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: January 27, 2003**

BAYER'S MOTION TO STRIKE CVM'S WRITTEN DIRECT TESTIMONY AND EVIDENCE

RESPONDENT Bayer Corporation, holder of the new animal drug application (NADA 140-828) that is the subject of the above-referenced Notice of Hearing, hereby moves to strike portions of CVM's submitted written direct testimony and other evidence on the grounds that the challenged portions of the testimony and evidence is either unreliable, irrelevant, immaterial or repetitive.

Bayer files this Motion to Strike certain written direct testimony and exhibits filed by CVM. CVM has filed a great volume of testimony and exhibits, amounting to well over 1000 pages. Much of this testimony and many of the exhibits rely upon or repeat certain common assertions and documents. Accordingly, Bayer's motion primarily focuses on certain themes and commonly cited testimony and documents which do not belong in the administrative record because they may not legally be relied upon by regulatory decision-makers and reviewing courts, under prevailing administrative rules and evidentiary standards. Accordingly, and being mindful of the administrative nature of this proceeding, Bayer's motion focuses on testimony and exhibits which do not meet the basic standards for legal and scientific reliability and relevance.

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These standards, and Bayer's objections, go to the legal and scientific integrity of the proceeding, not merely to the weight to be accorded to testimony and documents that are properly to be considered as a part of the administrative record. Thus, Bayer's Motion to Strike is guided by the FDA's regulations regarding the admissibility of evidence, the FDA's standards for data upon which the agency will rely in important matters, the APA's standard for the exclusion of evidence, and the evidentiary standards developed by Federal courts that obtain in adjudicatory proceedings. The necessary and proper application of these standards is critical to the integrity and legality of the administrative record upon which the decision in this preceeding must be made and reviewed, and therefore as well to the upcoming adjudicatory hearing and the decision itself.

The challenged testimony and evidence relates to the following topics:

1. All testimony and evidence that relies on the National Antimicrobial Resistance Monitoring System ("NARMS") data. (See Appendix A.) CVM relies on NARMS data to attempt to show rising fluoroquinolone resistance in *Campylobacter* isolates from humans and poultry since enrofloxacin was approved in 1996. Serious methodological flaws in the NARMS program render the resulting NARMS data and all testimony and evidence based on it unreliable, irrelevant and inadmissible as evidence.
2. All testimony and evidence that relies on the CVM/Vose risk assessment. (See Appendix B.) CVM relies on the CVM/Vose risk assessment to attempt to show adverse human health effects from the use of fluoroquinolones in poultry. Failure of the CVM/Vose risk assessment to meet even FDA's standards for risk assessment, as well as other widely accepted standards for risk assessment; its failure to use any generally accepted

methodologies, its use of untested and incorrect assumptions that human illness rates are proportional to chicken consumed (and that a single constant of proportionality holds in different states), its failure to consider benefits of use and risks of withdrawal of enrofloxacin, its misuse of Bayes' Rule to substitute subjective and demonstrably incorrect judgments for multiple years of data, its use of outdated data, rather than more recent available data, and other flaws, errors and omissions result in an estimate of risk to human health that is invalid, inaccurate and in conflict with available data. As such, the CVM/Vose risk assessment and all related testimony and evidence is unreliable, irrelevant and inadmissible as evidence.

3. All testimony and evidence that purports to show that infections with fluoroquinolone-resistant *Campylobacter* result in a longer duration of illness compared to infections with fluoroquinolone-susceptible *Campylobacter* infections. (See Appendix C.) CVM relies on certain epidemiology studies to attempt to show that fluoroquinolone-resistant *Campylobacter* infections result in a longer duration of diarrhea than fluoroquinolone susceptible *Campylobacter* infections. All of the epidemiological studies upon which said testimony relies fail to follow accepted epidemiological methods to control for confounding factors. When confounding with foreign travel is correctly controlled for, the claimed association disappears. As such, all testimony and evidence of this nature is unreliable, irrelevant and inadmissible as evidence.
4. All testimony and evidence that purports to show that pre-approval fluoroquinolone resistance in *Campylobacter* was nonexistent, including but not limited to the "Sentinel County Study" a/k/a the Sobel Data. (See Appendix D.) CVM relies on this study and data to attempt to show that pre-approval fluoroquinolone-resistant *Campylobacter* incidence in

humans was non-existent. Notwithstanding numerous requests, CVM and CDC have failed to produce *any* evidence or supporting information that would explain the purported reliability of pre-approval baseline data. In fact, CVM's testimony that pre-approval standards for *Campylobacter jejuni* speciation would necessarily discard quinolone-resistant *C. jejuni* calls into question all pre-approval resistance data on which CVM relies. Without such data or evidence, the studies, and any testimony relying upon them, are unreliable. In addition, in the absence of any information as to how the studies were conducted or the purpose of the studies, it is impossible to assess the relevance of the studies. Finally, multiple published peer-reviewed studies from at least 1978 forward have documented significant rates of fluoroquinolone and nalidixic acid resistance in both chicken and human isolates of *C. jejuni,* demonstrating that claims to the contrary are based entirely on ignoring relevant data.

5. The testimony of Kare Molbak and all testimony and evidence which relies on the Molbak testimony. (See Appendix E.) CVM relies on this testimony and evidence to attempt to show excess morbidity and mortality associated with fluoroquinolone-resistant *Campylobacter* infections versus fluoroquinolone-susceptible *Campylobacter* infections. The Molbak testimony fails to follow accepted epidemiological or statistical modeling methods, especially as regards construction of a representative sample for extrapolating to the general population. As such, all testimony and evidence relying on the Molbak analysis is unreliable, irrelevant and inadmissible as evidence.

6. All testimony and evidence referencing Mead et al (G-410), or any other source that states, implies or otherwise represents that (a) *Campylobacter* is currently the leading cause of bacterial gastroenteritis in the U.S., or (b) *Campylobacter* causes 2.4 million infections in the

U.S. annually, including all testimony and evidence that relies in whole or in part on 2.4 million annual *Campylobacter* infections as a basis for calculating the mortality or mobility of campylobacteriosis, whether from a fluoroquinolone sensitive or resistant organism. (See Appendix F.) CVM uses the 2.4 million estimate, published in 1999 (based on data collected in 1996-1997), to attempt to show the adverse health and other burdens on the U.S. population from campylobacteriosis. In fact, and according to CDC campylobacteriosis is no longer the leading cause of bacterial-caused gastroenteritis in the U.S., the annual incidence of campylobacteriosis has declined by at least 27 percent from 1996 - 2001, and CDC's Dr. Fred Angulo "estimates that *Campylobacter* infected 1.4 million persons in 1999." As such, all testimony and evidence either making this claim, using this figure, or making calculations based on this figure is unreliable, irrelevant and inadmissible as evidence.

7. All other testimony and evidence that is irrelevant, immaterial, unreliable or repetitive. (See Appendix G.)

I. LEGAL STANDARD: EVIDENCE THAT IS IRRELEVANT, IMMATERIAL, UNRELIABLE OR REPETITIVE MUST BE EXCLUDED

Admissibility of evidence in FDA proceedings is governed by 21 C.F.R. § 12.94. "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). Both testimony and written evidence are deemed admissible unless excluded by the administrative law judge. *Id.* §§ 12.94(c), (d). Under the Administrative Procedure Act, 5 U.S.C. § 556(d), an agency *shall* exclude irrelevant, immaterial, or unduly repetitive evidence.

The FDA has not issued regulations defining what constitutes "irrelevant," "immaterial," "unreliable" or "repetitive" evidence or prescribing standards for administrative law judges to

apply in making these determinations. In the absence of such regulations, the standards prescribed by Rules 702 and 703 of the Federal Rules of Evidence are an apt guidepost in considering the admissibility of expert testimony and evidence. Bayer recognizes that the Federal Rules are not binding in this proceeding. Nonetheless, the FDA Commissioner has looked to the Federal Rules in both the NADA and other contexts in assessing the admissibility of evidence, and the drafters of FDA regulations have done likewise. *E.g.*, *Nitrofurans; Withdrawal of New Animal Drug Applications*, 56 Fed. Reg. 41,902 (Aug. 23, 1991) (Commissioner's review of ALJ's decision) (applying Rule 401 of the Federal Rules of Evidence to assess relevance); *cf. Premarket Approval of Medical Devices*, 51 Fed. Reg. 26,342 (July 22, 1986) (noting that the definition of the term "statement of medical fact" in 21 C.F.R. § 814.3(i) was adopted from Rule 401 of the Federal Rules of Evidence).

Rule 401 prescribes the general standard for relevance (as opposed to the standard for scientific relevance) and states that "relevant" evidence is evidence that has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed. R. Evid. 401. Viewed differently, "any inquiry into relevance must begin with an identification of the ultimate fact to which the item of circumstantial proof is purportedly linked." 22 Wright & Miller, *Federal Practice & Procedure* § 5164.[1]

Courts have recognized, if indirectly, that the principle behind Rule 401 applies to the general admissibility of evidence in the administrative context. *See, e.g.*, *Leitman v. McAusland*, 934 F.2d 46, 51 (4th Cir. 1991) (noting that, while hearsay is admissible in administrative

[1] As is explained below, "relevance" has two aspects—(1) whether the evidence makes any material fact more probable or less probable, and (2) whether scientific evidence actually supports the proposition for which it is offered.

proceedings, it must have "rational probative value"—essentially what Rule 401 requires); *Cunanan v. INS*, 856 F.2d 1373 (9th Cir. 1988) (applying test of probativity).

In addition, an FDA regulation applicable in a different context also suggests that the Federal Rules provide a proper guideline for assessing the reliability of evidence. *See* 21 C.F.R. § 17.39(b) ("Except as provided in this part, the presiding officer shall not be bound by the 'Federal Rules of Evidence.' However, the presiding officer may apply the 'Federal Rules of Evidence' when appropriate, e.g., to exclude unreliable evidence.").[2] Finally, in the course of the rulemaking process relating to the types of statements that can be made regarding dietary supplements' effect on the human body, "[m]any comments argued that the proposed rule ignored the Supreme Court decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993)." *Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Human Body*, 65 Fed. Reg. 1000 (Jan. 6, 2000).

Daubert, as is discussed more fully below, is the seminal opinion interpreting the provisions of the Federal Rules of Evidence relating to the admissibility of expert testimony. The FDA's response to these comments does not reject the potential applicability of *Daubert* to all FDA proceedings:

> The comments did not explain how the rule was contrary to or even affected by the decision. *Daubert* involved the admissibility of scientific evidence in a judicial proceeding under the Federal Rules of Evidence. This rulemaking does not present issues regarding the admissibility of evidence in any proceeding, judicial or administrative, nor does it address expert testimony (which was at issue in *Daubert*). Thus, [the] FDA does not agree that the rule 'ignores' or is contrary to the *Daubert* decision.

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[2] Elsewhere, Section 17.39 states that "[r]elevant evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or by considerations of undue delay or needless presentation of cumulative evidence." 21 C.F.R. § 17.39(d). This standard is substantively identical to Rule 403 of the Federal Rules of Evidence, differing only in that the regulation omits the Federal Rule's reference to "confusing the jury," which is obviously not an issue in FDA proceedings.

Id. This statement recognizes that *Daubert* is not applicable in FDA rulemaking but leaves open the possibility that where the admissibility of expert testimony is at issue *Daubert* may be applicable. *Cf. Consol. Coal Co. v. Director, Office of Workers' Compensation Programs*, 294 F.3d 885, 893 (7th Cir. 2002) (noting that, although agencies are not technically bound by *Daubert*, as a practical matter it still applies and thus litigants must satisfy the ALJ that their experts "are qualified by knowledge, training, or experience to, and have in fact applied recognized and accepted medical principles in a reliable way").

II. RELIABILITY AND RELEVANCE OF EXPERT TESTIMONY

Daubert and its progeny are the cornerstone of any analysis of the reliability and relevance of expert testimony. The *Daubert* Court held that a judge "must ensure that any and all scientific testimony or evidence admitted is not only *relevant*, but *reliable*." *Daubert*, 509 U.S. at 589 (emphasis added). This holding dovetails with the FDA's regulation providing that irrelevant and unreliable evidence is to be excluded. Accordingly, in the absence of FDA regulations defining how relevancy and reliability are to be assessed, and in view of the Commissioner's own recognition of the guidance afforded by the Federal Rules of Evidence, *Daubert* and its progeny provide an appropriate framework for assessing the admissibility of the expert testimony proffered by CVM.

