs. For example, CVM's willful indifference towards Cox's explanations provided at the hearing, as well as the evidence supporting Cox's opinion, renders CVM's brief inaccurate and misleading.

Cox's December 1999 opinion regarding CVM's "Big K" model has not changed. CVM's allegations that Cox's opinion changes "depending on who is asking for it" and that one cannot "distinguish his opinion from his interest" are unfounded. [CVM PHB P.74] Cox's opinion regarding CVM's "big K" model has not changed. In December 1999 Cox was invited as a

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certainty of no harm" originating in the food additive context but still applying here are completely incorrect, particularly given that in the DES hearing the Commissioner explicitly noted that food additive regulations are not binding in new animal drug proceedings. *See* 54 FR 54,852, 54,883 (1979) ("In any case, the language cited by the manufacturing parties deals with safety in the context of GRAS substances and food additives, *not in the context of new animal drugs. It thus would in no case be binding in this proceeding.*") (emphasis supplied).

[12] Accordingly, CVM's proposed conclusions of law # 11 and 12 should be rejected.

recognized expert by CVM (at CVM's expense) to present his critique of the CVM Risk Assessment (RA) at a public meeting. [Tr. P.1012 L.18–P.1013 L.1] In his critique of the CVM model, Cox explicitly identified and emphasized "big K" as "the key assumption" and the "biggest assumption" that needed to be validated. [G-1810 P.41; Tr. P.1008 L.21–P.1009 L.6; P.1011] CVM's brief ignores Cox's detailed description of his own epiphany when he tried to validate CVM's "big K" model with real-world raw data obtained from the CDC 1998–1999 *CP* Case-Control Study, the Effler study, and the Smith study. Cox explained that he initially thought that the "big K" assumption, which is that human health risk is directly proportional to pounds of contaminated chicken consumed, "sounded plausible"; he then "went to try to validate the assumption that the big K framework is essentially correct"—not correct in every detail, but in the basic premise that "risk increases in proportion to exposure," and "quickly found out, as soon as [he] got some real data, that that big assumption—what [he] called ... the key assumption... just doesn't fit the data." That is when he began to examine microbial load and dose response. [Tr. P.1089 L.1–P.1090 L.13] To try to validate the CVM model, Cox "obtained three ... raw data sets ... the CDC case control[ ] data, the Smith data and the Effler data. And first thing [he] noticed is that those sources raised the apparent anomaly of chicken consumption at home being associated with reduction in risk ... and the algebraic form that risk is proportional to exposure can't be right for all the different groups that were exposed. It certainly can't be right for groups who were exposed at home." Because CVM's "big simplifying assumption [wasn't] right," Cox "used a non-parametric method based on what's called causal graph analysis to figure out how different factors relate to each other and how to back out confounding effects." [Tr. P.1103 L.1–P.1104 L.4]

In short, Cox's opinion was that CVM's model seemed plausible subject to validation. CVM never validated its model. Cox attempted to validate the model with real-world data and discovered the model simply did not hold up.[13]

[13] Cox is not alone in reaching this conclusion. Haas, another respected risk assessment expert, expressed similarly strong concerns about CVM's interpretation of the "K" value. [Haas (B-1907) P.10, 15] CVM has not addressed Haas' opinion in its PHB or on cross-examination.

Cox's testimony does not misrepresent the text of articles on which he relies. CVM's counsel spent 22 pages of cross-examination trying to prove that Cox misquoted Rosenquist [G-1788]. [Tr. P.942-963] Yet, when all was said and done, Cox's quote of Rosenquist accurately portrayed the substance of the article.

