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: July 18, 2003

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

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INTRODUCTION

On October 31, 2001 The Center for Veterinary Medicine ("CVM") proposed to withdraw approval of the new animal drug application (NADA) Baytril®[1] (NADA 140-828 3.23 % Concentrate Antimicrobial Solution, approved October 4, 1996). Notice of Opportunity for Hearing, 65 FR 64954-64965 (October 31, 2000). Bayer Corp., the sponsor of NADA 140-828, responded by filing a request for hearing on November 29, 2000. Likewise, the Animal Health Institute filed a request for hearing on February 21, 2001. A Notice of Hearing was filed on February 20, 2002. 67 FR 7700-7701 (February 20, 2002).

The Animal Health Institute (AHI), the national trade association of research based manufacturers of animal health products, filed a notice of participation, under the provisions of 21 CFR Part 12 for non-party participants, because of the importance of this matter to the animal health industry, and its implications for all animal health products. Indeed, the legal and evidentiary issues in this case will affect the sponsor of every NADA. Issues such as (1) whether CVM can withdraw approval of an NADA without any new evidence; (2) whether CVM can withdraw approval of an NADA without showing that serious questions of safety are raised under the approved conditions of use; (3) whether CVM can rely upon poor quality data that does not withstand scrutiny under various evidentiary standards and the FDA's own data quality guidelines; (4) whether CVM can rely upon a risk assessment that does not follow the National Academy of Sciences paradigm and which is contradicted by known data and ignores relevant, robust data in the possession of CVM; and (5) whether CVM can withdraw approval of an NADA with no evidence as to one of the species involved are questions of vital interest to the sponsors of animal health products.

The NOH sets forth the following issues for hearing:

Whether new evidence shows that enrofloxacin is not now shown to be safe for use under the conditions of use upon the basis of which the application was approved. The issue includes:

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[1] Enrofloxacin is the active ingredient in Baytril®. Enrofloxacin and Baytril are used interchangeably herein.

A. Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred, such as:

1. Whether enrofloxacin use in poultry acts as a selection pressure resulting in the emergence and dissemination of FQ-resistant *Campylobacter* spp. in poultry?

2. Whether FQ-resistant *Campylobacter* spp. in poultry are transferred to humans and whether they contribute to FQ-resistant *Campylobacter* infections in humans?

3. Whether FQ-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?

B. Whether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe.

AHI's brief addresses the legal and evidentiary standards applicable to the withdrawal of a new animal drug (section I), why the Campylobacter risk assessment used by CVM and other studies relied on by CVM do not meet the evidentiary standards and, therefore, cannot provide a reasonable basis for withdrawal of NADA 140-828, and why CVM's evidence on the use of enrofloxacin does not provide a reasonable basis to raise a serious question about safety (section III). AHI has largely left to Bayer to respond to the scientific data offered into evidence by CVM.

CVM has not sustained its burden to show by new evidence that there is a reasonable basis to raise a serious question about enrofloxacin use in poultry. When the evidence is taken as a whole, including the uncontroverted benefits, it clearly leads to the conclusion that enrofloxacin is safe. Rather than raise a question about the safety of enrofloxacin, new evidence only reaffirms that enrofloxacin is safe.

LEGAL STANDARDS AND APPLICABLE BURDENS

A. CVM Has the Initial Burden of Producing "New" Evidence

The Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 201 et seq., places the initial burden on CVM to bring forward some sort of *new* evidence in order to support a withdrawal of a new animal drug. The statute requires that CVM have

> new evidence not contained in [a previously-approved] application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved . . . .

21 U.S.C. § 360b(e)(1)(B).

The critical aspect of this first step of the analysis is the requirement that CVM have "new" evidence. The statute makes it plain that CVM cannot simply reassess the evidence presented or available to it at the time of the original application without also considering something new in addition to that 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").

The statute specifies four types of new evidence: First, "new evidence not contained in [a previously-approved] application." Thus, evidence that points to a different conclusion that was not contained in the original application would be new. Evidence that merely states the same conclusions as evidence in the original application is not new, because the same conclusions were contained in the original application. Nothing "new" is shown if it merely restates that which was before the FDA at the time of the original application. Rather than being new, it is redundant, because it was "evidence available to the Secretary when the application was approved" and does nothing to "undermine[ ] the previous conclusions as to safety." *Id.* at 992.

Second, "evidence not available to the Secretary until after such application was approved." Thus, evidence that points to a different conclusion that was not available at the time of the original application would be new. *See Upjohn Co. v. Finch*, 422 F.2d 944, 951 (6th Cir. 1970) (finding that data not available at time of original application that contradicted data available at time of application were "new evidence"). Evidence that merely restates the same conclusions as evidence in the original application is not new, even if it chronologically post-dates the approval, because the same conclusions were "available to the Secretary at the time of

the original application." Chronologically later evidence that merely confirms or restates the conclusions of evidence contained in the original application, but lacks any further characteristics that would render this later evidence unique or distinguishable from that which went before, could not "undermine[ ] the previous conclusions as to safety" because it is merely more of the same, rather than something new. *Hess & Clark*, 495 F.2d at 992.

Third, "tests by new methods." Testing methods that were developed since the time of the original application are new. *See, e.g., Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980) (finding that results of more sophisticated tests not available at time of original animal drug application were "new" evidence within meaning of § 360b(e)(1)(B)).

Fourth, "tests by methods not deemed reasonably applicable when such application was approved." Testing by methods otherwise available at the time of the original application, but not deemed reasonably applicable at the time, would be new evidence. *See, e.g., Bell v. Goddard*, 366 F.2d 177, 181 (7th Cir. 1966) (finding that "clinical experience in a manner not previously attempted" was new evidence).

In sum, CVM must adduce something "new." The prior evidence is still relevant in any reconsideration of the question of safety, but the reason is because it must be viewed *together* with something *new*. If CVM fails to produce something new, or if its purportedly new evidence merely confirms the conclusions of the evidence available at the time of the original application, the analysis is at an end, as CVM has failed to satisfy its initial burden of proof.

B. CVM Must Then "Show" That the New Evidence Raises "Sufficiently Serious" Questions About Safety Under the Conditions of Use Upon the Basis of Which the Original Application Was Approved

CVM's burden of producing "new evidence" is only the first of two steps it must take to carry its initial burden. CVM must also demonstrate what the new evidence "shows in terms of undermining the previous conclusions as to safety." *Hess & Clark*, 495 F.2d at 992. Put another way, CVM's initial burden is to present "new evidence raising questions about the safety of [the animal drug] that are sufficiently serious to require the manufacturers to demonstrate that [the

animal drug] is safe." *Rhone-Poulenc*, 636 F.2d at 752. The FDA construes this language as requiring CVM to "provide a reasonable basis from which serious questions about the ultimate safety of the drug may be inferred." *E.g.*, *Enrofloxacin for Poultry; Notice of Hearing*, 67 FR 7700, 7700 (Feb. 20, 2002).

Safety, however, is not an abstract standard. The new evidence must show serious questions about the drug's safety "*under the conditions of use upon the basis of which the application was approved* . . . ." 21 U.S.C. § 360b(e)(1)(B) (emphasis supplied). If the new evidence does not raise serious questions about the safety of Baytril in the proper context, i.e., *as it was approved for use in the United States*, CVM has not met its burden. If CVM's evidence arises from uses of enrofloxacin *outside* of the U.S., the evidence is not relevant or at most is 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. For example, use of FQ as an animal drug in Spain is virtually unrestricted [B-56; G-530 P.2; Tr. P.675 L.22 – P.676 L.1], whereas in the U.S., such use is highly restricted. Moreover, such evidence of foreign usage fails to take into account other variables affecting the incidence of FQ-resistant *Campylobacter* infections in humans, such as rates of contamination of the water supply, which cannot be assumed equivalent to U.S. rates. The ecology of *Campylobacter* differs throughout regions of the world and cannot simply be assumed to the same in different locations. [Nachamkin (G-1470) P.5 L.29-30; Tr. P.526 L.4-19; Tr. P.718 L.3 – P.720 L.4]

In sum, if CVM produces any *new* evidence, it must show that the new evidence, either alone or taken together with the "old" evidence, raises serious questions about the safety of Baytril under the conditions of use upon which the original application was approved. If CVM fails to carry this burden, this matter is at an end, as there would be nothing to change the status quo (whereby Baytril is "shown to be safe" under the approved conditions of use) and Bayer would not need to (nor could it be expected to) rebut non-existent evidence. *Only if CVM*

satisfies its initial burden is Bayer required to show that Baytril is "shown to be safe" under the approved conditions of use.

C. If CVM Carries Its Initial Burden, Bayer Must Establish That Baytril Is "Shown to Be Safe," i.e., That Its Benefits to Human Health When Used in Poultry in the United States Outweigh Its Risks When So Used

If CVM carries its initial burden of production, the burden of proof then shifts to Bayer to "show that the drug is safe." *Hess & Clark*, 495 F.2d at 992. In *Hess & Clark*, the D.C. Circuit held, in considering whether an animal drug is "safe" within the meaning of Section 512(e)(1)(b) of the FFDCA (21 U.S.C. § 360b(e)(1)(B)), that

> [t]he typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. *Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use.*

495 F.2d at 993–94 (emphasis supplied) Six years later, in *Rhone-Poulenc*, the D.C. Circuit emphasized that the *Hess & Clark* risk/benefit analysis requirement quoted above was a holding of the court that governs the FDA's animal drug safety determinations "until we are instructed otherwise by the Supreme Court or an *en banc* decision of this court." 636 F.2d at 754. The D.C. Circuit's decisions in *Hess & Clark* and *Rhone-Poulenc* are directly on point and control the legal standards applicable in this case.

The Supreme Court has subsequently confirmed that whether a product is "safe" under the FFDCA is determined by whether a "product's probable therapeutic benefits . . . outweigh its risk of harm." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000) (citing *United States v. Rutherford*, 442 U.S. 544, 556 (1979) ("[T]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.")).

Indeed, in this proceeding, the CVM has acknowledged that the determination of "safety" requires a risk/benefit analysis, at least as it involves human health:

> Because the safety concern in this hearing is human food safety and human health impact, the proper risk/benefit analysis would

> need to consider whether the benefits to human health from use of the drug in poultry are proven to outweigh the risk to human health from the use of this drug in poultry.

CVM Opp. to Bayer's Motion to Reformulate Issues for Hearing, at 12 (Apr. 22, 2002); *see also* CVM Memorandum in Support of its Motion To Strike the Written Direct Testimony of Bayer Corporation and the Animal Health Institute, at 40. Thus, it is undisputed by the parties—and this tribunal has already ruled—that determining the safety of Baytril requires considering the risks and benefits of Baytril as regards human health. [ALJ Davidson's March 3, 2003, Order (OR31), P.1] The question is whether the human health benefits from use – i.e., benefits that would be lost if enrofloxacin is withdrawn, outweigh the benefits that result from keeping the drug on the market.[2]

EVIDENTIARY STANDARDS

Evidentiary standards in this proceeding are governed by 21 C.F.R. § 12.94 and the Administrative Procedure Act ("APA"), 5 U.S.C. § 500 et seq. "The presiding officer may exclude written evidence as inadmissible only if – (i) The evidence is irrelevant, immaterial, *unreliable*, or repetitive." 21 C.F.R. § 12.94(c)(1)(i) (emphasis supplied). The same standard applies to witness testimony pursuant to 21 C.F.R. § 12.94(d)(1)(i).