Moreover, it is only proper that the admissibility of CVM's evidence should be subject to a thorough review now. "Reviewing courts must take the record as they find it in administrative cases and thus have no opportunity to develop the record. A rule which requires administrative consideration of probative value and reliability in the first instance comports with common sense and the limited review of administrative actions." *Calhoun v. Bailar*, 626 F.2d 145, 149-50 (9th Cir. 1980). In addition, *Daubert* is frequently referred to as assigning the role of evidentiary gatekeeper to a trial judge. Administrative law judges must perform a similar function. *See U.S.*

Steel Mining Co. v. Director, Office of Workers' Compensation Programs, 187 F.3d 384, 388-89 (4th Cir. 1999) ("[T]he agency process nonetheless requires that the ALJ perform a gate keeping function while assessing evidence to decide the merits of a claim."); *cf. Seaboard Lumber Co. v. U.S.*, 308 F.3d 1283, 1301-02 (Fed. Cir. 2002) (noting that, while *Daubert* concerns are of "lesser import" in a bench trial than in a jury trial, "the *Daubert* standards of relevance and reliability must nevertheless be met" in bench trials). Because of the similarity in role, *Daubert* is an appropriate guide in assessing the admissibility of evidence here.

The *Daubert* Court interpreted Rule 702 of the Federal Rules of Evidence, which "clearly contemplates some degree of regulation of the subjects and theories about which an expert may testify." *Id.* The rule provides that "[i]f scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue," an expert "may testify thereto." *Id.* The Court explained that "[t]he adjective 'scientific' implies a grounding in the methods and procedures of science. Similarly, the word 'knowledge' connotes more than subjective belief or unsupported speculation. The term 'applies to any body of known facts or to any body of ideas inferred from such facts or accepted as truths on good grounds.'" *Id.* at 590 (quoting *Webster's Third New Int'l Dictionary* 1252 (1986)). The Court then tied the "scientific" aspect of this standard to the requirement of reliability: "[I]n order to qualify as 'scientific knowledge,' an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation—*i.e.*, 'good grounds,' based on what is known. In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id.* The Court noted a number of factors that may be considered in assessing reliability:

- whether a theory or technique can be, and has been, tested;

- whether it has been subjected to peer review and publication;
- whether the technique has a high known or potential rate of error and whether there are standards controlling its operation; and
- whether the theory or technique enjoys "general acceptance" within the relevant scientific community. *Id.* at 592-94.

The Court then explained that the requirement that expert evidence or testimony "assist the trier of fact to understand the evidence or to determine a fact in issue" requires that the evidence or testimony be *relevant*: "Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful." *Id.* at 591. The Court described the issue as one of "fit": "[S]cientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes." *Id.* Thus, there must be "a valid scientific connection to the pertinent inquiry as a precondition to admissibility." *Id.* at 592; *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.").

Moreover, the *Daubert* Court held that, because the overarching inquiry analyzes "the scientific validity—and thus the evidentiary relevance and reliability—of the principles that underlie a proposed submission," *id.* at 594-95, in making both the "reliability" and "relevance" determinations "[t]he focus . . . must be solely on principles and methodology, not on the conclusions that they generate." *Id.* at 595. Thus, the crucial inquiry is always whether "an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." *Id.* at 597.

More recently, the Supreme Court has emphasized the requirement of analyzing the underlying methodology upon which an expert bases his conclusions:

> [C]onclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.

Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997). This rule applies equally in the administrative context—conclusory statements by an expert are not admissible in support of an agency determination because "[a]n expert who supplies nothing but a bottom line supplies nothing of value to the judicial process." *Redland Genstar, Inc. v. United States*, 39 Fed. Cl. 220, 232 (1997).

The Court has also clarified that the rules laid down in *Daubert* apply to *all* expert testimony, not just to "scientific" testimony. The Court has noted that there is

> no relevant distinction between "scientific" knowledge and "technical" or "other specialized" knowledge. . . . [A]ny such knowledge might become the subject of expert testimony. In *Daubert*, the Court specified that it is the Rule's word "knowledge," not the words (like "scientific") that modify that word, that "establishes a standard of evidentiary reliability." Hence, as a matter of language, the Rule applies its reliability standard to all "scientific," "technical," or "other specialized" matters within its scope. We concede that the Court in *Daubert* referred only to "scientific" knowledge. But as the Court there said, it referred to "scientific" testimony "because that was the nature of the expertise at issue."

Kumho Tire Co. v. Carmichael, 526 U.S. 137, 147-48 (1999) (citations omitted) (quoting *Daubert*, 509 U.S. at 589-90 & n.8).

Finally, the Court has clarified that the four "reliability" factors cited in *Daubert* are meant to be "helpful, not definitive," *id.* at 151, and that they were not meant to constitute an

exhaustive list nor a minimum list—that is, not all of the *Daubert* factors will be important in every case. Courts considering the *Daubert* standard since the *Kumho Tire* decision have typically explained that the inquiry is "flexible" and that the analysis requires a "focus on the principles and methodology employed by the expert, without regard to the conclusions the expert has reached or the [presiding judge's] belief as to the correctness of those conclusions." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 266 (2d Cir. 2002) (citing *Daubert*, 509 U.S. at 595). Thus, it is critical that an expert's analysis, and the studies upon which he relies, be reliable at every step—"*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 267 (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994)) (emphasis in *Amorgianos*).

Other factors that have been considered in addition to the original *Daubert* factors include:

- the relationship of the expert's technique to methods that have been proven to be reliable, the qualifications of the expert testifying as to the methodology, and the non-judicial uses to which the method has been put, *Yarchak v. Trek Bicycle Corp.*, 208 F. Supp. 2d 470, 495 (D.N.J. 2002) (citing *Paoli*, 35 F.3d at 742 n.8); *Elcock v. Kmart Corp.*, 233 F.3d 734, 745-46 (3d Cir. 2000) (same);
- whether the expertise was developed for litigation or naturally flowed from the expert's research, *Lauzon v. Senco Prods., Inc.*, 270 F.3d 681, 687 (8th Cir. 2001); and
- whether the expert ruled out alternative explanations, *id.*

In addition, when scientific evidence, such as a risk assessment, is prepared for judicial or administrative proceedings and is not peer-reviewed itself, the expert(s) must explain precisely

how they went about reaching their conclusions and must point to some objective source to show that they have followed the scientific method. *Metabolife Int'l, Inc. v. Wornick*, 264 F.3d 832, 845 (9th Cir. 2001). Finally, a corollary to the rule of "general acceptance" in the scientific community is the principle that a known technique that has garnered only minimal support may justifiably be viewed with skepticism. *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir. 2000).

The D.C. Circuit recently has succinctly summarized the Supreme Court case law on the admissibility of expert testimony and has noted that there are two considerations—(1) the basis for the purported knowledge and (2) whether it will assist the trier of fact. The first issue requires a focus on principles and methodology and not on the conclusions that they purportedly generate. Thus, scientific testimony must be grounded in the methods and procedures of science—i.e., it must be performed in accordance with standard scientific methods. *Meister v. Med. Eng'g Corp.*, 347 U.S. App. D.C. 361, 364-65, 267 F.3d 1123, 1126-27 (2001). Such methods require testing to determine whether the questions raised by case studies can be determined to have a causative relationship. *Id.* at 369, 267 F.3d at 1131. The D.C. Circuit has also emphasized the *Daubert* Court's discussion of the need for relevance as embodied in the requirement of "fit," focusing on the Court's statement that "scientific validity for one purpose is not necessarily scientific validity for other unrelated purposes." *Ambrosini v. Labarraque*, 322 U.S. App. D.C. 19, 24, 101 F.3d 129, 134 (1996) (quoting *Daubert*, 509 U.S. at 591).

In summary, *Daubert* and its progeny provide touchstones by which to judge the reliability of scientific testimony and evidence for the purposes of admissibility. These are:

- whether the technique or theory can be and has been tested, *Daubert*, 590 U.S. at 592, or, put another way, "capable of empirical test" or "falsifiable, refutable or testable," *id.* at 593;

- whether the theory has been subjected to peer review or publication so that "it increases the likelihood that substantive flaws in the methodology will be detected" by "the submission to the scrutiny of the scientific community," *id.*;

- whether the known or potential rate of error in the technique or theory has been considered, *id.*;

- whether and to what degree the theory or technique has been accepted within the scientific community, *id.*;

- the relationship of the expert's technique to methods that have been proven to be reliable, the qualifications of the expert testifying as to the methodology, and the non-judicial uses to which the method has been put, *Yarchak*, 208 F. Supp. 2d at 495;

- whether the expertise was developed for litigation or naturally flowed from the expert's research, *Lauzon*, 270 F.3d at 687; and

- whether the expert ruled out alternative explanations, *id.*

III. FDA IS RESPONSIBLE FOR ENSURING THE QUALITY OF INFORMATION DISSEMINATED TO THE PUBLIC

Pursuant to Section 515 of Public Law 105-554[3], 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"). 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, FDA has issued its own guidelines entitled *Guidelines for Ensuring the Quality of Information Disseminated to the*

[3] Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001; P.L. 106-554, § 515 (2001).

Public ("FDA Guidelines").[4] The FDA Guidelines require that when FDA disseminates information, but particularly in those cases involving influential information[5], the 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.

Bayer believes that the testimony and evidence submitted by CVM in this public hearing constitutes influential information[6] disseminated by the FDA, and therefore must meet the standards outlined in the FDA Guidelines to ensure the quality of information disseminated to the public. However, even assuming the testimony and evidence do not specifically fall within the scope and applicability of the FDA Guidelines, the FDA Guidelines are nevertheless useful as a guidepost for further 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.

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[4] FDA, *Guidelines for Ensuring the Quality of Information Disseminated to the Public*, http://www.hhs.gov/infoquality/fda.html.

[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 Fed. Reg. 8452 (February 22, 2002). 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, 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 fluoroquinolone enrofloxacin in poultry is reasonably expected to have an annual effect on the economy of $100 million or more and/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); Written Direct Testimony of Steven Woodruff (B-1918); Written Direct Testimony of Scott Russell (B-1912); Written Direct Testimony of John Glisson (B-1903); Written Direct Testimony of Bruce Tompkin (A-204); Written Direct Testimony of Ronald Prucha (A-203); Written Direct Testimony of L. Anthony Cox (B-1901); Written Direct Testimony of Charles Haas (B-1904)); Written Direct Testimony of Robert Harris (B-1919).

Additionally, the Centers for Disease Control and Prevention ("CDC") has issued similar guidelines[7], and to the extent that CVM relies on CDC data, such as NARMS, FoodNet, and the Sentinel Study, CVM and CDC are bound by these standards with which they likewise did not comply.

A. Information Disseminated Must Meet The High Standards Of Quality (Including Objectivity, Utility, and Integrity) Described in the OMB and FDA Guidelines

The FDA Guidelines establish a "number of quality assurance policies, standards, and processes for ensuring the quality of the information [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 "(1) utility, the usefulness of the information to its intended users, including the public; (2) objectivity, whether information is being presented in an accurate, clear, complete, and unbiased manner; and (3) integrity, the information is protected from unauthorized access or revision." FDA Guidelines, § V.

As described above, the FDA Guidelines apply special 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,

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[7] See CDC, *Guidelines For Ensuring the Quality of Information Submitted to the Public*, http://www.hhs.gov/infoquality/cdcinfo2.htm.

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 in the motion below, much of CVM's testimony and evidence do 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.

B. The FDA Guidelines Give Specific Guidance on Risk Assessments

The FDA Guidelines define for purposes of the guidance, "risk" as the likelihood that injury or damage is or can be caused by a substance, technology, or activity."[8] For quantitative risk assessments in support of the dissemination of influential information, such as the CVM/Vose Risk Assessment, the agency describes the type of data that should be used and the methods utilizing such data:

> 1. The agency will use:
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> 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;
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> b. data collected by accepted methods (if reliability of the method and the nature of the decision justifies use of the data);
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> 2. In the dissemination of public information about health risks, the agency shall ensure that the presentation of information is comprehensive, informative, and understandable, within the context of its intended purpose.
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> 3. In a risk assessment document made available to the public, the agency shall specify, to the extent practicable-

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[8] FDA Guidelines, § VII.C, "Risk Assessment".

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

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

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

d. 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

e. 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. As further detailed in Section V, the Vose Risk Assessment does not comply with the above guidance, for the following among other reasons. The CVM/Vose 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;

(3) does not ensure, in dissemination of public information about health risks, that the presentation of information is comprehensive; and

(4) 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.