Cox's written direct testimony is not "compromised" due to "vague" methods and conclusions as alleged by CVM. CVM's claim that Cox's analytical results are "vague," "misleading," "just exploratory," and not "serious data analysis" is not supported by the record. [CVM PHB P.75] What is clear from reading CVM's cited portion of cross-examination [Tr. P.1069 L.1–P.1074 L.7] is that Cox looked at chicken consumption and campylobacteriosis rate data at different levels of complexity to test CVM's "big K" theory, i.e., that the annual number of *CP* cases is directly proportional to the volume of chicken consumed each year, or $\lambda = K_{res} * V_i$. [*See, e.g.*, Cox (B-1901) P.37] The simplest test is to use real data to plot chicken consumed V_i on the X-axis and campylobacteriosis case rates λ on the Y-axis, and fit a line to the data to determine the slope. [Tr. P.1069 L.6–22] Simple algebra would dictate that the line $\lambda = K_{res} * V_i$ (recall the "slope-intercept" form of equation for a line $y = mx+b$) would have slope of K_{res} (CVM's "big K"). Cox's point of this "ecological study" [Tr. P.1070 L.4–6] performed as an initial "exploratory" analysis [Tr. P.1072 L.2] was to see if the slope of the $\lambda = K_{res} * V_i$ line was positive (i.e., does it "look anything like a straight line sloping upward to the right") as the CVM RA assumes. It was not. [Tr. P.1072 L.7–11; Cox (B-1901) P.37] But that was just the *beginning* of Cox's analysis that formed the basis of his opinions. [Tr. P.1080 L.2–9] The fact that CVM's counsel chose to stop cross-examination after questioning Cox about the exploratory analysis and did not inquire into Cox's more detailed analyses ("MR. SPILLER: I think the beginning is a good place for me to end, your Honor." [Tr. P.1080 L.10-11]) does not render Cox's overall analysis (as set forth in B-1901) "vague" or "misleading."

Cox's testimony does not misrepresent the findings of the Effler, Rodrigues, Friedman, Eberhart-Phillips, and Kassenborg studies. CVM alleges that "each of these studies actually does find that chicken consumption outside the home, not restaurant dining in and of itself, is a

major cause of campylobacteriosis" and that Cox misrepresents that they find restaurant dining as a cause. [CVM PHB P.75] Here it is CVM who is misrepresenting the findings, not Cox. In the Friedman study, for example, the highest population attributable fractions are for "ate chicken *prepared at a restaurant*" (24%) and "ate non-poultry meat prepared at a restaurant" (21%). [G-1488 P.23 (emphasis added)] Kassenborg's findings relate to "eating chicken or turkey *cooked at a commercial establishment.*" [G-337 P.15 (emphasis added)] Rodrigues states "travel abroad and consumption of chicken *in a restaurant* were statistically associated with being a [*Campylobacter jejuni* infection] case." [G-1711 P.1 (emphasis added)] Eberhart-Phillips finds "there was also an increased risk [of campylobacteriosis] with chicken eaten *in restaurants.*" [G-182 P.1 (emphasis added)] Effler reports "eating chicken *prepared by a commercial food establishment* in the 7 days before case illness onset ... were significant independent predictions of [*Campylobacter*] illness." [G-185 P.1 (emphasis added)]

Coupled with findings from these studies that chicken consumed at home is inversely associated with campylobacteriosis risk [i.e., G-1488 P.23: "ate chicken prepared at home," "ate turkey prepared at home"; G-337 P.15: "eating meat at home" (presumably including chicken and turkey); G-1711 P.4: "[consumed chicken] ready gutted without giblets, fresh, cooked at home," "[consumed chicken] bought new, fresh, cooked and eaten at home," "[consumed chicken] bought raw, frozen, eaten at home," "[consumed chicken] pre-cooked eaten at home"; G-182 P.3: "[consumed] any chicken prepared at own home"; G-185 P.3: "chicken eaten at home" all have odds ratios less than 1], the findings of a positive risk correlation for chicken or turkey *at a restaurant* and non-poultry meat *at a restaurant* begs the question whether the risk is chicken or turkey per se or some non-chicken source of *CP* present in restaurants. [*See* Bayer PHB P.23–24, 56] In light of this, Cox's reliance on these studies to support his hypothesis that restaurant dining is a major cause of campylobacteriosis does not misrepresent the studies.