Under the APA, a "rule or order [may not be] issued except on consideration of the whole record or those parts thereof cited by a party and supported by and in accordance with the *reliable*, probative, and substantial evidence." 5 U.S.C. § 556(d) (emphasis supplied). In enacting section 556(d), "'Congress was primarily concerned with the elimination of agency decision-making premised on evidence which was of poor quality—irrelevant, immaterial, unreliable, and nonprobative—and of insufficient quantity.'" *U.S. Steel Mining Co., Inc. v. Director, Office of Workers' Compensation Programs*, 187 F.3d 384, 389 (4th Cir. 1999) (citing

[2] AHI does not waive their argument that the risk/benefit analysis of "safety" extends to economic, environmental, and indirect human health as well as direct human health considerations. This tribunal, however, has previously ruled that the risk/benefit analysis for "safety" is limited to human health considerations. *See* ALJ Davidson's March 3, 2003, Order (OR31) (ruling on the parties' motions to strike and stating that "[e]conomic and environmental evidence is not relevant to the issues in this proceeding."). For purposes of this submission, therefore, AHI assumes that the risk/benefit analysis for "safety" is confined to direct human health issues.

Steadman v. SEC, 450 U.S. 91, 102 (1981)); *see also Former Employees of Barry Callebaut v. Herman*, 240 F. Supp. 2d 1214, 1219 (CIT 2002) (noting the "requirement that administrative agencies may not consider information unless it bears satisfactory indicia of reliability") (internal quotation marks and brackets omitted). Thus, under section 556(d), an ALJ has a "gate keeping function to evaluate evidence." *U.S. Steel Mining*, 187 F.3d at 389. Although this function arises later in the administrative process than it does in a jury trial, "the ALJ's duty to screen evidence for reliability, probativeness, and substantiality similarly ensures that final agency decisions will be based on evidence of requisite quality and quantity." *Id.*

It is critical, therefore, to assess whether proffered evidence is "reliable." "In a case involving scientific evidence, *evidentiary reliability* will be based upon *scientific validity*." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590–91 n.9 (1993) (emphasis in the original). Although *Daubert* does not directly apply in an administrative proceeding, its general principle—that evidentiary reliability is dependent upon scientific reliability—does govern "reliability" in administrative proceedings in the sense that evidence without any scientific basis cannot support a decision under the APA. *See Peabody Coal Co. v. McCandless*, 255 F.3d 465, 468–69 (7th Cir. 2001).[3]

Both CVM and Bayer have submitted epidemiological studies in support of their positions. Epidemiological studies, by their very nature, involve some degree of extrapolation of data, and as such they can only establish a *probability* that the cause studied leads to the effect. *Tyler ex rel. Tyler v. Sterling Drug, Inc.*, 19 F. Supp. 2d 1239, 1243 (N.D. Okla. 1998). However, because epidemiological studies raise only a *probability*, they create "a special robust

[3] Reliability is distinct from relevance. The reliability of scientific evidence depends on the scientific validity of that evidence. An epidemiological study's reliability turns on the methodology employed by the person(s) conducting the study. The study must be grounded in, and performed according to, proper scientific methods. Relevance can be subject to a sliding scale, because it is well-established that epidemiological studies inherently involve some degree of extrapolation of data and can only establish a probability that the cause studied leads to the effect. *Tyler ex rel. Tyler v. Sterling Drug, Inc.*, 19 F. Supp. 2d 1239, 1243 (N.D. Okla. 1998). Depending on the strength or weakness of the probability shown, a party may have to bolster the study with further evidence, but all such evidence must meet the requirement of reliability. Put simply, reliability is crucial because a study cannot show or even suggest a possibility of causation if the study is scientifically unreliable—an unreliable study shows nothing.

need for . . . gatekeeping." *In re Agent Orange Prod. Liab. Litig.*, 611 F. Supp. 1223, 1260 (E.D.N.Y. 1985). To be of any use—that is, to be *reliable*—a study must:.

A. Establish an actual causal link between the alleged cause (here, enrofloxacin usage in poultry) and the effect being studied (here, resistant *Campylobacter* infections in humans). An epidemiological study cannot show an adverse effect (and thus cannot meet CVM's burden of proof) if the study itself is defective and does not show what it is purported to show. A study offered to show causation must actually establish at least a strong probability of causation for it to be relevant. *Allen v. United States*, 588 F. Supp. 247, 405 (D. Utah 1984). Absent such a showing, a proffered study cannot provide a reasonable basis to raise serious questions.

B. *Affirmatively rule out* alternative or supervening causes of the condition whose cause is being sought. *Agent Orange*, 611 F. Supp. at 1263. In scientific terms, the alternative cause is known as a "confounder" or a "confounding factor." *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 n.8 (D.N.J. 2002) (noting that "[c]onfounding refers to a situation in which the effects of two processes are not separated. The distortion can lead to an erroneous result."). When test subjects are exposed to a confounder, the study is, in essence, contaminated. Its results become unreliable because the study is only relevant if it shows that the cause at issue led to the effect. If a confounder is introduced, this cannot be shown. Thus, a study must actually *exclude*, or *rule out*, alternative causes. It is not enough simply to observe the desired effect when the desired effect could have been caused by something else. For example, *if* foreign travel is associated with both getting a FQ-resistant *Campylobacter* infection *and* with a longer duration of illness, it would be a confounding variable in case control studies examining the risk of getting a FQ-resistant *Campylobacter* infection unless controlled for. [Tr. P.46 L.3-20] As discussed later, both Smith and Nelson claim that FQ-resistant infections

result in a longer duration of illness compared to susceptible infections, but neither analysis removes cases that had undertaken foreign travel, which AHI and Bayer contend is a confounding variable. [Smith (G-1473) P.10 L.4-6; Kassenborg (G-1460) P.7 L.5-8; Burkhart (B-1900) P.40 L.3-4] CVM at least agrees that the cases of relevance are domestically acquired FQ-resistant campylobacteriosis and apparently, also, that cases acquired through foreign travel are subject to uncontrolled confounding by other risk factors. [G-953 P.25, 55-57, 103]

C. Reflect a sampling group that is statistically relevant to the actual group to whom the study's results are being imputed. A study can only be scientifically relevant if the data in the study can be tied to the circumstances for which the study is offered as support. Where the group of people examined in the study is significantly different from the actual group at issue and the study's proponent cannot reconcile the differences, the study is not relevant. *See, e.g., Adams v. NVR Homes, Inc.*, 141 F. Supp. 2d 554, 568–70 (D. Md. 2001); *see also Astra Aktiebolag v. Andrx Pharms., Inc.*, 222 F. Supp. 2d 423, 488 (S.D.N.Y. 2002) ("Thus, even if the methodology used by the expert is considered to be reliable, the expert's testimony will nevertheless fail to meet the 'fit' requirement and should be excluded if the data relied upon by the expert is [sic] materially different from the data relevant to the facts of the case."). In this case, because the relevant population is people who eat FQ-treated chicken or turkey in the U.S., related studies must reflect some subset of that group, and must exclude all other groups. For example, the inclusion of people who have recently visited foreign countries where other sources of resistant *Campylobacter* infections are found confounds the conclusions in the Smith and Nelson studies and renders the conclusion of those studies irrelevant and unreliable. Inclusion of foreign-acquired infections makes it *impossible* to determine whether the infection is caused by the use of enrofloxacin in the U.S.

D. Reflect a truly *random* sample. It is not appropriate to draw inferences from a non-random sample. "While this type of sampling [i.e., nonrandom] has definite uses and usually is less complicated and cheaper to complete than random sampling, it can only be justified if there is no need to generalize the findings beyond the specific sample studies." *U.S. v. Johnson*, 185 F.3d 765, 769 (7th Cir. 1999) (alteration in original) (quoting Wemhoefer, *Statistics in Litigation* 50 (1985)). Here, the generalization of findings beyond the specific sample studies is the very heart of CVM's entire case. Insofar as CVM has failed to use proper random and representative sampling techniques, CVM has failed to carry its burden of showing a "reasonable basis from which serious questions may be inferred." CVM's evidence is anecdotal at best, and even if the study is scientifically valid, it cannot be said to be representative of the entire U.S. For example, CVM's retail studies are not random samples and cannot be said to be representative of prevalence of FQ-resistant, or susceptible, *Campylobacter* in the U.S. Similar problems affect the NARMS data.

In addition to these general principles, the FDA's "Guidelines for Ensuring the Quality of Information Disseminated to the Public" ("FDA Guidelines") also provide useful guideposts to the reliability of CVM's evidence. *See* 67 FR 61,343 (Sept. 30, 1982) (available at http://www.hhs.gov/infoquality/fda.html).[4] The FDA Guidelines require that when the FDA disseminates information, but particularly in those cases involving influential information[5], the

[4] Pursuant to Section 515 of Public Law 106-554 ("Data Quality Act"), the Office of Management and Budget ("OMB") has issued Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies ("OMB Guidelines"). *See* 67 FR 8451 (Feb. 22, 2002). The OMB Guidelines provide policy and procedural guidance to federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by federal agencies. The OMB Guidelines also require other federal agencies to issue their own implementing guidelines applicable to information disseminated by that agency. Pursuant to the OMB Guidelines, and as part of the U.S. Department of Health and Human Services implementation plan to comply with the OMB Guidelines, the FDA has issued the FDA Guidelines.

[5] The term *influential information*, when used in the OMB Guidelines in the phrase "influential scientific, financial, or statistical information," applies when the agency can "reasonably determine that dissemination of the information will have or does have a *clear and substantial impact* on important public policies or important private sector decisions." *See* 67 FR 8452 (Feb. 22, 2002). The FDA has defined *influential information* as "disseminated information that results from or is used in support of agency actions that are expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the economy, a sector of the economy,

FDA "strive[s] to ensure that the information is accurate and unbiased, as well as substantially reproducible and replicable. The goal is accomplished by using reliable data sources and sound analytical techniques ..." FDA Guidelines, § VII B.

AHI and Bayer believe that the testimony and evidence submitted by CVM in this public hearing constitutes influential information[6] disseminated by the FDA. Accordingly, even if the FDA Guidelines are not strictly applicable to this proceeding, they do nevertheless inform the evaluation of the reliability of CVM's testimony and evidence in this proceeding. This evaluation demonstrates that much of the testimony and evidence submitted by CVM in this hearing does not meet the requirements of the FDA Guidelines, and is further evidence of the unreliability of that testimony and evidence. This includes at a minimum the studies, as offered by CVM, of Smith [G-589], Kassenborg [G-337], Nelson/McClellan [G-1679; G-1489] Neimann [G-455; B-561], CVM's RA [G-952], and poultry and Human NARMS data as utilized by CVM.