These failures are further evidence that the CVM/Vose Risk Assessment and testimony which relies on the CVM/Vose Risk Assessment is unreliable and irrelevant.

IV. BAYER MOVES TO STRIKE ALL NARMS DATA AND ALL TESTIMONY AND DOCUMENTS RELYING ON NARMS DATA BECAUSE THE NARMS DATA ARE UNRELIABLE, NOT RELEVANT AND FAIL TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

CVM relies on data from the National Antimicrobial Resistance Monitoring System (NARMS) for the propositions that: (1) the prevalence of fluoroquinolone resistance in *Campylobacter* from US poultry is increasing year to year since Baytril approval; (2) the prevalence of fluoroquinolone resistance in *Campylobacter* isolated from humans is increasing year to year since Baytril approval; and (3) the two are temporarily and causally related. (See, e.g., testimony of Frederick J. Angulo G-1452, P. 8, L 5-21 regarding Human NARMS and testimony of Linda Tollefson G-1478, P. 8, L 35-38 and P. 14, L 26-43 regarding Poultry NARMS and Tollefson G-1478, P.5, L 29-32 and P. 14, L 29-43 regarding objective of NARMS to provide data on temporal trends). CVM's documentary evidence also includes NARMS reports and materials relying on NARMS data.

The NARMS program, however, is so fundamentally flawed in its monitoring of fluoroquinolone resistance in both human and poultry *Campylobacter* that the data generated is not reliable, not relevant and does not meet the standards of admissibility for scientific evidence. All testimony relying on Human and Poultry NARMS fluoroquinolone-resistant *Campylobacter*

data and all documents relating to human and poultry NARMS fluoroquinolone-resistant *Campylobacter* should be ruled inadmissible and stricken from the evidentiary record.[9]

Flaws include:

(a) Highly **variable compliance** by the state departments of public health submitting data, so that NARMS protocols have not been followed;

(b) **Selection of states** that do not represent the experience of the US population. For example, Wisconsin data showed 12% resistance levels in 1992-1995 (B-39), *before* the introduction of enrofloxacin. This was higher than the rates reported years later in Colorado, Connecticut, New York, or Tennessee in 2000. But the NARMS samples do not include data from Wisconsin;

(c) **Non-representative sampling,** so that the data collected do not statistically represent the experience of the general US population;

(d) **Multiple counting** (and hence over-representation) of relatively contaminated facilities (since clean plants "pass" and are sampled only once, while dirty plants "fail" and are sampled multiple times), thus biasing the chicken data toward the results from exceptionally contaminated plants;

(e) **Uncontrolled selection** biases in the submission of samples (i.e., no enforced randomization in the selection process to prevent submitters from choosing "interesting" but non-representative samples);

(f) **No baseline data** before 1997 for using the NARMS data to support temporal trend analysis and arguments. This makes any use of NARMS data by CVM to argue that introduction of enrofloxacin in 1996 caused an increase in resistance rates logically

[9] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix A.

flawed and contrary to widely accepted principles of valid causal inference from time series data;

(g) **No control for outliers.** For example, CVM interprets a unique "spike" in the Connecticut data in 1999 as evidence of a nation-wide increase in resistance rates, even though the average resistance rates outside Connecticut actually declined in 1999 (and even though the rate in Connecticut declined from 30% in 1999 to 8.9% in 2000);

(h) **Failure to measure microbial loads.** This is the information that is needed to estimate the quantitative extent of exposures. Since the NARMS data do not provide this information, they are unreliable as a basis for sound risk assessment or decision making and should be excluded; and

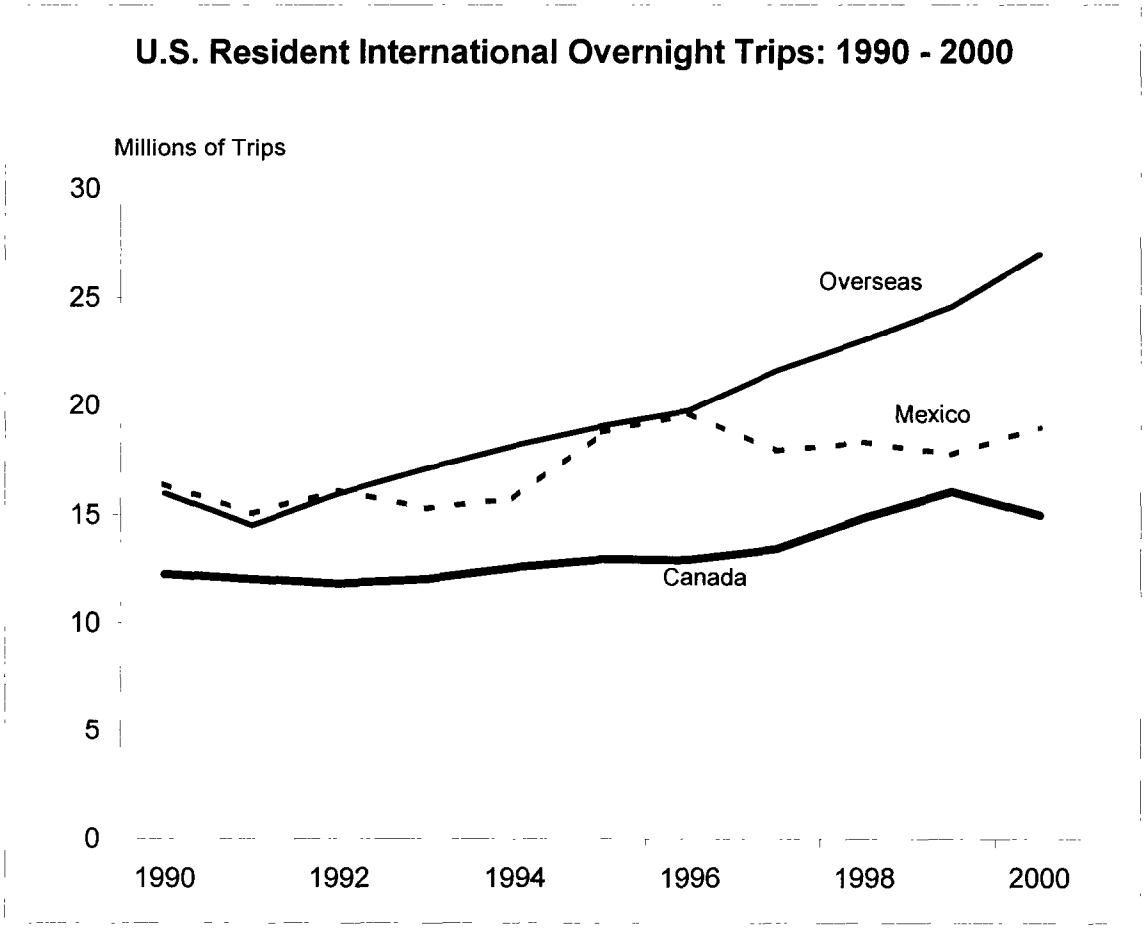
(i) **NARMS does not represent domestic cases.** NARMS contains data from all sources including isolates from people that acquired infection in foreign countries. Only cases related to domestically acquired infections are relevant to the hearing. Foreign acquired *Campylobacter* infections account for a large percentage of resistant infections reported in the US. Smith (G-589) reports 70% of the resistant *Campylobacter* infections found in Minnesota are associated with foreign travel, therefore NARMS very likely over represents the level of resistance from domestically acquired cases. Since NARMS provides no information on sources of infection, it does not represent resistance from domestically acquired infections so is not relevant to the hearing.

A. Human NARMS Data Are Unreliable

1. *Human NARMS Are Confounded By International Travel*

NARMS collects data from all patients irrespective of any patient characteristic, but collects no information except for that on patient demographics. Smith (G-589) reports that 70% of the resistant *Campylobacter* infections found in Minnesota are associated with foreign travel. Likewise, Friedman (G-228) found that a large percentage of resistant cases are due to exposures occurring during international travel. As shown in the following figure, the per capita rate of international travel in US residents increased during the 1990's. Hence, because NARMS data does not include information on foreign travel and because the likelihood of international travel has increased, the temporal trend of domestic cases can not be evaluated because the dataset is confounded by resistant cases caused by international travel.

INTERNATIONAL TRAVEL BY US RESIDENTS



NOTE: Overnight travel includes trips of at least one night or longer. Data for Canada and Mexico do not include same-day travel.

Sources: From: North American Trade and Travel Trends. US Bureau of Transportation Statistics, Report BTS01-07, http://www.bts.gov/publications/nattt/index.html

Original Sources: U.S. Department of Commerce, International Trade Administration, Office of Tourism Industries, "International Visitors (Inbound) and U.S. Residents (Outbound) (1990–2000)," and "Arrivals to the U.S. 1999 & 1998 (All Countries by Residency), and in Rank Order within Region," available at http://tinet.ita.doc.gov as of Aug. 3, 2001.

2. *NARMS Data Are Confounded By Prior Antibiotic Use*

NARMS collects data from all patients irrespective of any patient characteristic and collects no data other than that on patient demographics. Smith (G-589) and others have shown that prior fluoroquinolone use is a strong risk factor for finding fluoroquinolone

resistant Campylobacter. The per capita use of fluoroquinolone has increased throughout the 1990s. Therefore, because the NARMS data does not collect information on prior fluoroquinolone use, the data are confounded and can not be used to study temporal trends of domestic cases.

3. Human NARMS Does Not Adhere To Its Own Methodology

It is undisputed that the Human NARMS sample collection protocol calls for participating public health laboratories to submit the first *Campylobacter* isolate received in each laboratory each week to CDC for susceptibility testing. (Tollefson, G-1478, P. 7, L 32-34; Angulo G-1452, P. 7, L 26-30).

CVM's own testimony concedes that the protocol was followed only "in general" (Angulo G-1452, P. 7, L 45). Examination of the data in published reports (G-98, G-99, G-749) reveals that participating state laboratories frequently submitted multiple isolates per week or failed to submit any. This results in numerous instances of NARMS reporting on more or less than 52 isolates for a single participating state in a given year, thus making it impossible to reconcile the data with any expected rate of error. *Cf. Daubert*, 509 U.S. at 593.

Failure to adhere to the established methodology renders the Human NARMS data unreliable as a measure of the annual burden of resistant *Campylobacter* in the human population in the US.

4. Human NARMS Is Not Representative Of The Population Of Campylobacteriosis

Because under-reporting of gastroenteritis (GE) caused by *Campylobacter* is so significant (Tauxe G-1475, P. 2 , L 18-39, P. 14, L 17-19; Angulo G- 1452, P.6, L 14 - P. 7, L 5, Tollefson G-1478, P. 6, L 40-43), all estimates of *Campylobacter* incidence, and morbidity and

mortality based thereon, are biased because only on culture-confirmed cases. The bias occurs because the denominator is based on only cases that seek medical care, obtain a culture, and the culture is reported. Id. Incidence rates, days of diarrhea, rates of hospitalizations, deaths, etc., are all based upon patients who seek medical care for the illness. Because patients who have more severe disease and those with significant underlying disease are more likely to seek medical care (and more likely to get cultured) estimates based upon these patients are *conditional* in epidemiological parlance. Such estimates are not accurate as estimates of *Campylobacter* in the U.S. population but may be for the denominator of patients who seek care.

5. Human NARMS Overstates the Extent of Resistance

Even if the protocol for Human NARMS *Campylobacter* sample collection were to be followed, it would present an unreliable view of the extent to which the US population is infected with fluoroquinolone-resistant *Campylobacter*, because the system selects equally from high resistance/low incidence periods and low resistance/high incidence periods. It is undisputed that *Campylobacter* resistance and incidence both fluctuate seasonally; incidence peaks in late summer, but resistance peaks in winter. (Smith G-1473, P. 7, L 13-18). To accurately assess the overall annual burden of fluoroquinolone-resistant *Campylobacter* in the US human population, proper epidemiological surveillance would call for selecting a representative sample. This is accomplished by selecting isolates so that sample collection frequency would rise and fall with incidence frequency and the resulting samples would be representative of the broader set from which they are taken. NARMS does exactly that for *every* bacteria species it monitors *except* for *Campylobacter*. (See Tollefson G-1478, P. 7, L 23-34, stating that NARMS participating sites select every tenth non-typhi *Salmonella*, every tenth *Shigella*, and every fifth *E. coli* 0157).