Cox's testimony does not misrepresent CVM's RA. CVM claims that Cox's testimony misrepresents the CVM RA because he says the CVM model incorrectly assumes that risk is proportional to prevalence of contaminated chicken servings ingested, whereas the CVM RA was

based on the overall consumption of chicken, not chicken servings. [CVM PHB P.75–76] But this is a distinction without a difference; as pointed out by Cox, "if several quantities are all proportional to each other, then something that's proportional to one is proportional to all..." [Tr. P.945 L.14–16] In other words, if overall chicken servings ingested is proportional to overall chicken consumption (which CVM cannot dispute and has not disputed) and if overall chicken consumption is proportional to risk (as CVM's RA claims but Cox disputes), risk theoretically would also be proportional to chicken servings ingested. Thus, Cox does *not* mischaracterize the premise of the CVM RA.

CVM also claims that Cox misrepresents the CVM RA as being based on the "average exposure for an average individual." As Cox pointed out in his testimony, the phrase "average exposure for an average individual" may or may not have been a quote from the CVM RA. [Tr. P.999–1003] Nevertheless, it is an accurate depiction of what the CVM RA does; it looks at overall annual chicken consumption and tries to predict overall health impact without regard to individual sensitivities that impact the risk of being a campylobacteriosis case, such as being male or female, young or old, etc.

There is no confusion as to what Cox's final model is or what it finds. [CVM PHB P.76] Cox's final model is in the record as Exhibit B-1020. His model finds that in the most plausible case (assuming 21% of all campylobacteriosis cases are chicken-attributable) [B-1020 P.19] there are an estimated 985 persons with chicken-attributed FQ-resistant campylobacteriosis who are prescribed a FQ. [B-1020 P.24] Additional evidence demonstrates that the 21% chicken-attributable fraction is not a realistic assessment of the fraction of *CP* infections attributable to chickens because it does not taken into account the protective effect of the huge quantities of chicken prepared and consumed at home. A more realistic assessment using the CDC *CP* case-control data is somewhere between 0 and 3.1% for CP cases in general [Cox (B-1901) P.56] and minus 11.6% (i.e, –11.6%, protective effect) and 0.72% for resistant CP. [Cox (B-1901) P.22, 57] Quantitative attributable risk calculations applied to the CDC *CP* case-control data set reveal that chicken-attributable fractions for FQ-resistant campylobacteriosis are not statistically different from

zero. [Cox (B-1901) P.63] In other words, the Cox model and analysis shows that there is no human health impact from FQ use in chickens. As was clearly explained by Cox at the oral hearing, Exhibit A-17, submitted by AHI, was Cox's "final report" to AHI as of February 2001, but Cox "continued to work on a model over a period of years." [Tr. P.1024 L.5–17] A-17 merely represents an "early model" that Cox did not rely on in formulating his opinions [Tr. P.1102 L.19–22, P.1106 L.6–7], notwithstanding CVM counsel's continuing effort to portray Cox's AHI report as his final effort.

Cox's testimony is not in "irreconcilable conflict with itself." [CVM PHB P.76] Cox's testimony merely takes at face value CVM's contention that poultry is a major source of *CP* infections in humans and carries out his analysis to its logical conclusion. If enrofloxacin is withdrawn and the poultry industry loses its ability to better control air sacculitis, carcass uniformity, and microbial contamination, *CP* and *Salmonella* microbial loads will increase on carcasses. All Cox is saying is that overall campylobacteriosis rates will *increase* at a higher rate than FQ-resistant cases will *decrease*. Cox predicts 25 new days of *CP* illness for each hypothetical day of illness prevented. [Bayer PHB P.87] CVM's perceived "irreconcilable conflict" is just the conflict between present and future: between a present in which prudent use of enrofloxacin helps to keep human health risks from chicken very low and a possible future without enrofloxacin in which air sacculitis rates in chickens and resulting human health risks from increased microbial loads from air sacculitis–positive flocks will both increase. There is no conflict in saying that the risks are small now but that CVM's proposed action will increase them substantially.