The FDA Guidelines establish a "number of quality assurance policies, standards, and processes for ensuring the quality of the information the [FDA] disseminate[s] to the public." FDA Guidelines, § V. FDA documents must "undergo a rigorous review and clearance evaluation according to pre-established procedures, documented in [FDA] regulations and guidances." FDA Guidelines, § V. In addition to normal FDA "chain of command" review of documents, the Guidelines describe other mechanisms required to ensure the quality of information. Quality, as defined in the OMB and FDA Guidelines, encompasses, inter alia, "objectivity, whether information is being presented in an accurate, clear, complete, and unbiased manner." FDA Guidelines, § V.

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productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities." FDA Guidelines, § VII(A).

[6] CVM's proposed regulatory action to withdraw approval of the new animal drug application for use of the FQ enrofloxacin in poultry is reasonably expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the poultry industry, productivity in the poultry industry, the environment, and/or public health or safety. *See* Written Direct Testimony of G. Thomas Martin, Jr. [B-1907] While this tribunal has previously ruled that this evidence is not relevant to safety, it is relevant to whether CVM's evidence is "influential information" within the meaning of the FDA guidelines.

As described above, the FDA Guidelines apply special qualitative standards to the dissemination of information that is considered "influential." Such information must meet high standards of transparency of the data and methods used to facilitate the reproducibility of such information by third parties. In the case of transparency, the goal is to produce "accurate and unbiased" information. "This goal is accomplished by using reliable data sources and sound analytical techniques, and by employing a high degree of transparency about the data, methods, measures, assumptions and limitations used to develop the information to facilitate reproducibility by third parties." FDA Guidelines, § VII(B). This includes revealing biases, ensuring clarity, and utilizing a participatory process. *Id.* As is described below, much of CVM's testimony and evidence – especially the reports or testimony of Smith [G-1473, G-589], Kassenborg [G-337], Angulo [G-1452], McClellan/Nelson [G-1679; G-1489] and Neimann [G-455; B-561], as well as the CVM RA [G-952]–does not meet these requirements for ensuring the quality of information. CVM's failure to comply with the standards outlined in the FDA Guidelines is further evidence that its testimony and evidence is unreliable or irrelevant.

Furthermore, the FDA Guidelines demonstrate numerous flaws in CVM's RA. The FDA Guidelines define "risk" as the "likelihood that injury or damage is or can be caused by a substance, technology, or activity." FDA Guidelines, § VII.C, "Risk Assessment." In accordance with the Data Quality Act, the FDA Guidelines adopt as standards for quantitative risk assessment the approach set forth in the Safe Drinking Water Act. Additionally, for quantitative risk assessments in support of the dissemination of influential information, such as the CVM RA, the agency describes the type of data that should be used and the methods utilizing such data:

> 1. The agency will use:
>
> a. the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available;

b. data collected by accepted methods (if reliability of the method and the nature of the decision justifies use of the data);

* * * * *

3. In a risk assessment document made available to the public, the agency shall specify, to the extent practicable—

* * * * *

c. Each population addressed by any estimate of applicable effects;

d. The expected or central estimate of risk for the specific populations affected;

e. Each appropriate upper-bound and/or lower-bound risk estimate and the methodology used to reconcile the inconsistencies in the scientific data;

f. Data gaps and other significant uncertainties identified in the process of the risk assessment and the studies that would assist in characterizing the uncertainties; and

g. Additional studies not used to produce the risk estimate that support or fail to support the findings of the assessment, and the rationale of why they were not used.

FDA Guidelines, § VII.C. The CVM RA model does not comply with the above guidance for, *inter alia*, among the following reasons. The CVM model:

(1) does not use the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available;

(2) uses data not collected by accepted methods (where reliability of the method and the nature of the decision justifies use of the data); and

(3) does not identify, use, or explain why additional studies not used to produce the risk estimate that support or fail to support the findings of the assessment were not used; and

(4) does not follow the Safe Drinking Water Act approach for quantitative risk assessment.

These failures are further evidence that the CVM RA is unreliable and irrelevant.

Finally, Bayer obtained, though the federal Freedom of Information Act or its state equivalent, the raw data relied upon by CVM's experts Angulo, Friedman, Kassenborg, McClellan, Effler, and Smith in reaching their conclusions. AHI's and Bayer's experts Burkhart, DeGroot, and Cox independently reviewed these data and demonstrated that the conclusions of several of CVM's experts were incorrect. CVM did not rebut this showing, and, indeed limited its cross-examination of AHI's and Bayer's experts on this issue to Cox. In sum, AHI and Bayer have demonstrated, through their experts' independent and unrebutted review of the data forming the basis of CVM's expert opinions, that CVM's expert testimony is not reliable on several key findings, as demonstrated herein. Indeed, as demonstrated below, this independent review confirms that CVM has failed to raise a serious question as to the safety of enrofloxacin, because the data relied upon by CVM's experts show that the human health risks associated with enrofloxacin usage in poultry in the U.S. is less today than at the time of the original approval in 1996.

ARGUMENT

I. CVM'S RISK ASSESSMENT DOES NOT RAISE A SERIOUS QUESTION AS TO WHETHER POULTRY IS A SOURCE OF FQ-RESISTANT *CAMPYLOBACTER* INFECTIONS IN HUMANS

As discussed above, CVM has the initial burden of providing a reasonable basis from which serious questions about the safety of Baytril use in poultry may be inferred. Moreover, the evidence that provides this basis must be new, i.e., not available at the time CVM approved Baytril as being safe for such use in 1996.

According to CVM, at the time it approved Baytril for use in poultry, it was not aware of the impact that such use would have on human health, but that impact was subsequently revealed by the CVM *Campylobacter* risk assessment. [G-953; the "CVM RA"] According to CVM, the CVM RA provided CVM with evidence of the magnitude of the impact of FQ use in chicken by establishing that such use has a negative impact on human health. [CVM Interrog. Ans. 8; Tollefson (G-1478) P.16 L.30-34; Cox (B-1901) P.24]

This argument fails because the CVM RA is unreliable CVM's failure to comply with accepted scientific standards for quantitative risk assessments establishes that the CVM RA is not scientifically reliable. Although the parties appear to agree that risk assessments must comport with certain accepted guidelines and standards, such as demonstrating factual evidence of a causal relation between exposure and harm, the CVM RA does not do so. Additional reasons why the CVM RA is not reliable are: (1) it suffers from conceptual problems that make it unable to provide evidence of the objective nature and extent of the human health impact from use of Baytril in chickens, (2) it is not supported by, and indeed is contradicted by, relevant data, and (3) it miscalculates the impact it was intended to quantify. *See generally* Bayer Br. § I.B.2.g.

A. The CVM Risk Assessment Does Not Comport with Accepted NAS/NRC Guidelines and Standards.

The parties appear to agree that the CVM RA should follow certain accepted guidelines and standards, in particular including elements of the paradigm set forth by the National Academy of Sciences (the "NAS paradigm") in two documents produced by the National Research Council ("NRC"), *viz.* Risk Assessment in the Federal Government (1983) and Science and Judgment in Risk Assessment (1994). CVM asserts that the NAS Paradigm contains four elements: (1) hazard identification, (2) exposure assessment, (3) hazard characterization, and (4) quantitative health risk assessment. CVM further asserts that the CVM RA follows the NAS Paradigm. [CVM Interrog. Ans. 46] This latter assertion is incorrect.

The elements of the NAS Paradigm are authoritatively set forth at pages 26–27 of the second NRC report cited by CVM, Science and Judgment in Risk Assessment in the Federal Government (hereinafter "NRC Report," republished at http://books.nap.edu/books/030904894X/html/26.html#pagetop).[7] These elements are hazard identification, dose-response assessment, exposure assessment, and risk characterization.[8]

[7] 21 C.F.R. § 12.95(a) provides that "[o]fficial notice may be taken of such matters as might be judicially noticed by the courts of the United States or of any other matter peculiarly within the general knowledge of FDA as an expert agency." Federal courts have cited to the NRC Report, Science and Judgment in Risk Assessment as a reliable authority. *See In re Hanford Nuclear Reservation Litig.*, 1998 U.S. Dist. LEXIS 15028, at *209 n.104 (Aug. 21, 1998), *rev'd on other grounds,* 292 F.3d 1124, 1127 (9th Cir. 2002) (reversing based on grounds unrelated to the risk

CVM purports to recognize these elements of the NAS Paradigm's "four step analytic process for human health risk assessment" (NRC Report at 26–27). However, CVM uses different names and a different order. These departures are not merely nominal. Crucial substantive differences can be seen when the details of CVM's assertion that the CVM RA followed the elements of the NAS Paradigm are compared to the NRC's actual elucidation of its four steps.

1. The CVM RA Does Not Meet the Hazard Identification Step of Valid Quantitative Risk Assessments

First, the NRC Report states that the initial step, "hazard identification,"

> entails identification of the contaminants that are suspected to pose health hazards, quantification of the concentrations at which they are present in the environment, a description of the specific forms of toxicity (neurotoxicity, carcinogenicity, etc.) that can be caused by the contaminants of concern, and an evaluation of the conditions under which these forms of toxicity might be expressed in exposed humans.

Id. at 26. Thus, according to this definition, "hazard identification" entails (a) identification of the contaminants suspected to pose health hazards; (b) quantification of the concentrations at which they are present in the environment; (c) description of the specific forms of toxicity that can be caused by the identified contaminants; and (d) an evaluation of the conditions under which these forms of toxicity might be expressed in exposed humans.

With regard to such "hazard identification," CVM states that the CVM RA

> identifies the hazard as FQ resistance in *Campylobacter* attributed to use of FQs in chickens among persons who seek care for campylobacteriosis and are prescribed a FQ.

[CVM Interrog. Ans. 46] CVM's phrasing requires some interpretation to determine if the CVM RA does in fact match up with the NRC's definition of "hazard identification."

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assessment, specifically the district court's inappropriate "reliance upon cases that deal with the test to apply in order to determine whether a substance has the capacity to cause harm...") (citation omitted) Moreover, the NRC Report falls "within the general knowledge of FDA as an expert agency," since CVM has relied upon it in this hearing, *see* Travis (G-1479) P.3 L.14 - P.4. L.2, in addition to other NRC reports that were also not part of the evidentiary record in this hearing. *See* Vose (G-1480) P.2 L.49 – P.3 L.31. In sum, this assessment is the type of reliable material judicially noticed and, therefore, it should be officially noticed here as well.

[8] These elements are also referenced at Travis (G-1479) P.3 L.24 – P.4 L.2.

It would seem that "fluoroquinolone resistance in *Campylobacter* attributed to the use of fluoroquinolones in chickens" constitutes the "identification of contaminants suspected to pose health hazards," satisfying (a) above. It would seem that "among persons who seek care for campylobacteriosis and are prescribed a fluoroquinolone" constitutes "the conditions under which these forms of toxicity might be expressed in exposed humans," satisfying (b) above. But what are the "forms of toxicity," i.e., the third component of hazard identification under the NRC definition, which entails "description of the specific forms of toxicity that can be caused by the identified contaminants" as described in (c) above? CVM's account of how the CVM RA follows the NAS Paradigm does not specify any forms of toxicity caused specifically by FQ resistance of *Campylobacter* attributed to the use of FQs in chickens.