Selecting only the first isolate of any given week, regardless of incidence rate, means the sample set is not representative. Naturally, any data or conclusions drawn from a non-representative set of data are not reliable indicators of what is occurring in the broader population. This situation is particularly noteworthy with *Campylobacter*, where resistance and incidence are both seasonal, but peak at different times. In any given year participating public laboratories are asked to select only one isolate from summer weeks in which incidence is highest but resistance is lowest and also one isolate from the winter weeks where incidence is lowest but resistance is highest. This will skew the results to overstate the annual extent of resistance. A prime example of this is Minnesota, where in 2000 the Minnesota Department of Health reported 11% overall incidence of *Campylobacter* resistance from all cases (www.health.state.mn.us/divs/dpc/ades/surveillance/table2000.pdf) but Minnesota's NARMS-submitted samples were 25% resistant. (G-749, P. 13).

Sampling issues aside, the set of states from which the samples are taken does not represent the general US population. As stated by CVM's own witness, Dr. Molbak, rates of campylobacteriosis and resistance are extremely variable among FoodNet sites. (Molbak G-1468, P. 4, L 38-44; P. 6, Table 1; P.8, L 17-18; P. 9, Table 3). Both rates are far more variable across sites than the CVM/Vose model predicts or explains. As a result, it is impossible to estimate the rates of campylobacteriosis and resistance in the rest of the United States from the samples that have been collected in NARMS.

Thus, rather than being tied to methods that are known to be reliable, *Yarchak*, 208 F. Supp. 2d at 495, NARMS is tied to methods that are known to be unreliable.

Because NARMS samples are not representative and the data are unreliable, the NARMS data and all testimony and evidence relying on the data should be stricken.

B. Human NARMS Data Are Not Relevant

1. The Source of Human NARMS Samples Is Not Representative of the US Population

Human NARMS data are being used to show a purported national trend over a number of years. The samples from which Human NARMS data are drawn, however, are not representative of the national population. CVM's own testimony concedes these limitations in the NARMS data. Susceptibility testing of human *Campylobacter* isolates is conducted exclusively in FoodNet sites (Angulo G-1452, P. 3, L 46-47).

CVM's submitted testimony states that "populations in the FoodNet surveillance area was slightly more likely to be Asian and less likely to be Black or Hispanic. The population in the FoodNet surveillance area was also more likely to include urban residents and residents in countries with lower population density, and less likely to include persons living at or below poverty." (Angulo G-1452, P. 4, L 15-19). While CVM tries to discount these differences by pointing out similarities between the FoodNet surveillance area and the US population in age, gender and health indicators (Angulo G-1452, P. 4, L 21-26), the fact is that ethnicity and income can have a large impact on factors that may influence chicken consumption, chicken preparation, access to health care and access to prescription medicine. For example, CVM testimony indicates the highest incidence of laboratory-confirmed *Campylobacter* infection from 1996-1999 was among Asians (Angulo G-1452, P. 5, L 26-27), a group CVM concedes is over represented in the surveillance data. Similarly, CVM's testimony reveals that it has to guess at the number of persons ill with *Campylobacter* who do not seek medical care due to poor access to medical care. (Angulo G-1452, P. 6, L 30-33).

While CVM's testimony attempts to suggest that FoodNet data is representative of the US population (Angulo G-1452, P. 4, L 24-26), the rationale given is far from sufficient. Using

1996 United States Census Bureau data and Community Health Status Indicator Project data, CDC performed a demographic comparison between FoodNet surveillance areas and the United States. (Angulo G-1452, P. 4, L 8-13). Absent from Dr. Angulo's testimony is any explanation of why 1996 US data were used to compare FoodNet populations from 1998 to 2002 (the years *Campylobacter* data were collected from FoodNet sites.) Also absent from Dr. Angulo's testimony is any explanation of which particular configuration of the ever-changing FoodNet catchment areas was used in the analysis; the FoodNet Catchment area has changed every year (1998 - 2001) that *Campylobacter* data were collected. (Angulo G-1452, P. 4, L 37 - P.5, L 6).

The approach used by CDC to extrapolate the FoodNet data to the entire US is scientifically suspect and not statistically valid. There is so much variability from site to site that there is little to no scientific merit to extrapolate from these samples to a national pattern.

According to the CDC case-control study data, the different sites have very different demographics. For example, among those with INCOME = 9 (top category), less than 10% live in NY and more than half live in CT. Connecticut differs from other states in the following significant ways, among others: (1) Almost all isolates with CAMPSPEC different from "*jejuni*" come from Connecticut; (2) average incomes are much higher in Connecticut than elsewhere; (3) people in Connecticut are less likely to eat hamburger at home, more likely to eat hamburger in restaurants; (4) more likely to eat pink hamburger; (5) less likely to live on a farm; and (6) more likely to travel to other parts of the US. Similar profiles can be prepared that "fingerprint" the other FoodNet sites. For example, people with HMOs are almost 4 times more likely to live in California than people without HMOs.

By looking at only a few demographic variables, as CVM and CDC have done, one cannot conclude that the FoodNet sites are similar to national averages in ways that are relevant

for predicting campylobacteriosis rates. At a minimum this ignores the fact that different states have very different *combinations* of demographic and non-demographic factors and very different *Campylobacter* rates. CDC has ignored these combinations. (For example, two states could both have 50% of people with attribute A and 50% with attribute B, yet the frequency of people with A & B could be 0% for one state and 50% for the other. Looking at similarity of attributes one at a time does not capture this combination aspect, which is important for predicting risk.) CDC's comments about similarities do not consider these joint (i.e., combination) distributions of attributes.

Elsewhere, CVM's testimony admits the non-representiveness of the FoodNet catchment area of NARMS: "... [B]ecause some laboratory-diagnosed illnesses reported to FoodNet also might be acquired through non-foodborne route (e.g., through contaminated water and direct animal exposure), reported rates do not represent foodborne sources exclusively. Finally, although FoodNet data provide the most detailed information available for these infections, the data do not reflect the entire US population." (Molbak, P. 5, L 17-21). This admission is significant because, in point of fact, NARMS has no means of tracking the source of *any* of the *Campylobacter* infections on which it collects data. This means that NARMS collects isolates from patients who acquired their fluoroquinolone-resistant infections through non-foodborne routes and through foreign travel, which cases are obviously not related to fluoroquinolone use in poultry in the United States. Foreign acquired *Campylobacter* infections account for a large percentage of resistant infections reported in the US. Smith (G-589) reports 70% of the resistant *Campylobacter* infections found in Minnesota are associated with foreign travel, therefore NARMS very likely over represents the level of resistance from domestically acquired cases.

Since NARMS provides no information on sources of infection, it does not represent resistance from domestically acquired infections so is not relevant to the hearing.

Among states excluded from the FoodNet sample, Wisconsin showed 12% resistance levels in 1992-1995 (B-39). Other states may have had similarly high rates in the late 1980s and early 1990s – as high or higher than those in many FoodNet areas in 2000. But the NARMS samples do not include data from Wisconsin or most other states. Trying to extrapolate the pattern of resistance in the general US over time from the FoodNet sample is statistically invalid, given the very large differences among states.

A review of the NARMS system by a neutral observer (G-644) concludes that "this system does not yet provide data that can be interpreted as a representation of general patterns for the entire United States, nor will it answer the question of whether there is a causal link between emergent animal resistance and emergent human resistance."

If the FoodNet area from which Human NARMS draws its sample is not representative of the US population, then testimony trying to use Human NARMS to show national trends is not relevant.

2. *The Overall Pool Of Human Campylobacter Isolates Submitted To Human NARMS Is Not Representative Of The Annual Human Campylobacter Burden*

Similarly, if the total pool of *Campylobacter* isolates submitted annually to Human NARMS is not representative of the annual incidence of campylobacteriosis (from both susceptible and resistant strains), then testimony, data, or conclusions based on those samples are not relevant. Since NARMS submission protocol is routinely violated and random sampling is not enforced, it is to be expected that submissions may be biased toward samples that the submitting groups single out as "interesting," rather than being representative. Such non-

random, non-standard sampling removes the basis for valid statistical inference based on the submitted isolates.

C. Poultry NARMS Data Are Unreliable

1. Poultry NARMS Culture Procedures Skew Results Towards Resistance

A recently completed study by Dr. Margie Lee of the University of Georgia (A-200, P. 120-129) compares and contrasts the speciation profiles and antibiotic susceptibilities of *Campylobacter* colonies from the same source grown on different selective media. The research team found that the *Campylobacter* resistance data currently collected by NARMS may be skewed by the selective procedures used when detecting *Campylobacter*. Participating laboratories use selective media that contain antibiotics because it makes isolation of *Campylobacter* easier. Because of this, the frequency of occurrence of antibiotic-resistant and antimicrobial-resistant *Campylobacter* may be overestimated. (A-200, P. 121). A proper scientific study would include steps to correct for this factor. Because no such steps were taken here, the Poultry NARMS procedures fail to comport with accepted scientific procedure and must be excluded. *Amorgianos*, 303 F.3d at 266 (noting that *any* step rendering an analysis unreliable is grounds for excluding that analysis).

In light of the uncertainty introduced by selective media being used by participating Poultry NARMS laboratories, the Poultry NARMS data are not reliable. All such documents and data (G-119, G-205, G-206, G-207, G-760 and G-1363) and the testimony relying on Poultry NARMS should be stricken from the evidentiary record.

2. Poultry NARMS Results Are Confounded By Mixed Cultures

Dr. Paula Fedorka-Cray, the senior USDA scientist involved in developing and implementing the Poultry NARMS program (Tollefson G-1478, P. 4, L 41-44) and the scientist

conducting *Campylobacter* susceptibility testing for Poultry NARMS (Tollefson G-1478, P. 7, L 45 - P. 8, L 5), reports that use of antimicrobials during culture can confound recovery and that mixed populations and aggregation of some strains affects speciation and antimicrobial testing. (A-200, P. 77). Fedorka-Cray compared *Campylobacter* isolation methods (the spin enrichment method versus the micro-well dilution method) and their effect on resistance patterns. The study concluded that different strains and resistant patterns were found depending on which method was used. (A-200, Attachment 2, P. 78).

The fact that the scientist in charge of Poultry NARMS finds different strains and resistance patterns depending on which method is used for selection and isolation of *Campylobacter* calls into question just what NARMS is finding. The data are not reliable.

3. Poultry NARMS Data Cannot Be Compared Year-to-Year

As pointed out by a neutral scientist examining the NARMS program (G-644, P. 4):

> The animal sampling might introduce some selection bias. Although the National Animal Health Monitoring studies are representative of the animal population that is sampled, the participants are volunteers, and the studies vary by species and geographic region each year. Thus, the species and numbers tested for antimicrobial resistance vary from year to year. This is also true for the samples taken from USDA field studies. In addition, the slaughter house isolates gathered from abattoirs are also variable and may be inconsistent. For example, *Salmonella* sampling and testing have been consistent, but the time period for sampling *Campylobacter* has varied from year to year. In 1998, *Campylobacter* samples were taken for 3 months while in 1999, samples were taken for the full year. In 2000, isolates were taken for 9 months. Thus, data on *Campylobacter* and antimicrobial resistance patterns from year to year cannot really be compared.

The *Daubert* Court noted that general acceptance within the scientific community is an important factor in assessing reliability. *Daubert*, 509 U.S. at 592-94. Where, as here, the scientific community has *rejected* evidence, its reliability must be considered highly suspect.

D. Poultry NARMS Data Are Not Relevant

Not only are the Poultry NARMS data unreliable because of the isolation method's influence on speciation resistance, but Poultry NARMS data are not relevant to the risk they are supposed to be monitoring – poultry consumed by the general public. Specifically, for some time periods (1998-2000) Poultry NARMS received samples from carcass rinses from all classes of chickens in the "Chicken Monitoring Program." These would include spent hens and other birds typically slaughtered for further processing such as for soups, etc. and the *Campylobacter* loads would not be relevant to those to which the public would be exposed. Moreover, the source of isolates changed over time, including the Chicken Monitoring Program from 1998-2000 and the Nationwide Young Chicken Microbiological Baseline Data Collection Program from November 1999 to November 2000, which was primarily looking at broilers. (Tollefson G-1478, P. 9-12).

The treatment history of birds in the different programs could be very different because older birds (spent hens) are alive longer, but such birds also are put to very different end uses as far as a consumer is concerned. Such birds are usually sent to further processing, such as for soups. Further processing involves a kill step, which would render any microbiological organisms on the carcass harmless. Therefore, the resistance measured by NARMS in some periods from 1998 to present is not indicative of what consumers may have been exposed to. This lack of "fit" makes the Poultry NARMS data irrelevant and it should be excluded. *Cf. Daubert*, 509 U.S. at 592 ("[S]cientific validity for one purpose is not necessarily scientific validity for other unrelated purposes").