VI. CVM'S ATTACK ON THE PATTERSON TESTIMONY IS UNWARRANTED; CVM'S OWN DOCUMENTS SHOW WATER IS A SOURCE OF FQ-RESISTANT CAMPYLOBACTERIOSIS

CVM attacks Bayer witness Patterson's written direct testimony claiming that it is "beset with irrelevant and incorrect statements." [CVM PHB P.72] But Patterson's overall conclusion—that sporadic *CP* infections (including FQ-resistant infections) are waterborne, in addition to being foodborne—is supported by other evidence including government exhibits and the CVM RA. [G-

953 P.49–50] Tauxe writes at G-615 P.4 that "waterborne transmission of Campylobacter organisms has occurred because of drinking unboiled surface water, contamination of groundwater with surface water, faulty disinfection, and contamination by wild-bird feces. In remote mountain wilderness areas, the [Campylobacter] infection is associated with drinking surface water from cold mountain streams; it can be more common than giardiasis in this setting..." Friedman states:

> The contribution of drinking water to the burden of sporadic [campylobacteriosis] cases varies around the world but may be substantial in the developed and developing world. Even pristine mountain streams can be sources of infection, presumably as a result of contamination by the feces of wild birds... If poultry ultimately acquire and spread infection through water, and if cattle are also infected in the springtime by drinking contaminated surface water, the waterborne route may be the common underlying pathway linking waterborne, milkborne, and poultry-associated campylobacteriosis in humans to an underlying cycle involving birds and the water they drink.

[G-1644 P.12 (citations omitted)]. In other words, a common environmental source (water contaminated by wild birds) may account for *CP* infections in both poultry and humans (as well as cattle). Such a cycle was recognized by CVM even before approving enrofloxacin. Prior to approval, CVM director Sundlof notes that "evidence and data have emerged and been published in peer-reviewed literature that supports the concept/notion that bacteria do not exist in discrete separate populations, but that flow occurs backward and forward among man, animals and the environment..." [G-1003 P.2][14]

VII. CVM HAS FAILED TO CARRY ITS BURDEN ON TURKEYS

CVM has not satisfied its burden to justify withdrawal of use of enrofloxacin in turkeys. CVM's efforts to satisfy this burden by relying on evidence *relevant only to chickens under the guise of "poultry"* must fail in light of the significant physical, clinical, pathological, processing, and other differences between the different species.[15] *See* AHI PHB § III.

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[14] Accordingly, CVM's proposed finding of fact # 163 should be rejected.

[15] CVM has not satisfied and cannot satisfy its burden to justify withdrawal of use of enrofloxacin in turkeys. [AHI PHB P.36–42] In fact, the epidemiological shows that risk of campylobacteriosis from turkey consumption is minor, about 4% when turkey is consumed in a restaurant. [G-1488 P.23] This is only $^1/_6$ the "attributable risk" for chickens consumed in a restaurant (24%), as found in the same study. [*Id.*] Turkey consumed at home is not a risk factor in the CDC data or the Effler data. [G-185] Retail studies suggest substantially lower prevalence of FQ-resistant *Campylobacter* on turkeys compared to chickens. [G-727; Meng (G-1466) P.2 L.26–35, P.3 L.16–17; Gonder (A-201) P.12 L.22–P.13 L.3; White (G-1484) P.4 L.12–15]

CVM's repeated attempts to substitute chicken data for turkey data under the guise of "poultry" are also without evidentiary merit.[16]