It appears that the most precise specification of the forms of toxicity presumed to be caused by such resistant *Campylobacter* may be found at page 7 of the CVM RA. [G-953 P.7] There, it is stated, "The health risk associated with antimicrobial resistant bacteria represents an increase in risk to consumers because resistance to an antimicrobial used in human medicine can compromise the effectiveness of therapy." [*Id.*] It is important to note the peculiar limits of this specified "form of toxicity" (beyond the fact that it is an unproved speculation presented as a fact, and that it appears to be contradicted by available data specifically for FQs, as detailed in the section on Health Risks). The CVM RA does not identify any specific toxic outcome of ineffective therapy of FQ-resistant *Campylobacter*. For example, it does not assess whether, or to what extent, such resistant *Campylobacter* might result in more severe or longer illness [*Id.* at 15]

Thus, although CVM states that the CVM RA "answered" the question of the impact that Baytril use in poultry would have on human health [CVM Interrog. Ans. 8], as Bartholomew testified, the CVM RA stopped with the quantification of persons estimated to have resistant campylobacteriosis and treated with FQs; it did not attempt to quantify how many people respond how fully to such treatment. [Tr. P.744 L.21 – P.745 L.8] Consequently, the CVM RA,

which CVM states answered the question of health impact, stopped short of doing that. It only estimated the number of people with chicken-related resistant *Campylobacter* who were treated with FQs. In addition, as developed below, this failure compromises the accuracy and the sufficiency of the CVM RA. [*See also* Cox (B-1901) P.25]

A further significant gap between the CVM RA's "hazard identification" and the NRC's definition of "hazard identification" is the lack of any quantification of the concentrations of FQ-resistant *Campylobacter* that are present on domestic chicken consumed in the U.S. To be sure, the CVM RA reports data on the prevalence of such *Campylobacter* at various points in the processing, distribution, and sale of chicken and estimates how much chicken is consumed. However, the CVM RA expressly and intentionally does not use the *concentration*, or "microbial load," of such *Campylobacter* on chicken at any point in those environments. [*See* G-953 P.8-9; Vose (G-1480) P.10 L.4-13, L.24-40, P.11 L.12 - P.14 L.4; Bartholomew (G-1454) P.4 L.27–47] Moreover, even with regard to prevalence, the CVM RA does not quantify such *Campylobacter* pertaining to chicken prepared and consumed at commercial establishments. As discussed below, this failure is especially important with regard to the accuracy and the utility of the CVM RA.

The CVM RA's "hazard identification" also incorporates an arbitrary and capricious assumption that all FQ-resistant *Campylobacter* that are present on domestic chicken consumed in the United States are attributable to use of FQs–specifically, enrofloxacin–in broilers. Rather than meeting the burden of identifying (or presenting objective evidence for) an actual causal relation between enrofloxacin use in chickens and FQ resistance rates in human campylobacteriosis cases – a causal relation that is countered by CVM's own witnesses and data [Hanninen (G-1458) P.8 ¶ 13; Tr. P.649 L.10-13, P.699 L.22 – P.700 L.7, P.715 L.9 – P.716 L.6, P.716 L.14-22]–CVM simply assumes that there is one. This vitiates the proper role of hazard identification as setting forth objective, data-based evidence that the presumed hazardous activity

or exposure (e.g., enrofloxacin use) actually causes the harm that is feared from it (e.g., increased resistance rates and resulting treatment failures in humans).

Therefore, the CVM RA does not, in fact, follow the NAS Paradigm's first, "hazard identification" element. It fails to quantify any specific form of toxicity or health impact. It fails to quantify the concentrations of the contaminant it identifies as being of interest, i.e., FQ-resistant *Campylobacter* attributed to the use of FQs in chicken, and it fails to show any objective evidence that use of enrofloxacin in chickens actually causes increased resistance rates in humans or any increased harm to human health.

Finally, the CVM RA neglects the fact that risk management decisions that affect the one contaminant CVM has focused on–FQ-resistant *Campylobacter*–will necessarily also affect other contaminants, including FQ-susceptible *Campylobacter* and *Salmonella*, that are quantitatively more important in creating adverse health outcomes. The total human health impacts of proposed risk management interventions cannot be assessed by considering effects on resistant bacteria alone. Thus, CVM's hazard identification has not successfully completed "identification of the contaminants that are suspected to pose health hazards," but instead has focused on *one* hazard (resistant *Campylobacter*) to justify an action that will have far larger impacts on other components of hazard (susceptible *Campylobacter* and *Salmonella*) that the CVM RA has chosen to ignore [Cox (B-1901) P.7 L.15-18, P.9, 12-13, 25, 74-75, 83-87] Such incomplete hazard identification, emphasizing small components of hazard while ignoring larger ones, cannot serve the purposes of rational risk management.

2. The CVM RA Does Not Meet the Dose-Response Assessment Step of Valid Quantitative Risk Assessments

As noted above, the NAS Paradigm's second element is "dose-response assessment." According to the NRC Report, this element

> entails a further evaluation of the conditions under which the toxic properties of a chemical might be manifested in exposed people, with particular emphasis on the quantitative relation between the

> dose and the toxic response. The development of this relationship may involve the use of mathematical models.

NRC Report at 26.[9]

With regard to this "dose-response assessment," which CVM refers to as a "hazard characterization," CVM states that the CVM RA

> characterizes the hazard by relating the quantity of chicken contaminated with FQ-resistant *Campylobacter* to the number of persons who seek care for campylobacteriosis which is attributed to chicken and whose *Campylobacter* isolates are resistant to FQs.

CVM Interrog. Ans. 46. The CVM RA provides a further explanation of what the "quantitative relation between the dose and the toxic response" (to use the NRC Report's words) would mean to it in the present circumstances:

> The dose-response relationship describes the probability of being infected (or becoming ill, or suffering various degrees of illness, or death) given some ingested dose. Each individual consumption event has associated with it some dose-response relationship. This is because for any specific number of organisms ingested the probability of infection, etc. depends on the age, size, health status, etc. of the exposed person, as well as the immediate circumstances surrounding the ingestion event....

G-953 at 9.

The CVM RA did not utilize the number of organisms ingested (microbial load) and dose-response relationship models, however. [Bartholomew (G-1454) P.5 L.30-31] There is no specific construction or utilization of a dose-response relationship, despite the availability of data [B-577; B-748], and despite the fact that other noted risk assessors have used a dose response model using the NRC/Codex paradigm in an assessment of the impact of FQ-resistance

[9] The definition of "dose-response assessment" provided by Cox is very similar to that provided by the NRC Report. Cox writes "For other microbial risk assessments, FDA (with CDC and USDA) has previously defined risk assessment as a process that 'consists of the following steps: hazard identification, exposure assessment, *hazard characterization (dose-response)*, and risk characterization...' It defined dose-response assessment as 'The determination of the relationship between the magnitude of exposure and the magnitude and/or frequency of adverse effects.' Similarly, the Codex Alimentarius Commission states that 'For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.'" [Cox (B-1901) P.18 (emphasis in original)] Cox also states: "The crucial need for a dose-response analysis in risk assessment is expressed as follows in an EPA discussion of risk assessment basics: 'Under the NAS paradigm and in most EPA practice, however, *risk assessment is complete only when human exposure assessment information is joined with dose-response analysis* and all relevant information to characterize risk'" [Cox (B-1901) P.18 (emphasis in original)]

Campylobacter jejuni derived from cattle. [B-147; Haas (B-1904) P. 9 L.6-9][10] To be sure, CVM did not do so because it believed that doing so would introduce large uncertainties, and because it believed that it did not need to do so because it had found an alternate means for predicting numbers of human cases (i.e., partitioning the annual numbers of human cases for 1998 and 1999 based on CDC estimates). [Bartholomew (G-1454) P.5 L.27-29] Nevertheless, it is not correct to say that the CVM RA followed the NAS Paradigm in respect of the second, dose-response assessment element, since it utilized neither microbial loads nor dose-response relationships nor models keyed to microbial loads. Moreover, as discussed below, CVM's decision to attempt to circumvent this standard dose-response step leads to crucial difficulties in that the CVM RA does not provide a useful fit to the actual data.

3. The CVM RA Does Not Meet the Exposure Assessment Step of Valid Quantitative Risk Assessments

The third element of the NAS Paradigm is "exposure assessment." This step

> involves specifying the population that might be exposed to the agent of concern, identifying the routes through which exposure can occur, and estimating the magnitude, duration, and timing of the doses that people might receive as a result of their exposure.

NRC Report at 26–27. [11]

CVM states that the CVM RA follows this step in that it

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[10] One of the authors of this study is Dr. Lester Crawford, now Deputy Commissioner of FDA.

[11] Cox states: "A traditional definition of exposure assessment (Joint Expert Consultation of the FAO/WHO ...) is 'the qualitative and/or quantitative evaluation of the *degree of intake* likely to occur'. (emphasis added). The traditional risk assessment framework considers that the *amount* of contamination ingested by individuals (e.g., expressed as a population frequency distribution of CFUs, or colony-forming units, of Campylobacter ingested in meals) is crucial for quantifying risk. This reflects the fundamental principle that 'the dose makes the poison'.

FDA has recognized this key concept in its own previous definitions for other microbial risk assessments, e.g., in defining exposure assessment as 'A component of a risk assessment that characterizes the source and *magnitude* of human exposure to the pathogen', while equating magnitude of human exposure (i.e., 'dose') to 'The *amount* or *number* of a pathogen that is ingested or interacts with an organism (host)'... Similarly, EPA experts have stated that 'Questions raised in the exposure analysis concern the likely sources of the pollutant...its concentration at the source, its pathways (air, water, food) from the source to target populations, and actual levels impacting target organisms.' ... In the context of campylobacteriosis, the 'actual levels impacting target organisms' part of this definition would refer to the number of ingested CFUs of *Campylobacter* (total or FQ-r, depending on the risk being quantified)." [Cox (B-1901) P.16 (emphasis in original)]

> assesses exposure of humans to FQ-resistant *Campylobacter* by quantifying the amount of chicken consumed per year, the proportion of chicken that carry *Campylobacter* and the prevalence of resistance among the chicken with *Campylobacter* tested for FQ sensitivity.

[CVM Interrog. Ans. 46]

This rendition of the concept of exposure assessment differs significantly from the NRC Report's, however. It differs by substituting *prevalence* of resistant *Campylobacter* on chicken for microbial load, or *concentration*, of resistant *Campylobacter* on chicken. This creates a twofold difficulty as can be seen by reference to the discussion of exposure assessment in the NRC Report.

First, the NRC Report defines "human exposure" in a way that inextricably involves concentration:

> Human exposure to a contaminant is an event consisting of contact with a specific contaminant concentration at a boundary between a human and the environment (e.g., skin or lung) for a specified interval; total exposure is determined by the integrated product of concentration and time.