E. Both Human NARMS And Poultry NARMS Data Are Being Used For Purposes Beyond Their Reliability And Relevance

In this action, CVM is using NARMS data to compare trends year to year in humans and poultry and to ascribe cause and effect to fluoroquinolone use in chickens. For example, CVM's Linda Tollefson has testified in this action that "the goals and objectives of NARMS are: to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in enteric organisms from the human and animal populations..." (Tollefson, G-1478, P. 5, L 29-32). She further testifies that "we designed the system to allow us to track changes over time in both [human and poultry] populations and thus to be able to draw comparisons between the two populations." (Tollefson, G-1478, P. 14, L 40-43). This is exactly what Tollefson and other commenters at the inception of NARMS said could *not* be done. "Data on *Campylobacter* and antimicrobial resistance patterns from year to year cannot really be compared." (G-644, P. 4). Even CVM's Linda Tollefson, who was involved in the design of NARMS (Tollefson G-1478, P. 4, L 41-44), recognized the limitations to NARMS in an article:

> NARMS does not provide sufficient information to ensure continued safety of specific food animal antimicrobials after approval. The monitoring program is only a sentinel system and has a number of inherent limitations. Although it is possible to identify that a problem exists, the magnitude of the problem can not be estimated with the monitoring system data alone. NARMS is not capable of identifying how or why resistance occurred. Data related to the resistance findings, such as demographic information and history of drug use, are not collected in the animal populations. Therefore, the data can not be linked to particular practices of concern. (G-642)

While not addressed by Dr. Tollefson in this article, her comment is equally true of Human NARMS.

At the 2002 NARMS Annual Scientific Meeting on November 19-22, 2002 at Hilton Head Island, South Carolina, CVM's Dr. Fred Angulo similarly recognized that the Human

NARMS program does not estimate the National prevalence of fluoroquinolone-resistant *Campylobacter* in the national population because NARMS does not have a population-based sampling methodology but instead relies on an artificially-created once a week sample. (See, e.g., Carnevale A-199, P. 37-38).

In summary, because both the Human NARMS and poultry NARMS data are being used in this administrative proceeding beyond any reliability and relevance they may have in other contexts, the testimony and evidence relying on Human NARMS and Poultry NARMS to show temporal trends and causal associations should be excluded.

F. NARMS Data Do Not Meet The Criteria For Admissibility Of Scientific Evidence

The NARMS data and testimony and evidence relying on NARMS data do not meet FDA's Guidelines nor do they meet the standards for scientific reliability or relevance as set forth by *Daubert* and its progeny. Neither the Human or Poultry NARMS data are sufficiently representative of the monitored populations to describe national trends or to support the trend-based case CVM attempts to make. The data are not relevant to national trends because no representative national sample has been taken, sampling protocols have not been followed even within sampled areas, and the sampled data show such extreme state-to-state variability that reliable or useful extrapolation to other states or to the nation as a whole is impossible. Given the methodological problems with NARMS, the data are not scientifically reliable. This administrative body should reject the NARMS data as unreliable and not relevant from a scientific evidence perspective and strike all such testimony and evidence.

V. BAYER MOVES TO STRIKE ALL CVM TESTIMONY AND EVIDENCE RELYING ON THE CVM/VOSE RISK ASSESSMENT BECAUSE THE CVM/VOSE RISK ASSESSMENT IS UNRELIABLE, IRRELEVANT, AND FAILS TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

CVM relies on the CVM/Vose Risk Assessment (G-953) to support its contention that in 1999 an estimated 9,261 persons acquired fluoroquinolone-resistant *Campylobacter* infections from fluoroquinolone treated chicken, sought medical care, were prescribed a fluoroquinolone, and were at potential risk of a treatment failure . (See, e.g., testimony of Linda Tollefson G-1478, ¶ 40; testimony of Clark Nardinelli G-1471, ¶ 33). The CVM/Vose Risk Assessment is flawed because, among other things, it fails to meet the FDA's standards for valid risk assessments, fails to use best available science and data, and uses methods that are not generally accepted in the risk assessment field. These failures render the CVM/Vose risk assessment unreliable, irrelevant and inadmissible as scientific evidence. All testimony and evidence relying on the CVM/Vose risk assessment should be excluded.[10]

A. The CVM/Vose Risk Assessment Is Not Reliable

1. The CVM/Vose Risk Assessment Does Not Meet The FDA's Controlling Standards For Valid Risk Assessments

As described in Section III, FDA recently published Guidelines on the dissemination of information, including the controlling standards for FDA risk assessments. The FDA Guidelines provide requirements for the dissemination of risk assessments, like the CVM/Vose Model:

> [W]e have adapted the general principles for risk assessments from the [Safe Drinking Water Act] to fit these situations. The principles we intend to apply to risk assessments involving the dissemination of influential information affecting product approval actions or regulations that do not lend themselves to quantitative risk assessment are as follows:

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[10] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix B.

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 justify use of the data)

2. In the dissemination of public information about risks, the Agency will ensure that the presentation of information about risk effects is comprehensive, informative, and understandable.

In situations requiring a quantitative risk assessment, we generally follow basic risk assessment principles in the NAS paradigm of 1983. Our needs for quantitative risk assessments range over a wide variety of hazards including physical hazards encountered during use of a medical device, food chemical residues, and antimicrobial resistance genes in bacteria. Thus, we also ascribe to the statement from NAS when it revisited the risk assessment process in 1994 (*Science and Judgment in Risk Assessment*, NAS 1994): "Risk assessment is not a single process, but a systematic approach to organizing and analyzing scientific knowledge and information. "In each of the areas we regulate, we apply risk assessment practices to the specific task that are widely accepted among relevant domestic and international public health agencies.

For quantitative risk assessments in support of the dissemination of influential information, FDA intends to apply the following principles:

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)

2. In the dissemination of public information about health risks, the agency shall ensure that the presentation of information is comprehensive, informative, and understandable, within the context of its intended purpose.

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

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

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

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

d. 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

e. 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 "basic risk assessment principles in the NAS paradigm of 1983" referenced above were set forth by the National Academy of Sciences ("NAS") in 1983 (in a study partially sponsored by the FDA) in "Risk Assessment in the Federal Government: Managing the Process," National Academy Press, Washington, DC, 1983. These are also in more recent updates and in other authoritative sources and guidelines (e.g., *Codex Alimentarius*). The term "risk assessment" under the NAS criteria conventionally means a process for studying the relation between exposures (and perhaps risk management acts that affect exposures) and their probable human health consequences. The conventional meaning of "risk assessment" includes the following steps: (a) *Hazard identification*, using data to establish the possibility of a causal relation between exposure and adverse human health response; (b) *Exposure assessment,* presenting data-based estimates of the frequency and magnitudes of individual exposures in a human population; (c) *Exposure-response modeling*, or dose-response modeling, quantifying the causal relation (if any) between levels of exposure and probability of specific adverse human health consequences; (d) *Risk characterization,* integrating the exposure assessment and the

exposure-response models and presenting their implications for the frequency and magnitude of exposure-related adverse health effects in the exposed population; and (e) *Uncertainty characterization,* addressing uncertainties, variabilities, and sensitivities in the estimated exposure-response relation for the exposed population. Uncertainty characterization should address both model uncertainties and data uncertainties, and variability analysis should address the extent of inter-individual heterogeneity in risks.

The FDA also recently issued an FDA Draft Guidance ("Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," September 6, 2002) which adopts a risk assessment approach promulgated by the Office of International Epizootics Ad Hoc Group on Antimicrobial Resistance (OIE). The OIE approach sets forth specific tasks to be undertaken in a *qualitative* risk assessment of new drug approvals. It is noteworthy that, while the draft guidance does not forbid *quantitative* risk assessment, it only discusses *qualitative* risk assessment. The OIE approach is similar to the traditional NAS approach and consists of four stages: release assessment, exposure assessment, consequence assessment, and risk estimation. Release assessment describes the pathways for entry of an adverse agent into the environment. Exposure assessment quantifies the likelihood and extent of such introduction to occur, and the resulting impact (in terms of dose) to the (human) population affected. Consequence assessment relates the exposure to the probability and nature of the adverse human health outcomes. Risk estimation integrates the results of the prior stages into a measure of the adverse outcome predicted to occur.

The CVM/Vose Risk Assessment does not adhere to *any* of the standards for judging valid quantitative risk assessments. In particular, the approach used by the CVM/Vose Risk

Assessment is at variance with the NAS steps and the analogous OIE steps. These steps are generally regarded as the best available science for conducting a quantitative risk assessment (which is required to comply with the FDA Guidelines) and the generally accepted method for conducting a quantitative microbial risk assessment: (1) hazard identification that indicates some reason to believe that exposure *causes* adverse effects (rather than just dividing effects by exposure without regard for causation, as in the CVM/Vose Risk Assessment); (2) exposure assessment that considers the *extent* of exposures, (not just whether exposures are present or absent, as in the CVM/Vose Risk Assessment – an approach described as "qualitative" in a recent quantitative risk of campylobacteriosis by Rosenquist et al., 2002, (G-1788) and demonstrated by them to give results incompatible with those from a correct quantitative analysis); (3) at least approximate qualitative or quantitative *dose-response assessment* that reflects at least the most important aspects of the relation (e.g., non-linearity at low doses), rather than use of a direct proportionality relation that conflicts with all available data (including human feeding studies as well as epidemiological data); and (4) risk (or hazard) characterization that integrates the estimated human health harm from a proposed action as well as the estimated benefits.

In addition to not using the best available science, the CVM/Vose risk assessment does not use "supporting studies conducted in accordance with sound and objective scientific practices" and does not "specify 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" as required by the FDA Guidelines. Specific examples of "additional studies not used to produce the risk assessment" include the CDC case-control study data. (See, e.g., G-228), the Effler study (G-185) and the Rodrigues study (G-1711).

Failure to adhere to the FDA's own controlling standards results in the CVM/Vose Risk Assessment being unreliable.

2. *The Methods Of The CVM/Vose Risk Assessment Are Not Scientifically Sound*

Not only does the CVM/Vose risk assessment fail to use accepted methods, but the methods it does employ are not scientifically sound. All the CVM/Vose model does is take the ratio of two aggregate quantities (cases of campylobacteriosis and chicken consumption) and then misinterpret this ratio as a causal parameter that can be used to make predictions about the effects of risk management interventions. This is scientifically and statistically unsound, as documented at book length by methodological texts such as Shipley (2000). (One could equally well divide the number of flat tires per year in each FoodNet area by quantities of orange juice consumed there to "establish a relation" between orange juice consumption and the risk of flat tires. Although it can be done, it provides no valid basis for making causal predictions or for asserting that the denominator causes the numerator, as CVM has done.)

It is scientifically unsound and misleading to present such aggregate ratios as causal relations. This is especially true when available scientific data demonstrate that the causal connection does not exist. For example, even CVM's own witness Heidi Kassenborg testifies that her research "found that eating chicken or turkey *at a commercial establishment* was the only risk factor that remained independently associated with illness." (Kassenborg, G-1460, P. 8, L 14 – 16, emphasis added). This research does not indicate how much of the restaurant chicken risk factor is due to the restaurant as opposed to the chicken. Thus, the ratio of aggregate illnesses to *total* chicken consumption (home-cooked as well as restaurant chicken) is inappropriate as a basis for predicting or attributing risks to chicken, by Dr. Kassenborg's own finding. Her research also found that eating chicken at home was *negatively* associated with

(i.e., not a cause of) campylobacteriosis. This significant negative relation between home-cooked chicken and campylobacteriosis risks was found in multiple independent recent studies but was completely omitted from the CVM/Vose risk assessment, which simply divides aggregate cases by aggregate chicken consumption without distinguishing between effects of home-cooked and restaurant-cooked chicken. At no point does the CVM/Vose risk assessment acknowledge or model the effects of this negative association, making it incomplete as a basis for predicting the relation between chicken consumption and illness. Indeed, the CVM/Vose risk assessment avoids using *any* modern (post-1990) data that distinguishes between home-cooked and commercially prepared chicken for purposes of quantifying illnesses attributed to chicken, thus making its selected data (from two small, non-representative samples by Harris (B-387, G-268) et al. and Deming (G-162) et al. in the early 1980s which Bayer also moves to strike) irrelevant for assessing current risks.