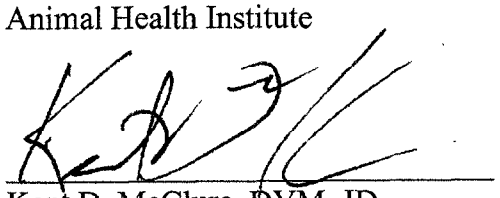
In sum, CVM believes that, with respect to the ultimate issue of whether there is a human health impact from FQ-resistant *Campylobacter* infections as a result of poultry consumption, there are no relevant differences between chickens and turkeys. CVM asserts this despite the fact that enrofloxacin has separate label indications for use in chickens and turkeys, and that it is not approved for use in "poultry." Accordingly, CVM has not met its threshold burden, and CVM's proposed conclusions of law nos. 1, 2, 3, 4, 8, and 9, should be rejected as without merit.

CONCLUSION

CVM has produced no credible, reliable new data that is sufficient to provide a reasonable basis seriously to raise a question about the safety of enrofloxacin in chickens. It has produced virtually NO data on turkeys but frequently merely links turkeys and chickens together as "poultry." CVM has also failed to consider the human health benefits of enrofloxacin. The evidence overall demonstrates that enrofloxacin use has even less risk associated currently than at the time of approval and that, in any event, enrofloxacin is safe, as the benefits to human health outweigh the risks. Therefore, CVM's attempt to withdraw approval for the NADA for enrofloxacin must be rejected.

[16] For example, CVM posits on pages 37–38 of its Post-Hearing Brief that "Smith's study in the U.S. made an even more striking finding by molecularly linking domestically-acquired quinolone-resistant *Campylobacter* illness with quinolone-resistant *Campylobacter* from *poultry*. WDT G-1473: P.13 L.41–P.14 L.18." (emphasis supplied) Smith's study, however, only looks at chickens. [*See* G-589] Similarly, on page 19, CVM points to the WDT of Newell (B-1908) as showing that "[e]xperiments have demonstrated that once *poultry* are colonized by FQ-resistant *Campylobacter* they remain colonized for the production span of the *poultry* . . . WDT B-1908 P.5 L.2-6." (emphasis supplied) Again, Newell does not discuss poultry in this excerpt—just chicken. Finally, CVM misrepresents the cross-examination testimony of Smith when it substitutes "poultry" for "chicken." [*See* CVM PHB P.38 (citing Tr. P.557 L.15–P.558 L.1)]

Respectfully submitted,
Animal Health Institute

By: 

Kent D. McClure, DVM, JD
Animal Health Institute
1325 G Street, NW Suite 700
Washington, DC 20005
(202) 637-2440 phone
(202) 637-1667 fax

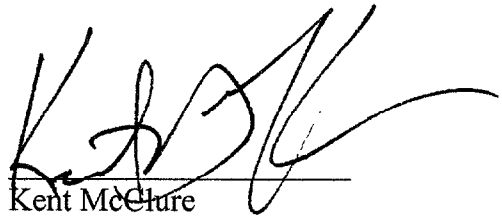
Of Counsel:

Robert B. Nicholas
Gregory A. Krauss
M. Miller Baker
Jeffrey C. Bates
McDermott, Will & Emery
600 Thirteenth Street, N.W.
Washington, D.C. 20005
(202) 756-8000
Attorneys for Bayer

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Non-Party participant Animal Health Institute's Brief was served on the 15th day of August, 2003 as follows:

Nadine Steinberg – Via Mail
Office of the Chief Counsel
Mail Code – GCF-1
Room 777
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706
Attorney for FDA



Kent McClure

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

MCDERMOTT, WILL & EMERY

August 15, 2003

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

Re: Enrofloxacin for Poultry: Withdraw of Approval of New Animal Drug Application
FDA Docket: 00N-1571

Dear Sir/Madam:

Enclosed for filing please find an original and copy of Non-Party Participant Animal Health Institute's Reply to CVM's Post-Hearing Brief.

Please call if you have any questions.

Sincerely,

Robert B. Nicholas

Enclosures

cc: Nadine Steinberg, Esquire (w/o enclosure)
Kent McClure, Esquire (w/o enclosure)