NRC Report at 44. The point of this definition is that *quantity matters*. This reflects the fundamental principle that "the dose makes the poison." For *Campylobacter*, the quantity of exposure–the number of colony forming units ("CFUs") ingested in a meal–matters in determining risk. Use of prevalence, however, omits this crucial information. As discussed by Cox [Cox (B-1901) P.16-18, 64-65, 69, 74-75], prevalence does *not* provide an adequate basis for predicting risk (unless microbial loads remain constant). Where changes in use of enrofloxacin are contemplated, neither the antimicrobial load of susceptible CFUs nor the microbial load of resistant CFUs is expected to remain constant, and so prevalence is an inadequate exposure metric, in that risk cannot be accurately predicted from it when microbial loads change [Cox (B-1901) P.16-20, 22, 64-67, 69, 74-75] And the latter is a real life fact. There are a number of assumptions made in the CVM RA which are not explicitly grounded in data. For example, at a public meeting it was questioned whether there is support for a linear

assumption between disease burden and frequency of consumption of *Campylobacter* positive portions. [Haas (B-1904) P.23 L.1-9]

Second, the NRC Report states that there are three ways to estimate exposure, of which the second, "environmental monitoring," is most relevant here:

> Exposure to a contaminant can be estimated in three ways. It can be evaluated directly by having a person wear a device that measures the concentration of a pollutant when it comes into contact with the body. Environmental monitoring is an indirect method of determining exposure, in which a chemical's concentration is measured in an environmental medium at a particular site, and the extent to which a person is exposed to that medium is used to estimate exposure. Finally, exposure can be estimated from the chemical's actual dose to the body, if it manifests itself in some known way through a measurable internal indicator (biological marker), such as the concentration of the substance or its metabolite in a body tissue or excreted material (NRC, 1991a).

NRC Report at 44–45. Thus, the NAS Paradigm for exposure assessment depends upon measuring or estimating the contaminant's concentration in a medium, and *then* measuring or estimating the extent to which persons are exposed to the medium.

The CVM RA, however, measures the extent to which persons are exposed to the medium of chicken without measuring concentration, or microbial load. One can only begin to call this approach an "exposure assessment" by making the assumption that concentration on a particular portion of chicken—i.e., "at a particular site," to use the NRC Report's language–does not matter. This assumption itself entails an underlying assumption that the relevant human exposure is not, as the NRC Report states, "an event consisting of contact with a specific concentration." It entails yet a further assumption that the concentration or microbial load ingested "at a boundary between a human and the environment"—e.g., the mouth or intestine, to paraphrase the NRC Report—does not matter. Thus, the CVM RA cannot take credibility from conformity to the carefully considered process that is the essence of the NAS Paradigm. On the

contrary, it must demonstrate that it is credible despite its failure to follow this process and paradigm.

Thus, as was the case with the dose-response element, CVM concluded that it did not need to measure concentration or load to estimate exposure. However, it is still, and for this very reason, incorrect for CVM to maintain that it followed the NAS Paradigm. It is incorrect to claim that the spirit of the NAS framework has been preserved in CVM's extension and application of risk assessment principles to "antimicrobial risk assessment." This neologism was introduced early in CVM's foray into developing its own alternative risk assessment methodologies, evidently in hopes that creating a terminological distinction between risk assessment of animal antimicrobials and risk assessment of other agents would justify omitting the essential content of established risk assessment methodology. [Haas (B-1904) P.10 L.13-17; Vose (G-1480) P.4 L.37 – P.5 L.16, P.10 L.24-40, P.16 L.43-44] Moreover, as further discussed below, and as was the case with CVM's circumvention of the process's dose-response step, this decision not to use exposure concentrations also results in crucial inconsistencies between the CVM RA and the actual data.

4. The CVM RA Does Not Meet the Risk Characterization Step of Valid Quantitative Risk Assessments

The fourth, and last, element in the NAS Paradigm is "risk characterization." This step

> involves integration of information from the first three steps to develop a qualitative or quantitative estimate of the likelihood that any of the hazards associated with the agent of concern will be realized in exposed people. This is the step in which risk-assessment results are expressed.

NRC Report at 27.[12]

[12] Cox writes: "In the traditional risk assessment framework, risk characterization is supposed to integrate hazard identification, exposure assessment, and dose-response information to determine the probable frequency and severity of adverse health effects that exposure to a hazard causes in a population. For example, the Joint FAO/WHO Expert Consultation defines risk characterization as the 'integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties'. FDA has previously used exactly this definition in micrrobial [sic] risk assessment ..." [Cox (B-1901) P.20]

CVM's account of the NAS paradigm substitutes the term "quantitative health risk assessment" for "risk characterization." [CVM Interrog. Ans. 46] "Quantitative health assessment" is defined by CVM as a step that

> quantifies the health risk as the probability of experiencing the hazardous outcome.

[*Id.*]

As can be seen in the light of the above discussion of CVM's departures from "the first three steps" of the NAS Paradigm, the CVM RA's relating of the quantity of chicken consumed to persons who seek care and receive a FQ does not estimate the likelihood of any specified adverse human health effect: It does not identify any specific "form of toxicity." It does not quantify the concentrations—microbial loads—at which FQ-resistant *Campylobacter* are present in the relevant pathway (poultry consumed by humans). It does not quantify or model any dose-response relationship. It quantifies the medium consumed, but not the exposure concentration. Thus, contrary to CVM's assertion, the CVM RA does not follow the standard-setting NAS Paradigm. [Haas (B-1904) P.7 L.20 - P.8 L.4] Its failure to do so not only deprives it of the credibility that the paradigm provides, but also involves it in intrinsic conceptual difficulties and conflicts with actual data that render its results meaningless and useless as a guide to rational action, accurate prediction, or sound policy-making. Interestingly, the recent risk assessment of the risks of FQ-resistant *Campylobacter* from use of FQs in cattle, conducted at Georgetown University and authored in part by Lester Crawford, currently FDA Deputy Commissioner, does appear to follow the NAS. [B-147] Additionally, the FDA's Center for Food Safety and Applied Nutrition described the NAS paradigm as the generally accepted methodology for microbial risk assessments. [A-34 P.4]

B. The CVM Risk Assessment Does Not Comport with Data Quality Act Standards

Additionally, and for many of the reasons discussed above, the CVM RA also does not meet the quantitative risk assessment standards adopted by the FDA Guidelines. [Haas (B-1904)

P.20 L.7-10] For example, two additional U.S. studies that were not used to produce the risk assessment include the CDC case-control study data as analyzed by Friedman [G-228; G-1488] and Effler [G-185] Friedman was clearly available to CVM before the CVM RA was finalized. Notwithstanding that Effler was published *before* CVM's written direct testimony was filed in December 2002, CVM continued to rely in its testimony on the two outdated studies and did not modify its RA based on more relevant data. As an additional example, the CVM RA "predictive model approach" [Vose (G-1480) P.6 L.38] has not been generally accepted in the risk assessment field. [Haas (B-1904) P.17 L.19-20; Cox (B-1901) Att. 1, P.24 ¶¶ 2 ("CVM has interpreted..."), 3] The model has not been published in a peer review journal or otherwise gained acceptance by the scientific community, notwithstanding that it was finalized more than 2 1/2 years ago. [Haas (B-1904) P.17 L.9 – P.20 L.6; Cox (B-1901) Att. 1, P.25 ¶¶ 2, 3] For example, the World Health Organization ongoing *Campylobacter* risk assessment has not utilized the CVM RA model, [B-975], nor has the Crawford *Campylobacter* risk assessment. [B-147] For these reasons, the CVM RA is not reliable as evidence in this proceeding.

C. The Risks of Enrofloxacin Use are No Greater Than Those Accepted by FDA Under the SDWA

Ironically, if the CVM RA were to be utilized despite its flaws, correcting certain of the basic data inputs to ameliorate some of the more significant and easily repaired difficulties would support the conclusion that the use of Baytril in poultry is safe, in accordance with the FDA's accepted standard for microbial food contaminants. This standard is the one the FDA has accepted in connection with its regulations setting risk-based limits for microbial contaminants in bottled water. In short, in setting these limits, the FDA adopted the risk-assessment standards set by the EPA for drinking water supplies regulated under the Safe Drinking Water Act. 58 FR 52,042, 52,044–45 (Oct. 6, 1993) (proposed rule); *see also* 21 U.S.C. § 349; 42 U.S.C. § 300f *et seq*. This Safe Drinking Water Act approach is all the more relevant now that Congress, OMB, and the FDA have adopted the SDWA approach as the federal government's standard via the

recent data quality legislation and regulations. Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001.[13]

Under this approach, the FDA adopted a population risk-based standard for safety for microbial contaminants in bottled water of 1 x 10^{-4}, or one in ten thousand. If one uses the etiologic fraction for chicken-associated resistant *Campylobacter* from Kassenborg as being based on the CDC data recommended for such use in the CVM RA, the percent resistance from NARMS from the years 1998 and 1999, and a treatment failure range from the Piddock and Sanders studies, the risk level is in the range of 10^{-5} to 10^{-6}. See Table 1, P.40.

Similarly, if one substitutes the conservative end of the etiologic fraction range calculated by Cox, then the population risk range is approximately 10^{-7} to 10^{-8}, below even the range used by the FDA and other federal agencies for regulating cancer risks. Indeed, the EPA, which implements the Safe Drinking Water Act, utilizes a 10^{-4} to 10^{-6} range for regulating cancer risks. 40 C.F.R. § 300.430 (e)(2)(i)(A)(2). See Table 2, P.40.

II. ADDITIONAL CVM EVIDENCE IS EITHER NOT RELIABLE OR NOT NEW

A. Under the Evidentiary Principles Outlined Above, Other CVM Evidence Is Not Reliable

The Smith study is unreliable because it does not support the proposition in support of which CVM has offered it. Smith's analysis does not show any association between poultry consumption and FQ-resistant *Campylobacter* infections in humans. He acknowledged that his results could not rule out the possibility of a common third source for both chickens and people, and he recognizes that the genetic typing used in his study does not establish causation but is "one piece of evidence that has to be considered with everything else." *See generally* Bayer Br. § I.B.2.b.iii.

[13] P.L.106-554 § 515 (2001); OMB "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies" at 67 FR 8452–8460 (Feb. 22, 2002); FDA "Guidelines for Ensuring the Quality of Information Disseminated to the Public" (at http://www.hhs.gov/infoquality/fda/html); and Safe Drinking Water Act Amendments of 1996 (42 U.S.C. § 300 g-1(b)(3)(A) and (B)).

Kassenborg's study is unreliable because, while she found that foreign travel is a risk factor for FQ-resistant *Campylobacter* infection, her study did not evaluate whether those cases associated with foreign travel could have been a consequence of FQ use in food-producing animals, as opposed to some other cause. She also acknowledged that her findings depended on the model she used and that other models could produce different results, thus rendering all of her conclusions suspect. Finally, Kassenborg's study found that consumption of poultry is a risk only when poultry is eaten at a commercial establishment, and she simply assumed that consumption at home is a risk factor. *See generally* Bayer Br. § I.B.2.b.iii.