The failure of the CVM/Vose risk assessment to meet widely accepted standards for risk assessment, its failure to use *any* widely or generally accepted risk assessment methodologies (relying instead on the technically unsound aggregate-ratio approach), its use of untested and incorrect assumptions that human illness rates are proportional to chicken consumed (and that a single constant of proportionality holds in different states, despite clear evidence to the contrary; see, e.g., the statements of CVM's witness Dr. Molbak on variability of rates among FoodNet sites), as well as more technical errors (such as the misapplication of Bayes' Rule[11] to override data with subjective and demonstrably incorrect judgments about resistance rates) result in an estimate of risk to human health that is invalid, inaccurate and in conflict with available data. As

[11] Bayes' Rule provides a way to use data to revise "prior" probabilities (those held before the data are available) to form "posterior" probabilities (those formed after taking the data into account). This is accomplished via a mathematical operation called "conditioning" that re-weights the prior probabilities of different hypotheses (e.g., estimated values of a parameter) according to their ability to explain the observed data.

such, the CVM/Vose risk assessment and all related testimony and evidence is unreliable, irrelevant and inadmissible as evidence. *Cf. Daubert*, 509 U.S. at 593 (noting that general acceptance within the scientific community is an important factor in assessing admissibility).

In light of the unconventional and erroneous approach taken by the CVM/Vose risk assessment as outlined above, it is clear that the CVM/Vose risk assessment methodology is flawed and therefore unreliable.

3. The CVM/Vose Risk Assessment Does Not Use "Data Collected By Accepted Methods" Or "Studies Conducted In Accordance With Sound And Objective Scientific Practices;" It Ignores Recent Relevant Data And Uses Obsolete Data

The CVM/Vose risk assessment is unreliable because it does not use the best available science or data in its assessment.

Specifically, the CVM/Vose risk assessment uses *unreliable and non-representative data* sources for its estimation of chicken-attributable risk. The need to use comprehensive and recent data is recognized by CVM's witness David Vose in his own written testimony, which correctly identifies the desirability of using more comprehensive and recent data. (Vose G-1480, P. 5, L 47 - P. 6, L 3.) Although CDC has made such data available, CVM/Vose has repeatedly refused to make use of it. Instead, the CVM/Vose model continues to rely on two relatively small studies (one in a student population where meals were routinely prepared outside the home) performed approximately twenty years ago. Multiple recent studies in the US and other countries have documented that the population-attributable risks from these early studies cannot be reproduced using modern data that correctly account for other risk factors and confounders. To the contrary, multiple studies since 2000 have documented the reduced risk of campylobacteriosis associated with chicken consumption and have implicated other sources, such as restaurant dining (not necessarily associated with chicken) and drinking water, as

important risk factors. The CVM/Vose risk assessment thus uses obsolete data and fails to take into account the recognized risk factors identified in more recent literature.

Additionally, the CVM/Vose risk assessment uses an *inaccurate value* of about 57% for the fraction of domestically acquired campylobacteriosis cases that it attributes to chickens. This is more than twice the 24% value estimated in written testimony by CDC (Angulo G-1452, P. 10, L 41-44) and is more than ten times the correct value calculated from the most recent, largest, and representative data set made available by the CDC. Unlike CDC's 24% estimate, the CVM/Vose incorrect value ignores the facts that (a) only chicken eaten in restaurants or outside the home is associated with increased campylobacteriosis risk; (b) non-poultry meats eaten in this setting are also about equally strongly associated with campylobacteriosis risk; and (c) home-cooked chicken is associated with a statistically significant *reduction* in risk of campylobacteriosis. Thus, CVM/Vose attributes to chicken a risk that is actually associated with restaurant dining (of chicken or of other foods).

Finally, the CVM/Vose model uses an *inaccurate value* of nearly 20% for the fraction of domestically acquired campylobacteriosis cases that are resistant to fluoroquinolones. This is more than three times the actual historical value (ranging from about 5% in 1978 to about 6.4% in 1998 and 1999). CVM supports this inaccurate parameter value with a psuedo-Bayesian argument in which they repeatedly combine a uniform prior (having a mean of 50%) with the empirical value (about 6%). But the uniform prior is inappropriate given national and international data showing that the true rate is far lower. Additionally, the use of the same uniform prior multiple times to prevent learning from accumulating data is an incorrect application of Bayesian methodology. It conflicts with correct Bayesian updating procedures for

sequentially acquired data, e.g., as set forth in Morris H. DeGroot's text *Probability and Statistics* (Addison Wesley, 1975, p. 265).

4. The CVM/Vose Risk Assessment Does Not Meet Criteria For A Valid Risk Assessment As Set Forth In CVM's Own Testimony

The CVM/Vose Risk Assessment does not even meet the criteria that CVM's own witnesses suggest for valid risk assessments. For example, Vose's written direct testimony cautions that "[i]n concentrating on just one pathogen, one can also underestimate the benefit of some action that will affect the human health burden from several pathogens at the same time." (G-1480, P. 5, L 10-12). Yet this limitation applies directly to the CVM/Vose model itself. For example, by focusing on just *Campylobacter*, the CVM/Vose model ignores the human health benefit of the continued use of enrofloxacin due to the reduction in salmonellosis. By focusing just on fluoroquinolone-resistant *Campylobacter*, the CVM/Vose model ignores the much larger human health risks from increases in fluoroquinolone-susceptible *Campylobacter* expected if enrofloxacin is withdrawn. Such a partial analysis of effects and pathways is incapable of quantifying the full impacts on human health risks and benefits from different risk management alternatives that affect human health through multiple pathways simultaneously. *Cf. Lauzon*, 270, F.3d at 687 (notes that for scientific evidence to be reliable it should account for alternative explanations).

Moreover, CVM's witness Dr. Bartholomew (G-1454, P. 4, L 23-25) states that for the CVM/Vose risk assessment "[i]t was sufficient to identify other sources of resistance, estimate their contribution to the total pool of resistant *Campylobacter* infections, and remove them to determine those that could be attributed to uses of fluoroquinolones in chickens." But the CVM/Vose risk assessment has *not* "identified and removed" contributions from many other sources of resistance, including: (1) contamination of restaurant, institutional, and commercial

foods (unrelated to chicken consumption) by food workers and other sources; (2) contaminated drinking water, e.g., water contaminated by run-off from hospital wastes carrying fluoroquinolone-resistant ciprofloxacin; (3) resistance acquired from pets (and having genotypes not found in or originating from chickens); (4) resistance acquired from farm animals (with genotypes not found in or originating from chickens); (5) resistance acquired from eating fruits and vegetables (and not due to chicken); (6) resistance acquired from swimming in contaminated water; and (7) spontaneous resistance in human isolates, such as the (unknown) causes of the 11% resistance rate documented by Svedhem et al., 1981 (B-1851), the 12% resistance rate found in Wisconsin in 1992-1995 (B-39), the 15% resistance found by Hollander R. (1983), the 5 % resistance found by Barrett in 1988 (Barrett G-1453, P. 3, L 7-10) or the 20% pre-approval resistance found by Nachamkin in 1995 (A-200, P. 130).

5. The CVM/Vose Risk Assessment Has Not Passed Peer Review

The CVM/Vose model has not been peer-reviewed. Although the CVM/Vose model was critically reviewed and recommendations for essential improvements were made at CVM workshops (*see, e.g.*, Vose G-1480, P. 6, L 30-33), there was no obligation on the part of CVM/Vose to accept or even address the comments of the reviewers. Few, if any, of the criticisms leveled at the CVM/Vose model at the workshops, including that the model had not been validated, was addressed by CVM/Vose before the model was released in October 2000 and January 2001. Moreover, given the keen interest in microbial risk assessments, including the number published in the Society for Risk Analysis Journal (*Risk Analysis: An International Journal*), it is noteworthy that the "unique" and "novel approach" of the CVM/Vose model has not been published in a peer-reviewed journal. This is especially suspect since it has been three years since the model was made available to the public and two years since the model's

completion. While Bayer understands an article on the Vose model will be published (Bartholomew G-14545, P. 4, ¶ 12, L 13-17), to the best of Bayer's knowledge information and belief the publication is not a peer review publication.

Peer-review increases the likelihood that the methodology is correct and that the resulting data are reliable. *Daubert*, 509 U.S. at 593 (noting that peer-review "increases the likelihood that substantive flaws in the methodology will be detected"). Here, the reliability of the CVM/Vose model is questionable.

6. The CVM/Vose Risk Assessment Model Has Not Been Tested Or Validated And Attempts To Do So Prove It Is Invalid

The CVM/Vose Risk Assessment is unreliable because it has not been tested or validated. CVM concedes that the model has not been validated. (Vose G-1480, P. 7, L 30-34). Moreover, attempts to validate it with real data quickly demonstrate that it is not a valid model and is incapable of describing even the most obvious aspects of the data.

The CVM/Vose model, as explained by Bartholomew (G-1454, P. 4-5, ¶ 12-14), describes a proportionality constant K_{res} which, when multiplied by the quantity of chicken consumed containing fluoroquinolone-resistant *Campylobacter*, yields the average number of people with fluoroquinolone-resistant *Campylobacter*. In the model, K_{res} is necessarily positive (as it is the ratio of two positive quantities), yet real-world data from the CDC Population Survey and the CDC Case Control Study (see, e.g., date from Friedman G-228) indicate that K_{res} is negative, perhaps because chicken consumption at home is protective – a qualitative feature of the data omitted from the CVM/Vose model and analysis. In other words, a plot of CDC data shows that human campylobacteriosis tends to *decline* with greater chicken consumption. The CVM/Vose model does not account for this. Moreover, the model falsely assumes that the same K_{res} applies to all individuals, all FoodNet areas, all states, etc. Yet, as noted in the testimony of

Dr. Molbak, the variability among states in *C. jejuni* illness rates (and resistance rates) is very high, contradicting the modeling assumption that the same K_{res} holds in different locations. (Molbak G-1468, P. 4, L 38-44; P. 6, Table 1; P.8, L 17-18; P. 9, Table 3). This invalidates the use of the model for making predictions for the general US population as a whole. The model also makes other errors (e.g., a misapplication of Bayes' Rule and use of an incorrect formula for attributable risk), as noted previously. It has not been tested or validated. The model is therefore unreliable and all testimony and evidence relying on the model should be excluded.

7. The CVM/Vose Model Has Not Been Generally Accepted in the Scientific Community

The CVM/Vose risk assessment "predictive model approach" (Vose G-1480, P. 6, L 38) has not been generally accepted in the risk assessment field. For example, the World Health Organization, in considering how to assess the human health risks of *C. jejuni,* was familiar with the CVM/Vose approach, but chose instead to use the more reliable and accepted farm-to-fork approach that Vose repeatedly seeks to denigrate in his testimony and in various forums. The CVM/Vose model is essentially just a ratio of two aggregate quantities (number of persons with fluoroquinolone-resistant *Campylobacter* infections and pounds of chicken meat with fluoroquinolone-resistant *Campylobacter*) that are not causally connected. In fact, CDC case-control data reveal that the chicken consumption and campylobacteriosis are negatively correlated, in direct violation of one of the CVM/Vose model's key untested modeling assumptions. The World Health Organization and other risk assessors (e.g., Rosenquist et al., 2002, G-1788) have chosen not to use this flawed approach and have instead applied the widely accepted risk assessment principles and procedures that Vose attacks.

The CVM/Vose model ignores, rejects, or fails to follow such generally accepted risk assessment practices as quantitative exposure assessment, dose-response modeling, use of

reliable, current data and validation of the model prior to use. *Cf. Daubert*, 509 U.S. at 593 (noting that a technique should be generally accepted in the scientific community before evidence based upon it is admissible). Its quest to develop and apply an "innovative" approach that would avoid these steps has led to an analysis that produces predictively useless results, that does not describe available data, and that misrepresents ratios as causal relations, while overlooking all of the real human health risks from withdrawal of enrofloxacin.

B. The CVM/Vose Risk Assessment Is Not Relevant

1. The Output Of The CVM/Vose Risk Assessment Is Not Predictive Of The Number Of Poultry-Attributed Fluoroquinolone-Resistant Campylobacteriosis Cases That Are Treated With A Fluoroquinolone

The CVM/Vose risk assessment cannot be considered a reliable basis for estimating the impact of enrofloxacin use on occurrence of fluoroquinolone-resistant *Campylobacter* in humans. In particular, the flaws, errors and omissions outlined above are likely to have resulted in a substantial overestimate of the risk to humans. Moreover, since the aggregate ratio used as a basis for prediction has no known causal relevance and does not correctly describe available data, it cannot be used to draw valid causal inferences or to make valid predictions of the likely consequences of risk management options, including withdrawing enrofloxacin.