Human NARMS data are not reliable because the data are not generalizable to the U.S. population as a whole and because the sampling scheme is arbitrary and unrepresentative of the national pool of FQ-resistant *Campylobacter* infections. The collection of human Campylobacter isolates for antibiotic susceptibility testing in the NARMS program differs from that of the other bacteria studied, is not representative of the cases received at the participating state laboratories, and does not control for known confounders like foreign travel and prior human use. [*See e.g.*, Carnevale (A-199) P. 10 – 19]. *See generally* Bayer Br. § I.B.2.d.i.(b).

Likewise, the data derived from analysis of chicken Campylobacter isolates in the animal NARMS program is unreliable and will not support a determination of the prevalence of fluoroquinolone resistant Camplyobacter on chicken carcasses. A consistent sampling methodology has not been utilized, which renders year-to-year comparison meaningless. [Carnevale (A-199) P. 4 – 10]. Additionally, the isolation and culture methods have not been the same for each year. [*Id.*] Variations in culturing methods and variation among sample sources make comparisons of chicken NARMS *Campylobacter* susceptibility patterns from year to year or among sample populations scientifically inappropriate. [*Id.*] *See generally,* Bayer Br. § I.B.2.d.i.(b).

CVM's "temporal association" evidence is unreliable because it does not support the proposition in support of which it is introduced—in fact, it supports the opposite proposition. As

an initial matter, CVM acknowledges that "temporal association" evidence cannot be equated with evidence of causation. In addition, there is ample evidence from several of countries of measurable levels of FQ resistance in poultry or people at times long before any FQs were used, but CVM's evidence simply ignores this evidence and does not attempt to explain why it should not be considered credible. *See generally* Bayer Br. § I.B.2.d.

CVM's retail studies are unreliable because they cannot be generalized to the U.S. market as a whole and because they do not realistically track the actual conditions in the marketplace. The samples utilized are minuscule, fewer than 200, compared with the multi-billion-chicken and multi-million-turkey marketplace. CVM's studies also employ methodologies that *introduce* confounding factors into the studies (the exact opposite of the proper scientific methodology). It is thus impossible for the studies to rule out alternative causes of resistance. Additionally, CVM's studies provide no information at all on the issue of dose, even though CVM acknowledges that the risk that a given meal will lead to campylobacteriosis depends at least in part on the number of *Campylobacter* ingested. *See generally* Bayer Br. § I.B.2.f. See generally Bayer Br. § I.B.2.g.

B. CVM's Evidence is Also Not New

As described herein and in Bayer's Post-Hearing Brief, CVM's evidence is nto new, or if it is new, does not raise serious questions about the safety of enrofloxacin. For the convenience of the trier of fact, AHI has attached as Appendix A a list of all documents in evidence that were published prior to the approval of enrofloxacin (October 4, 1996), and therefore available to CVM. Attached as Appendix B are documents published some time in 1996 where the precise date is undetermined.

III. CVM HAS NOT MET ITS BURDEN OF SHOWING THROUGH NEW EVIDENCE THAT ENROFLOXACIN USE IN TURKEYS RAISES SUFFICIENTLY SERIOUS QUESTIONS ABOUT SAFETY

In order for the FDA to withdraw the approval for use of enrofloxacin in turkeys, the FDA must meet the same burden of proof it must meet to justify withdrawal of use of enrofloxacin in chickens, only with evidence specific to turkeys. As described in Section I, *supra*, CVM must present new evidence that "shows" that enrofloxacin is not now shown to be safe for its intended use in turkeys before such approval may be withdrawn. 21 U.S.C. § 360b(e)(1); *see also Hess & Clark* and *Rhone-Poulenc, supra*. Moreover, what CVM "shows" must provide a reasonable basis from which serious questions about the safety of use of enrofloxacin in turkeys in the U.S. may be inferred. For chickens and separately for turkeys, as described below, CVM has not met this threshold burden.

As described in the Bayer brief, CVM has not supplied sufficient evidence with respect to chickens to support the withdrawal of the NADA for enrofloxacin use in chickens. Clearly, this chicken data cannot therefore support the removal for turkey. Neither the limited turkey data which is in evidence nor the chicken data raise serious questions about the safety of enrofloxacin. In addition, the epidemiological evidence that is available for turkeys shows that the risk of campylobacteriosis attributable to turkey consumption is minor, about 4% when turkey is consumed in a restaurant. [G-1452, Att. 3, P.101] This is only 1/6th the attribution to chickens (24%). [*Id.*] Thus, even the minimal evidence that is available for turkeys shows that the potential health hazard from FQ-resistant *Campylobacter* infections that the FDA foresaw prior to the drug's approval for use in turkeys (and chickens) is in fact better, not worse, than originally anticipated.

A. FDA Required Separate Label Indications for Use in Chickens and Turkeys for Enrofloxacin's Approval

Throughout the proposed withdrawal process, CVM has focused on enrofloxacin use in poultry as a whole and has provided virtually no evidence with respect to turkeys. [*See* NOOH,

NOH, CVM Narrative Statement, CVM Responses to Bayer Interrogatories (discussed below)] For example, the CVM RA is based only on chicken consumption, not turkey; Animal NARMS monitors only resistance in chicken, not turkeys. Moreover, the evidence that CVM has provided is inadequate to meet its statutory burden. The deficiency with CVM's approach, treating chicken and turkey identically, is that enrofloxacin is not approved for use in "poultry." Rather, enrofloxacin has separate label indications for use in chickens and turkeys:

- Enrofloxacin is approved for the control of mortality in chickens associated with *Escherichia coli* susceptible to enrofloxacin.
- Enrofloxacin is approved for the control of mortality in turkeys associated with *Escherichia coli* and *Pasteurella multocida* (fowl cholera) susceptible to enrofloxacin.

[JS 39; A-54; McDermott (G-1465) P.2 L.11-13]

As the product Sponsor, Bayer was required to provide the FDA with "full reports of investigations" separately demonstrating in chickens and turkeys the safety and efficacy of enrofloxacin. [21 U.S.C. § 360b(b)(1)] Had Bayer failed to provide these reports for either chickens or turkeys, the FDA would have refused to approve the application (NADA 140-828). [21 C.F.R. § 514.111] In general, sponsors seeking approval of a new animal drug for use in a major species are barred from relying on data extrapolated from another species because such data would not show that such drug is safe or effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling. [*Id.*] Therefore, any attempt to withdraw enrofloxacin should require separate evidence on both chicken and turkey.

B. CVM Has Treated Chickens and Turkeys as Posing Identical Risks for FQ-Resistant *Campylobacter* Infections

CVM has stipulated that in late 1993 or early 1994, before FQs were approved for use in chickens and turkeys, CVM management understood and accepted that 1) FQ use in chickens and turkeys could act as a selection pressure, 2) the potential existed for FQ-resistant *Campylobacter* to be transferred from chickens and turkeys to humans and to contribute to the

development of FQ-resistant *Campylobacter* infections in humans, and 3) FQ-resistant *Campylobacter* infections have the potential adversely to affect human health. [JS 2, 3, 5 (emphasis added)] CVM has stipulated to these facts for both chickens and turkeys because 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. This is aptly demonstrated in CVM's Responses to Bayer's Interrogatories, in which Bayer requested that CVM identify specifically when CVM first understood each issue in the case (i.e., selection pressure, source of campylobacteriosis, and impact on human health), and whether CVM's current understanding of each issue differs from its understanding prior to approval. [Interrogatories 1-3, 6-8, 51-53] In every instance, CVM's response with respect to turkeys was to "see the answer for chickens" [CVM Interrog. Ans. 1-3, 6-8, 51-53] Thus with respect to each of the issues of the case, CVM has acknowledged that its presentation of the facts and evidence is the same for both chickens and turkeys. As demonstrated below, this collapsing of the issues fails when the FDA's burden is applied.

C. Turkeys and Chickens Are Inherently Different and These Differences Are Significant in Calculating the Potential Risks of Transmitting Campylobacteriosis

CVM's efforts to conflate the use of enrofloxacin in chickens and turkeys under the single moniker of "poultry" must fail in light of the numerous physical, clinical, pathological, processing, and other differences between chickens and turkeys. As a result of fundamental differences in how chickens and turkeys are colonized by microflora, how they are raised, and how they are processed, the risk of transmitting *Campylobacter jejuni* infection to humans is inherently different between the two. [Gonder (A-201) P.11 L.12-14] Therefore, evidence with respect to chicken cannot be imputed to turkey. In fact, when the evidence on chickens and turkeys is properly evaluated separately, it is clear that these differences are significant and that turkeys represent a much smaller risk of campylobacteriosis when compared to chickens.

To begin, turkeys and chickens are members of different species. [Gonder (A-201) P.11 L.10] Therefore, factors that influence the diagnosis, prevalence, and treatment of disease in one are not the same as in the other. [Gonder (A-201) P.11 L.10-12; Wages (B-1917) P.19 L.20-22]

Grow-out differences between turkeys and chickens contribute to reduced bacterial loads on turkeys as compared to chickens. [Gonder (A-201) P.11 L.14-16] Turkeys have more frequent house clean-out and their live-haul equipment is more routinely sanitized between processed flocks, which can lead to a reduction in infectious materials. [Gonder (A-201) P.11 L.16-17]

Turkey processing plants are significantly different than chicken processing plants, and these differences can greatly impact pathogen loads. For example, turkey processing utilizes higher scalding temperatures than chickens, which kills more *Campylobacter*. [G-9; Gonder (A-201) P.11 L.21 through P.12 L.2] Most significantly, because turkeys are usually less uniform in size than chickens, in addition to being larger and heavier animals [Minnich (G-1467) P.6 L.11], turkey processing plants tend to be less automated (or mechanical) than chicken processing plants. [Minnich (G-1467) P.2 L.17-18] Instead, turkeys are normally subject to *manual* evisceration and cropping. [Gonder (A-201) P.12 L.4] There is evidence of a reduction in enteric pathogen contamination as a result of manual evisceration rather than mechanical. [Gonder (A-201) P.12 L.4-5] Indeed, size and processing line speed are key factors influencing overall carcass contamination rates. [G-9; Logue (G-1464) P.7 L.31 – P.8 L.1] This is consistent with the results of Russell's study, which found that mechanical evisceration of underweight birds led to increased processing errors.