2. The CVM/Vose Risk Assessment Ignores Relevant Human Health Benefits From Continued Use Of Fluoroquinolones

The CVM/Vose Risk Assessment fails to analyze the entire risk because it fails to assess the risks associated with the withdrawal of the enrofloxacin approval. For example, without enrofloxacin available to treat airsacculitis, broiler chickens in airsacculitis positive flocks will be less uniform, have weaker digestive tracts and be more likely to be contaminated with enteric pathogens. This can lead to an increase in human gastroenteritis and diarrhea, the exact endpoint the CVM/Vose Risk Assessment calculates. By failing to quantify any of the human health risks

associated with a withdrawal of enrofloxacin, the Vose/CVM risk assessment has omitted critical information needed to guide rational risk management decision-making. This violates the principle repeatedly stressed in Vose's own testimony, that risk assessment should serve the purposes of risk management decision-making.

C. The CVM/Vose Risk Assessment Does Not Meet The Criteria For Admissibility of Scientific Evidence

In light of the preceding methodological flaws, lack of peer review and failure to gain general acceptance in the risk assessment community, the CVM/Vose Risk Assessment does not meet the FDA Guidelines or the scientific reliability criteria for admissibility. Also, because it fails to predict the number of poultry-attributed fluoroquinolone-resistant campylobacteriosis cases that are treated with a fluoroquinolone, and fails to assess the human health risks of the withdrawal of enrofloxacin, the CVM/Vose Risk Assessment model does not meet the scientific relevance standard of admissibility. This Administrative Hearing should reject the CVM/Vose model and all related testimony as unreliable and not relevant.

VI. BAYER MOVES TO STRIKE ALL CVM TESTIMONY AND EVIDENCE PURPORTING TO SHOW LONGER DURATION OF FLUOROQUINOLONE-RESISTANT *CAMPYLOBACTER* INFECTIONS BECAUSE THE UNDERLYING EPIDEMIOLOGICAL STUDIES ARE SCIENTIFICALLY UNRELIABLE AND FAIL TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

A. The Underlying Epidemiology Studies Are Not Reliable

CVM relies on a handful of epidemiological studies (Smith G-589, Marano G-394, Neimann G-780, McClellan G-1367, and Nelson G-1489) to contend that infections with fluoroquinolone-resistant *Campylobacter* are associated with an increased duration of diarrhea compared to infection with sensitive strains. (*See, e.g.*, Molbak G-1468, P. 19, L 15-33). The cited studies, however, are unreliable and incorrect because they fail to use generally accepted

epidemiological methods in analyzing the data. Moreover, many have not been peer-reviewed or published. As such, the studies and all testimony relying on the studies should be excluded.[12]

1. The Underlying Epidemiology Studies Do Not Follow Accepted Epidemiological Methods

A fundamental tenet of epidemiologic analysis is that confounding variables must be identified, controlled for and corrected for (B-1902, P. 147-148) before interpreting associations in terms of cause and effect. In each of the studies relied on by CVM for the proposition that fluoroquinolone-resistant infections lead to longer duration of diarrhea, however, foreign travel of the case subjects is a confounding variable. Persons who become infected with *Campylobacter* while traveling in a foreign country very well may be delayed in seeking medical treatment and/or may contract different strains from domestically-acquired cases. Moreover, people who travel abroad are well known to be at increased risk of contracting fluoroquinolone-resistant campylobacteriosis. Thus, foreign travel is a confounding variable when measuring the association between resistance and duration of illness. When the Smith, Marano and McClellan and Nelson case-control data are analyzed and corrected to remove the confounding effect of foreign travel, there is no remaining statistically significant difference in the duration of diarrhea between persons with fluoroquinolone-resistant infections and fluoroquinolone-susceptible infections, whether the person is treated with a fluoroquinolone or not. In other words, the entire claimed association between resistance and duration of illness is explained away by the fact that both are positively associated with foreign travel. Restricting attention to domestically acquired cases removes the entire claimed effect.

Whether the same holds true for the Neimann data remains unknown, however, because Neimann refused to allow Bayer to analyze his data for any purpose other than to do causal

[12] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix C.

graph modeling. Neimann's decision to refuse Respondent Bayer permission to use his data was supported by his superior, CVM witness Henrik C. Wegener (G-1483). (Letter attached; see Declarations of Roger Feldman and Tony Cox, Appendix I). Wegener in fact relies on Neimann's study (P. 14; P. 28, L 16-19). Other CVM witnesses, also associated with Neimann, also rely on Neimann's data, including his external thesis advisor Tauxe (G-1475, P. 4, L 40-41; P. 9, L 16-19) and collaborator Molbak (G-1468, P. 19, L 25-26.)

There are additional reasons to question Neimann's conclusions and other reliance thereupon. Even though eating undercooked poultry (which may be a marker for careless preparation and consumption habits of many other foods, as is the case in US restaurants) was identified as a risk in the Neimann study, the number of people actually developing campylobacteriosis after eating undercooked chicken, was low. For duration of illness, the day of prescription of an antibiotic and the day the treatment was initiated were not registered in relation to when symptoms were noticed. Neimann himself writes *"It is not possible to evaluate whether a longer duration of illness and more severe symptoms among patients treated with antibiotics in our study was due to late onset of treatment"*. Bearing this in mind, and understanding that time of treatment in relation to when the illness started can significantly impact duration, any proposed differences in duration of illness are speculative.

Failure to follow proper and generally accepted epidemiological methods results in the Smith, Marano, McClellan and Nelson studies being unreliable. The reliability of the Neimann data is suspect since he will not allow independent review. All testimony relying on these studies for the proposition that resistant infections lead to longer illness should be excluded.

2. Many of the Underlying Epidemiology Studies Have Not Been Peer Reviewed or Published

Peer review and publication is one of the benchmarks of scientific reliability set forth by *Daubert*. *See, Daubert*, 509 U.S. at 593 (noting that peer review "increases the likelihood that substantive flaws in the methodology will be detected"). Similarly, the FDA guidelines endorse value of peer review. Neither the Marano, Neimann, McClellan or Nelson studies were published in a peer-reviewed scientific journal. As such, their reliability is suspect.

B. The Underlying Epidemiology Studies Are Not Relevant

1. The Underlying Epidemiology Studies Do Not Assess Whether Poultry-Attributed Fluoroquinolone-Resistant Campylobacteriosis Cases Acquired in the US Are Associated With A Longer Duration Of Illness

A central issue for this Administrative Hearing is whether fluoroquinolone-resistant *Campylobacter* infections in humans *in the United States* that may have been acquired from enrofloxacin-treated poultry have any adverse impact on human health compared to susceptible *Campylobacter* infections. Any conclusions based on cases of campylobacteriosis acquired *outside* the United States are not relevant to the central issue unless those cases are removed from the analysis. Since the Smith, Marano, Neimann, McClellan and Nelson studies all include cases of campylobacteriosis acquired through foreign travel, testimony relying on them are not relevant to the issues in this hearing.

C. The Underlying Epidemiology Studies Do Not Meet The Criteria For Admissibility of Scientific Evidence

The Smith, Marano, Neimann and McClellan and Nelson studies do not follow proper epidemiological methods; they are scientifically unreliable and should not be admissible. The Smith, Marano, McClellan and Nelson studies include cases of foreign-acquired campylobacteriosis which make them a poor "fit" to the issue in this hearing – cases acquired in

the US. Cases acquired abroad simply are not probative and bear no relation to domestic cases. As such, the studies are not scientifically relevant and would not be admissible in Federal Court for the purposes being offered here. This Administrative Hearing should likewise exclude such unreliable and irrelevant studies and the testimony relying on them.

VII. BAYER MOVES TO STRIKE ALL CVM TESTIMONY AND EVIDENCE RELYING ON THE SENTINEL COUNTY STUDY BECAUSE THE STUDY IS SCIENTIFICALLY UNRELIABLE, ITS RELEVANCE CANNOT BE DETERMINED, AND IT FAILS TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

A. The Sentinel County Study Is Not Reliable

CVM relies on the "Sentinel County Study" for the proposition that the prevalence of ciprofloxacin resistance among *Campylobacter* in the United States was very low in 1989-1990 (pre-approval of enrofloxacin), and use these data to attempt to support CVM's position that a purported rise in fluoroquinolone-resistant *Campylobacter,* was temporally associated with and caused by the use of enrofloxacin in poultry. (*See, e.g.*, Tollefson G-1478, P.15, L 16-22; Angulo G-1452, P. 14, L 1-36).

Although CDC and CVM have referred to the "Sentinel County Study" repeatedly, neither have made it clear exactly what constitutes the Sentinel County Study. According to Angulo (G-1452 P. 14, L 5-7), "[I]n 1989-1990, the CDC conducted a 12-month *Campylobacter* sentinel study. Detailed methods of this study are described elsewhere." (B-589 Patton). Dr. Angulo further describes a preliminary report of the results of the isolates collected in the sentinel county study, published in 1992, which reported no fluoroquinolone resistance in *Campylobacter jejuni.* (Angulo G-1452, P. 14, L 11-20 citing G-624 Tenover et al.). Dr. Angulo further states that "none of the 313 isolates [obtained in the Sentinel County Study] were ciprofloxacin-resistant (CDC unpublished data)." (Angulo G-1452, P. 14, L 22-26). Accordingly we use "Sentinel County Study" to describe all the underlying data and studies

including B-589 (Patton), G-592 (Sobel), G-624 (Tenover) and the Sentinel County Survey, including the "CDC unpublished data" referenced by Angulo above.

The reliability of the "Sentinel County Study" is unknown, however, because no protocol for the study has been produced, and the number of isolates analyzed varies depending on which report is referenced.[13]

1. The Sentinel County Study Results Are Unreliable Because The Protocol For Collection And For Susceptibility Testing Are Unknown

Bayer repeatedly sought the protocol questionnaire and key for the Sentinel County Study from CVM and CDC. (Letters attached as B-1570 and B-1571; see Declaration of Nathan A. Beaver, Appendix I). CVM disclaimed having any protocol and CDC has been unable to produce one pursuant to FOIA.[14] CVM's testimony acknowledges that a questionnaire was used (Angulo, P. 15, L 2-3), but none was ever produced. Like CVM in its testimony (Angulo G-1482, P. 14, L 7), CDC points only to the Patton article (B-589) for anything close to a study protocol. But the Patton article does not contain any protocol for sample selection, isolation or speciation of the *Campylobacter*. Other reports about the Sentinel County Survey (G-624 and G-95) in combination with the Patton article raise more questions about the reliability of the study. For example, G-624 reports that the study collected 700 isolates from humans, the majority of which were *C. jejuni*. But of those, only 332 *C. jejuni* isolates were resistance tested (G-624, P. 2). Patton only discusses 298 *Campylobacter* isolates, 288 of which were *C. jejuni*. No

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[13] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix D.

[14] Today, just hours before Bayer was to submit its Motion to Strike, Bayer Counsel received a response from CDC containing additional information on the Sentinel County Study, purporting to be the case questionnaire and protocol. This letter, dated January 17, 2003, was sent to us by regular US Mail and was postmarked January 21, 2003. This was despite our written request that we asked to be contacted when any materials were ready so that we could arrange to have them sent via Federal Express, an arrangement CDC has accommodated in other instances. Due to this 11th hour receipt of these materials, we have been unable to review the materials in any detail, and are unable to address them substantively in the motion. Bayer reserves its right to comment on these materials, after appropriate review, in a subsequent response.

explanation is provided for these discrepancies in numbers. The fate of the missing *C. jejuni* isolates is unknown.

The samples were collected in 1989-1990, and only a "preliminary analysis" of susceptibility was presented in 1992. (G-624, P. 2). It is not clear how the samples were stored or handled in the two or three years between collection and testing, which raises serious questions regarding the viability and reliability of reviving and testing these isolates. It also does not appear that 12 years after the data were collected, anything more than "preliminary analysis" was ever done or published, as a peer review publication or otherwise. Without a protocol, the propriety of sample collection speciation, susceptibility testing and handling is unknown. Without the questionnaire and key to the data, its reliability is not able to be tested. The Sentinel County Study data is therefore not reliable and should be excluded. *Cf. Wornick*, 264 F.3d at 845 (noting that when scientific evidence is prepared for litigation and is not peer-reviewed, its proponent must show precisely what was done so that reliability may be assessed).