After evisceration, turkeys further undergo extended chilling to reduce carcass temperature due to larger body mass. [Gonder (A-201) P.12 L.6] This utilizes more chlorinated water and chilling capacity than chicken processing such that bacterial loads are further reduced since chlorination, chilling, and washing all reduce *Campylobacter* levels during processing. [Gonder (A-201) P.12 L.6-11; Logue (G-1464) P.7 L.17-19 and L.29-31; JS 24 & 31]

Both at the processing stage and the point of sale, turkeys are more physiologically and immunologically mature than chickens, with more stable intestinal microflora. [Gonder (A-201) P.12 L.11-12 and P.14 L.15-16] Chickens are generally marketed at 6-9 weeks of age, whereas turkeys are marketed at 13-21 weeks of age in most situations. [Gonder (A-201) P.14 L.14-15] This maturity should result in an intestinal microflora more closely resembling that of a competitive exclusive culture, which should reduce the number of enteric pathogens, including *Campylobacter*, that are present. [Gonder (A-201) P.14 L.16-19; B-1861]

Although few studies have been undertaken in turkeys [G-686] and the data are limited with respect to the prevalence of foodborne pathogens among turkey carcasses at slaughter, including *Campylobacter* [Logue (G-1464) P.2 L.26-28], there is evidence for differences between chickens and turkeys in the pathological consequences of infection, on-set and rate of dissemination of colonization, chronicity of infection and shedding, and diversity of infective strains. [Newell (B-1908) P.4 L.1-7] Overall these observations suggest that *Campylobacter* colonization in broilers and turkeys may have significant host-specific differences, including prevalence and level (or number) of *Campylobacter* in the average colonized chicken versus the average colonized turkey. [Newell (B-1908) P.4 L.11-12; Jacobs-Reitsma (G-1459) P.7 L.28-32; Gonder (A-201) P.13 L.3-9; Wages (B-1917) P.20 L.6-7]

Finally, as compared to chickens, far more turkey meat is produced for further processed sales. [Gonder (A-201) P.14 L.19-20] Such further processing usually includes cooking, which kills bacteria, including *Campylobacter*, that may otherwise be present on the raw carcass. [B-1857; Gonder (A-201) P.14 L.20-22] In fact, several major producers now cook all their turkey product in-plant and do not provide turkey to the non-processed market. [Gonder (A-201) P.15 L.3-4] Consumption patterns show, moreover, that modern consumers buy very little raw turkey, even at Thanksgiving. [Gonder (A-201) P.14 L.22-23] In 2001, there were 8.6 billion broilers (chickens) raised for slaughter in the U.S. [JS 43] In contrast, only 270 million turkeys

were similarly raised. [JS 44] Plainly, chickens and turkeys comprise or are a part of two different industries. [Hofacre (A-202) P.2 L.18-19]

These differences plainly demonstrate that CVM's efforts to collapse turkeys and chickens into "poultry" and treat them interchangeably with respect to the issues of the case is patently incorrect. These differences speak directly to the risk of turkey as a source of campylobacteriosis, and each of the differences points to the conclusion that turkey is much less of a risk factor than chicken. Under such scrutiny, it is clear that turkeys cannot be treated simply as "big chickens."

D. CVM Knew and Evaluated the Potential Risks of Enrofloxacin Use in Turkeys Prior to Approval and Concluded That Enrofloxacin Was Safe for Use in Turkeys

As noted above, CVM has stipulated that, prior to the approval of enrofloxacin in late 1993 or early 1994, CVM management understood and accepted that 1) FQ use in turkeys could act as a selection pressure, 2) the potential existed for FQ-resistant *Campylobacter* to be transferred from turkeys to humans and to contribute to the development of FQ-resistant *Campylobacter* infections in humans, and 3) that FQ-resistant *Campylobacter* infections have the potential adversely to affect human health. [JS 2, 3, 5 (emphasis added)] CVM knew of this potential health hazard, considered it, and nevertheless approved enrofloxacin for use in both chickens and turkeys. As is described further below, the new evidence that exists is with respect to turkeys shows that turkeys are, at worst, a very minimal source of human campylobacteriosis, and may not be a source at all.

E. CVM Has Not Met Its Burden of Proof with Respect to Turkeys

Despite the weight of the evidence demonstrating that chickens and turkeys have significant differences which ultimately affect both prevalence of *Campylobacter* on turkeys and the incidence rate of human campylobacteriosis attributable to turkey, CVM's case rests on the proposition that all evidence specific to chicken may be extrapolated to turkeys. Not only does the legal framework prohibit CVM from extrapolating in this instance, but the facts demonstrate

that turkey, even more so than chicken, presents only a minimal risk factor for human cases of campylobacteriosis. Turkey eaten in the home, like chicken, is a negative risk factor for campylobacteriosis, while turkey eaten in restaurants presents a lower risk factor than even chicken eaten alone. [Angulo (G-1452) P.10 L.22-32; G-1452, Att. 3, P.88; G-945 P.5] Rather than presenting the facts for turkey separately, CVM lumps together turkey and chicken as "poultry," and obscures the fact that turkey, even assuming CVM's numbers are correct, is much less a risk factor than chicken.

1. *CVM Has Presented No Evidence That Enrofloxacin Use in Turkeys Does Act as a Selection Pressure*

The parties have stipulated that FQ use in chickens and turkeys can act as a selection pressure for FQ-resistant bacteria in the chicken and turkey digestive tract. [JS 7, 45] However, CVM has presented no evidence that demonstrates that the use of enrofloxacin in turkeys does act as a selection pressure for FQ-resistant *Campylobacter* in turkeys. The laboratory studies which show that enrofloxacin acts as a selection pressure have all been conducted on chickens, not on turkeys [G-315, B-868, G-1746], and CVM has presented no evidence to demonstrate that, with respect to turkeys, chicken data may be extrapolated. The numerous physical, clinical, pathological, processing, and other differences between chickens and turkeys (highlighted above) clearly undermine or negate CVM's ability to make such a legitimate inference. The record thus reflects a complete lack of evidence that FQ use in turkeys does act as a selection pressure for FQ-resistant bacteria. As such, CVM cannot have met its burden with respect to this issue.

2. *The Most Recent and Robust U.S. Data Indicate Turkey Is at Worst a Very Minor Source of Campylobacteriosis*

The evidence in the record shows that foreign travel is a significant risk factor for acquiring *Campylobacter* infection. [G-589 P.4 Table 1; G-1452 Att. 1, P.46; Wegener (G-1483) P.13 L.12; Kassenborg (G-1460) P.9 L.10-11; Nachamkin (G-1470) P.4 L.25-26] The evidence also shows that the largest risk factor for acquiring a domestic *Campylobacter* infection is eating meat (including poultry) in restaurants. [Angulo (G-1452) P.10 L.36-44; G-1452 Att. 3, P.101;

G-1488 P.23 Table 1] Of this meat eaten in restaurants, turkey comprises a very small amount. In fact, CVM acknowledges that the most recent and robust U.S. data show that turkey represents, at most, a 4% population attributable risk (PAR) for campylobacteriosis (and may be as little as zero). [Angulo (G-1452) P.10 L.39-41] (This compares to a PAR of, at most, 24% for chicken eaten in a restaurant). [*Id.* L.37-38]

Moreover, this 4% figure represents only turkey eaten outside of the home, since, like chicken, turkey eaten in the home is associated with a negative risk of human campylobacteriosis. [G-1644; Cox (B-1901) P.29; G-945 P.5; Burkhart (B-1900) P.9, L.39-41] Other recent U.S. data go even further (e.g., Effler's Hawaii epidemiological study) and do not even demonstrate any risk ("borderline statistical significance") from eating turkey outside the home. [G-185; Tauxe (G-1475) P.9 L.5-9] These facts demonstrate that, even with respect to turkey eaten in a restaurant, the numbers are very small, and an order of magnitude lower than for chicken.

The bulk of the evidence that CVM does provide with respect to turkeys is focused on prevalence, and does not address the significant issues of either dose or source. For example, CVM's primary witness on turkeys, Logue, acknowledges that data on turkey is limited and that few studies have been undertaken on *Campylobacter* colonization in turkeys. [Logue (G-1464) P.2 L.26-28; G-686 P.1] Logue's study [G-1464], which shows that *Campylobacter* may be present on turkey carcasses at slaughter (and other evidence related to the prevalence of *Campylobacter* in and on turkeys), is irrelevant in the face of epidemiological evidence which demonstrates that not only is eating turkey in the home associated with a negative risk of human campylobacteriosis, but that the risk factor associated with eating turkey in a restaurant is minimal. Simply stated, prevalence of *Campylobacter* on carcasses has no relevance to disease. Even assuming prevalence were relevant, retail studies show that *Campylobacter* prevalence of turkeys is substantially lower than it is for chicken. [Jacobs-Reitsma (G-1459) P.7 L.28-32; Gonder (A-201) P.13 L.3-9]

In addition to the fact that retail studies show that *Campylobacter* prevalence of turkeys is substantially lower than it is for chicken, another factor which divorces prevalence from disease is proper food handling and cooking procedures. Food handling practices and consumer knowledge of microbial food safety has markedly improved over the past decade, particularly from 1993, before enrofloxacin approval, to 2001, as demonstrated by several consumer studies conducted by the FDA. [Tompkin (A-204) P.9 L.29-30] These studies showed significant improvement in consumers' habits related both to cross contamination and to eating potentially risky food in the period between 1993 and 1998. [Tompkin (A-204) P.10 L.14-17] The studies also noted an additional but small improvement in habits between 1998 and 2001. [*Id.*] Since it is undisputed that proper cooking kills *Campylobacter* [Wegener (G-1483) P.9 L.21-23], proper food handling and cooking procedures renders *Campylobacter* prevalence irrelevant.

Finally, limited genotyping articles in the record also support the proposition that turkey is a very minor source of *Campylobacter* in humans. For example, in a recent U.K. study comparing *Campylobacter* strains from humans, cattle, sheep, and turkey, the predominate human biotype was found in only 4% of turkey isolates. [G-218 P.2] Conversely, the predominate turkey biotype was found in only 3% of the human isolates. [*Id.*] These results belie CVM's assertion that this study shows a "high degree of similarity" between turkeys and humans [Wegener (G-1483) P.16 L.33-37] or a "link." [Nachamkin (G-1470) P.8 L.3-4] Rather, this study supports the epidemiological evidence that shows that turkey is at worst a very minor source of human campylobacteriosis.

The record thus reflects that, with respect to turkey as a source of campylobacteriosis, turkey is at worst a very minor source and perhaps not a source at all. As such, CVM has not raised serious questions and has not met its burden with respect to this issue.

3. *Even If Prevalence Were Relevant, Retail Studies Suggest Substantially Lower Prevalence for Turkeys Compared to Chickens*

From June 1999 to July 2000, Meng's laboratory conducted a survey of retail fresh meats for *Campylobacter*, *E. coli*, and *Salmonella* in the Washington, D.C., area. The prevalence of *Campylobacter* in retail chicken and turkey was 70.7% and 14.5%, respectively. [G-727; Meng (G-1466) P.2 L.26-35] In Meng's study [G-727], both *C. jejuni* and *C. coli* were isolated more frequently from retail chicken than from turkey, pork, or beef. [Meng (G-1466) P.3 L.16-17] This is supported by FSIS studies which indicate that only 8.5% of ground turkey samples were positive for *Campylobacter jejuni/coli*, while 73 of 162 (45%) of ground chicken samples were positive (Food Safety & Inspection Service, USDA, Nationwide Raw Ground Chicken Microbiological Survey and Nationwide Raw Ground Turkey Microbiological Survey). [Gonder (A-201) P.12 L.22 – P.13 L.3] Preliminary data as of November 2002 for the retail meat arm of NARMS show that 58% of 356 chicken breast samples analyzed and only 8% of 372 turkey samples were positive for *Campylobacter*. [White (G-1484) P.4 L.12-15] Thus, even if prevalence were relevant, prevalence data shows *Campylobacter* prevalence of turkeys to be smaller than compared to chickens.

4. *CVM Has Presented No Evidence That Enrofloxacin Use in Turkeys Presents a Harm to Human Health*

CVM has provided no separate data to support the assertion that FQ-resistant *Campylobacter* infections in humans occur as a result of eating turkey and contribute to an adverse human health outcome. The record thus reflects a complete lack of evidence and, as such, CVM cannot have met its burden with respect to this issue.

F. Even Assuming CVM's Risk Assessment Were Valid, It Provides No Evidence with Respect to Turkeys and Calculating the Risk with Available Data Shows Turkey to Be a Minimal Risk

Assuming only for the sake of argument that CVM's RA were reasonable with respect to chicken, CVM's RA ignores any data on turkeys, and is not a tool for evaluating the risk of associated illness from turkey. For the sake of argument, were CVM's model correct, where

CVM uses a 57% PAR for chicken, the most recent and robust data regarding turkey shows at most a 4% PAR for turkey. [Angulo (G-1452) P.10 L.43-44]

Using the CVM RA model and the 4% turkey attributable fraction, one can arguably calculate the risk associated from turkeys. The CVM RA concludes that 9,261 people had FQ-resistant *Campylobacter* illness from chickens and received a FQ in 1999. [G-953 P.64] In arriving at that number, CVM estimates that 57% of all cases are chicken related. Dividing 9,261 by 0.57 reveals that a total of 16,247 people with FQ-resistant *Campylobacter* illness from *all sources* that received a FQ in 1999. Applying the turkey attributable fraction of 4% (16,247*.04) yields a mere 650 people having a FQ-resistant *Campylobacter* illness from *turkeys* and receiving a FQ in 1999, out of a total U.S. population of approximately 272 million people.

Of course, the CVM RA merely estimates the number of people having a FQ-resistant *Campylobacter* illness from chicken and receiving a FQ in 1998 and 1999, and presumes an adverse health affect for 100% of people in that group. [G-953 P.64] The CVM RA does not include any factor to correct its estimate to account for people who have a so-called resistant case, receive a FQ, and have an effective treatment. Evidence in the record shows that the treatment failure rate of resistant cases is at most between 25% and 42% [B-1920, P.4 reporting that between 58% and 75% of resistant cases responded to treatment] and could be as low as 2.56% [B-50, P.2 reporting only one of 39 patients with resistant infections failing to respond to treatment] Correcting the above turkey estimate to account for between a 42% - 25% failure rate reduces the turkey attributable impact to between 273 and 163 people impacted.

G. Animal and Human NARMS Resistance Data Do Not Include Turkey

It is undisputed that the poultry arm of NARMS only tests for prevalence and FQ-resistance of *Campylobacter* in chicken. [Tollefson (G-1478) P.10 L.8-11; DeGroot (A-200) P.7 L.2-9); Tr. P.112 L.14-19] Tollefson's testimony states that the animal NARMS surveillance program reports levels of resistance to FQs in only the chicken carcass isolates of *Campylobacter jejuni*. [Tollefson (G-1478) P.12 L.2-7] Thus, no baseline for turkey has been or can be

established with respect to any FQ-resistance on a nationwide basis. Likewise, the Human NARMS program does not identify infection by source, so it is impossible to attribute any of the human illnesses to turkey consumption as well. Therefore, one of the pillars of the FDA's case with respect to chicken provides no basis of evidence for the withdrawal of enrofloxacin with respect to turkey.

H. Enrofloxacin Is Effective in Turkeys and There Are No Practical Alternatives

FDA approved enrofloxacin for use in turkeys for the control of mortality in turkeys associated with *Escherichia coli* and *Pasteurella multocida* (fowl cholera) susceptible to enrofloxacin on the basis that it is safe and effective. [Revised JS 39] In fact, enrofloxacin is the most efficacious antibiotic available in the U.S. for treatment of *E. coli* infections in broiler chickens and *E. coli* and *Pasteurella multocida* infections in turkeys. [Glisson (B-1903) P.5 L.21 – P.6 L.1] Moreover, enrofloxacin is the only efficacious drug for treating *E. coli* or *Pasteurella multocida* infections in turkeys. [Gonder (A-201) P.36 L.5-6] As described above with respect to chickens, due to high resistance to tetracyclines and sulfa drugs, and the residue concerns with sulfa drugs, there are no practical alternatives to enrofloxacin. [Gonder (A-201) P.36 L.6-7]

IV. ENROFLOXACIN IS SAFE FOR USE IN TURKEYS BECAUSE THE BENEFITS TO HUMAN HEALTH FROM ENROFLOXACIN USE IN TURKEYS OUTWEIGH ANY POTENTIAL RISKS

Bayer has presented evidence on the human health benefits from the use of enrofloxacin in chickens showing that these benefits outweigh any potential risks of enrofloxacin use. Assuming only for the sake of argument that the 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.

CONCLUSION

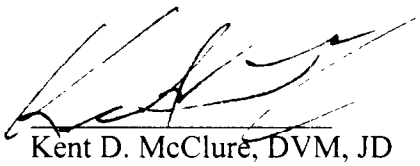
For the reasons provided above and in Bayer's brief, this tribunal should find that CVM has failed to carry to its initial burden of showing new evidence that raises serious questions about the safety of enrofloxacin under its approved conditions of use, and that in any event, enrofloxacin is safe for its approved conditions of use in chickens and turkeys because the human health benefits of such usage outweigh any potential human health risks.

FINDINGS OF FACT/CONCLUSIONS OF LAW

AHI hereby incorporates by reference Bayer's findings of fact and conclusions of law numbered 1-99.

Respectfully Submitted,

Animal Health Institute

By: 

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Appendix A
Articles Published Prior To The Approval Of Enrofloxacin

A-1	B-609	B-1710	G-411	G-1712
A-2	B-625	B-1713	G-424	G-1712
A-3	B-626	B-1724	G-440	G-1713
A-62	B-631	B-1725	G-445	G-1718
A-104	B-634	B-1761	G-446	G-1745
A-132	B-655	B-1762	G-474	G-1758
A-159	B-667	B-1763	G-491	G-1783
A-184	B-686	B-1771	G-497	
A-196	B-735	B-1819	G-499	
B-7	B-736	B-1821	G-505	
B-8	B-739	B-1822	G-524	
B-15	B-743	B-1823	G-525	
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B-187	B-932	G-121	G-599	
B-193	B-1017	G-157	G-615	
B-196	B-1087	G-162	G-622	
B-213	B-1102	G-172	G-624	
B-214	B-1127	G-180	G-652	
B-217	B-1190	G-188	G-653	
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B-283	B-1255	G-240	G-671	
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B-300	B-1263	G-253	G-705	
B-313	B-1264	G-256	G-707	
B-339	B-1266	G-267	G-720	
B-360	B-1329	G-268	G-810	
B-364	B-1376	G-285	G-817	
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B-384	B-1414	G-303	G-1003	
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Appendix B
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TABLE 1

Table 1. Summary of Kassenborg-Based Population with Domestically-Acquired FQ-r *Campylobacter* Infections Acquired from Eating Chicken or Turkey at a Commercial Establishment and for Which an FQ Was Prescribed

	1998	1999	References
(a) U.S. Population	270,248,003	272,690,813	P. 26 of CVM RA (G-953)
(b) Mean Number of *CP* Infections/Year	1,769,018	1,376,073	P. 26 and 44 of CVM RA (G-953)
(c) % FQ-r *CP* Infections/Year	14%	18%	P. 75 Angulo (G-1452 Att. #2)
(d) % of PAF for Domestically Acquired FQ-r *CP* Infections From Eating Chicken or Turkey at a Commercial Establishment	38%	38%	P. 9 and 14 Kassenborg (G-1460)
(e) % of Patients who took FQ for their *CP* Infections	111 / 858 = 12.94%	12.94%	P. 1 Marano (G-394)
(f) Population with FQ-r *CP* Infection Acquired from Eating Chicken or Turkey at a Commercial Establishment and Treated with an FQ = [(c)/100 x (b) x (d)/100 x (e)/100]/a	**4.5×10^{-5}**	**4.5×10^{-5}**	calculation
(g) Treatment Failure "Bookends"	2.6% to 42%	2.6% to 42%	1/39 failed = 2.6% (B-50); 58% achieved a cure (B-1920 P.4) so 100-58% = 42% failure rate. Note: B-1920 reported hypothetical maximum cure rate of 75%, but 25% failure rate not used
(h) Population in (f) that may fail treatment = (f) x (g)	**1.2×10^{-6} to 1.9×10^{-5}**	**1.2×10^{-6} to 1.9×10^{-5}**	calculation

TABLE 2

Table 2. Summary of Cox-Based Population with Domestically-Acquired FQ-r *CP* Infections Acquired from Eating Chicken or Turkey at a Commercial Establishment and for Which an FQ Was Prescribed

	1998	1999	References
(a) U.S. Population	270,248,003	272,690,813	P. 26 of CVM RA (G-953)
(b) Mean Number of *CP* Infections/Year	1,769,018	1,376,073	P. 26 and 44 of CVMRA (G-953)
(c) % FQ-r *CP* Infections/Year	14%	18%	P. 75 Angulo (G-1452 Att. #2)
(d) % of Population-Attributable Fraction for Domestically Acquired FQ-r *CP* Infections From Eating Chicken or Turkey at a Commercial Establishment	0.72%	0.72%	P. 22 of Cox (B-1901)
(e) % of Patients who took FQ for their *CP* Infections	111 / 858 = 12.94%	12.94%	P. 1 Marano (G-394)
(f) Population with FQ-r *CP* Infection Acquired from Eating Chicken or Turkey at a Commercial Establishment and Treated with an FQ = [(c)/100 x (b) x (d)/100 x (e)/100]/a	**8.5×10^{-7}**	**8.5×10^{-7}**	calculation
(g) Treatment Failure "Bookends"	2.6% to 42%	2.6% to 42%	1/39 failed = 2.6% (B-50); 58% achieved a cure (B-1920 P.4) so 100-58% = 42% failure rate. Note: (B-1920) reported hypothetical maximum cure rate of 75%, but 25% failure rate not used
(h) Population in (f) that may fail treatment = (f) x (g)	**2.2×10^{-8} to 3.6×10^{-7}**	**2.2×10^{-8} to 3.6×10^{-7}**	calculation

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of Non-party participant Animal Health Institute's Brief was served on the following on the 18th day of July, 2003 as follows:

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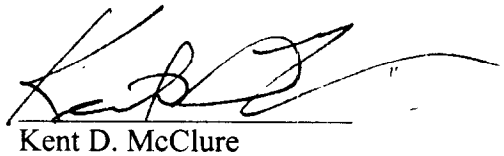

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MCDERMOTT, WILL & EMERY

July 18, 2003

Received 7/18/03
5:20 p.m. jcb

VIA HAND DELIVERY

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 Participant Animal Health Institute'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)

2000N-1571

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