2. The Sentinel County Study Results Are Unreliable Because Resistant C. Jejuni Would Likely Have Been Discarded

The Sentinel County Study is also unreliable as a pre-approval baseline of fluoroquinolone-resistance in *Campylobacter* because standard practice at the time was to distinguish *Campylobacter jejuni/coli* from other species of *Campylobacter* for example, *Campylobacter lari,* by testing for nalidixic acid resistance. (Barrett G-1453, P. 3, L 1-3; McDermott G-1465, P. 7, L 25-36; Tollefson G-1478, P. 9, L 36-47; P. 10, L 1-6). In otherwords, a *Campylobacter* that was resistant to nalidixic acid would have been discarded, as not being a *Campylobacter jejuni* or *coli*. In fact, the *Campylobacter* may have been a quinolone-resistant *Campylobacter jejuni.*

For example, out of 700 isolates in the Sentinel County Study, 332 were thought to be *C. jejuni* after "preliminary analysis" because they were susceptible to nalidixic acid (Angulo G-1452, P. 14, L 16-20 and G-624). What is *not* known is how many of the 368 other isolates (700 minus 332) were discarded as not being *C. jejuni* because they were resistant to nalidixic acid, a quinolone for which there is high cross-resistance to ciprofloxacin (Weber G-1482, P. 8, L 9-13; Smith G-1473, P. 8, L 5-9; Tollefson G-1478, P. 4, L 12-16). Even those close to the Sentinel County Study (i.e., Fred Tenover, author of G-624) found it remarkable that the Sentinel County Study revealed no ciprofloxacin resistance among the *C. jejuni* isolates (G-624, P. 2 "A larger number was expected..."). Tenover's expectation that there would be a greater than zero baseline resistance in 1989-1990 is not surprising considering that others found pre-approval fluoroquinolone resistance in *Campylobacter* from humans anywhere from 3% (B-67) to 12% (B-39) in the United States and 11% in Sweden in 1981 (B-1851). Even CVM's witness Timothy Barrett found U.S. pre-approval quinolone resistance of 5% in *C. jejuni* in 1988 (Barrett G-1453, P. 3, L 7-10) and CVM's witness Irving Nachamkin found 20% pre-approval resistance in 1995 among his Pennsylvania cohort (G-1571; A-200, P. 130).

The above shows that there is too much unknown about the Sentinel County Study (especially the extent to which quinolone-resistant *C. jejuni* may have been present in the 368 isolates that were thought to be non- *C. jejuni*) for it to be deemed reliable and CVM and CDC's failure to make the data available or to otherwise explain its absence does not enhance the reliability of the data.

B. The Sentinel County Study Is Not Relevant Because The Population From Which The Sentinel Study Was Drawn Is Unknown

The lack of protocol or procedure for the Sentinel County Study prevents any discernment of the representativeness of the samples to the US population. All that is known is

that the isolates were selected "from persons with sporadic cases of diarrhea, and were collected from 19 randomly chosen counties in all geographic (census) regions of the United States." (Patton, B-589). Without more, it is unknown whether the samples are representative of, and therefore relevant to, the baseline of fluoroquinolone-resistant *Campylobacter* in the US population.

C. The Sentinel County Study Does Not Meet The Criteria For Admissibility of Scientific Evidence

Given that the reliability and relevance are unknown, the Sentinel County Study would not be admissible in Federal Court nor does it meet FDA Guidelines. This Administrative Hearing should likewise exclude the study and all documents and testimony relying on it.

VIII. BAYER MOVES TO STRIKE THE TESTIMONY OF KARE MOLBAK AND ALL CVM TESTIMONY AND EVIDENCE RELYING ON MOLBAK BECAUSE THE MOLBAK TESTIMONY IS SCIENTIFICALLY UNRELIABLE AND FAILS TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

Molbak's testimony purports to prove that persons with fluoroquinolone-resistant cases of campylobacteriosis have increased morbidity, increased disease duration and increased mortality compared to susceptible strains (Molbak G-1468, P. 12, L 21 - P. 21, L 36).

Molbak's testimony is unreliable and irrelevant, however, because his methodology is unproven and questionable and there are serious questions about the specific types of *Campylobacter* disease that form a basis of his study cohort.[15]

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[15] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix E.

A. Molbak's Testimony is Unreliable

1. Molbak's Methods Are Not Valid And Not Generally Accepted

Molbak's method was to seek to associate adverse health events to a previous *Campylobacter* infection by comparing a cohort of culture-proven *Campylobacter* cases one year after infection to the general population. His review was based on administrative billing claims data and not based on actual medical record review. This approach is considered controversial because of imperfect adjustments for comorbidity, lack of validation, and inappropriate statistical modeling methodology.

The comorbidity index of Charlson et al., which was used by Molbak to attempt to adjust comorbidity has not been validated for applications involving campylobacteriosis. Its validity has been questioned and its predictive power has been shown to be limited or inadequate in many other applications. For example, in a recent review, Harboun M, Ankri J., 2001 state that "However, the Charlson index was found to be limited in recording the entirety of the old patients' pathologies, and in patients with cognitive deficits, only CIRS appeared to be sufficiently trustworthy because it allows a comprehensive recording of all the comorbid disease from clinical examination and medical file data." In general, the comorbidity index does not include the effects of unmeasured covariates, including aspects of diet, lifestyle, or immune system status that may predispose individuals to campylobacteriosis and to other illnesses. Dr. Molbak's testimony does not address the residual confounding due to factors (e.g., drinking contaminated water) that may not be adequately measured or accounted for in the index but that nonetheless predict both increased campylobacteriosis rates and increases in other adverse health effects.

Dr. Molbak's description of statistical methods in paragraph 37 of his testimony is inadequate and calls into question his expertise in statistics and the relevance of testimony based on these analyses. (His testimony in paragraph 33 that "a statistical analysis showed a significant decline (40%) in the number of infections, mainly because of the withdrawal of poultry" repeats an erroneous interpretation that purports to extract a conclusion about causes from a set of data and analyses that only investigated associations, not causality. This impossible inference reveals that Dr. Molbak is willing to reach and/or repeat conclusions, citing statistical analysis for justification, even when they are not in fact justified by statistical analysis.) In paragraph 37, he offers no reason why "diagnostic groups with relative mortality rates less than 1.2 were not included in the models." Of course, one way to increase the apparent size of relative mortality rates is to omit all those that are small, but this should perhaps not be characterized as a "Statistical method".

The crucial claim in paragraph 37 that "By forcing this index into the survival analyses, any difference between the relative mortality of patients and the general population quantifies excess mortality beyond what is attributable to underlying illness" is unproved speculation. For, the index is not perfect, as documented in many studies (e.g., Bravo G, Dubois MF, Hebert R, De Wals P, Messier L., 2002, who conclude that "Findings suggest that the Charlson Comorbidity Index can be improved upon when used to measure comorbidity in long term care patients.") Dr. Molbak has not demonstrated that comparing sick, or even terminally sick, people (campylobacteriosis patients, disproportionately many of whom already had AIDS or cancer, as testified by Dr. Molbak in paragraph 39) to well controls, and then attributing any differences in their future health to *Campylobacter* after conditioning on the comorbidity index, has any validity whatsoever. In the absence of such validation, his method remains purely speculative.

Moreover, the conjecture that cancer patients and AIDS patients die at an increased rate because of *Campylobacter*, as opposed to other reasons, has not been proved or made plausible in Dr. Molbak's analysis. Treating it as a conclusion (Molbak G-1468, P. 14, ¶ 42), rather than as a hypothesis to be tested, suggests that Dr. Molbak is not aware of correct statistical methodology for testing and establishing causal hypotheses based on data.

Using an unvalidated statistical model to attribute AIDS-related deaths and cancer-related deaths to *Campylobacter* (rather than recognizing that AIDS and cancer compromise immunity and lead to increased campylobacteriosis as well as to increased mortality) is a way to greatly inflate the hypothetical mortality rate attributed to *Campylobacter* but it conflicts with more traditional numbers (Molbak G-1468, P. 14, ¶ 42). However, this use of statistics does not offer any evidence of a causal relation between campylobacteriosis illness and increased mortality or morbidity rates. The use of an imperfect comorbidity index to try to invert the medically obvious causal logic and conclude that *Campylobacter* causes AIDS-related and cancer-related deaths, rather than being caused by these serious immuno-compromising conditions, suggests a fundamental misunderstanding of statistical methodology, casting doubt on all of the statistical and causal claims in the testimony. The ttestimony related to statistical and causal methods and conclusions appears to be too deeply flawed to be anything other than speculation.

Dr. Molbak states that he uses a conditional proportional hazards model. However, no justification has been given for this model. It is well known that the proportional hazards model can give incorrect and biased results in the presence of missing data, errors in the recorded values of the explanatory variables, missing confounders and covariates, and other realistic conditions. The proportional hazard model must then be replaced by more appropriate methods. Dr. Molbak does not discuss these issues or offer any justification for ignoring them. In the

absence of discussion, the extent to which the results of the proportional hazards model have been biased by not accounting for missing covariates (e.g., immune status indicators, cooking habits) and other limitations in the data cannot be estimated.

Administrative data, used by Molbak, are not as accurate as an actual medical record review. Medical records give a more complete view of the patients' medical conditions to allow for a better adjustment of co-morbidity. Moreover, comparing patients to the general population may involve many uncontrolled confounders (e.g., cases may have been more likely to have had compromised immunity, unhealthy lifestyles or other risk factors predisposing them to both increased risk of campylobacteriosis and increased risks of other ills). Molbak's failure to use the best techniques to adjust for co-morbidity (e.g., the Charlson index used by Molbak does not use data on smoking, and drinking both of which are important to consider when comparing morbidity and mortality between two groups) is compounded by not using administrative data in the one-year follow up period. A patient developing ischemic heart disease in this period for example would not have had that co-morbidity identified. Molbak also did not use the pharmacy database to help adjust for co-morbidity. His one year analysis of morbidity and mortality also did not use medical record review to identify specific endpoints. Additionally, and significantly Molbak did not establish a clear definition of his "case" at the outset, so as to ensure that the endpoints selected were meaningful. His analysis of acute mortality appears to have only been based on Kaplan Meir (used to look at short term morbidity and mortality) and does not appear at all to adjust for co-morbidity. Molbak's suggested interpretation that campylobacteriosis causes subsequent increased risks of other harms does not correct for these selection bias.

2. Molbak's Methods Have Not Been Peer Reviewed

Molbak's testimony relies on a paper he authored with Helms and Vastrup (G-1495) "Health Effects Associated with Antimicrobial Drug-Resistance in *Campylobacter* spp." on its face indicates "*This report is a working paper and should not be cited.*"

Neither the paper, methodology nor data have undergone peer review. The paper has not even been submitted for publication. In light of this and of what appear to be crucial methodological flaws (e.g., failure to match cases and controls on health status or health history), the exhibit and all testimony relying on it should be excluded.

B. Molbak's Cohort May Include Non-C. Jejuni Infections Such As Serious C. Fetus Infections

As noted earlier, Molbak's testimony relies on his unquotable paper "Health Effects Associated with Antimicrobial Drug-Resistance in *Campylobacter* spp." (G-1495, which Bayer is also moving to strike.) *Campylobacter* spp. refers to *Campylobacter* of all species and would necessarily include not only *C. jejuni* and *C. coli* but also *C. fetus*. *C. fetus* causes serious systemic and septicemic disease in humans but is not a zoonatic pathogen from poultry.

There is no indication anywhere in Molbak's testimony or paper that the data that forms a basis of his testimony distinguished between species of *Campylobacter*. The fact that his testimony and paper refer to *Campylobacter* spp. generically creates the presumption that his research includes patients with *Campylobacter* fetus infections, which have more serious after effects. Because of this, any review of extra morbidity and mortality one year after infection is inherently unreliable.

C. Molbak's Testimony Is Not Relevant

Molbak's morbidity and mortality testimony relates to patients infected with all species of fluoroquinolone-resistant *Campylobacter*, from all sources, in *Denmark*. The focus of this hearing, on the other hand is fluoroquinolone-resistant *Campylobacter jejuni* or *coli* from

chickens or turkeys that may be causing infections in the *United States*. As such, Molbak's morbidity and mortality testimony and evidence is not relevant.

Moreover, the fact that Molbak's research does not correct for diseases that may be caused by the far more serious enteric pathogen *Campylobacter* fetus, which does not come from poultry, but can impact morbidity and mortality, underscores the lack of relevance.

D. Molbak's Testimony Does Not Meet The Criteria For Admissibility Of Scientific Evidence

Because of the failure to adhere to acceptable methodology and the fact that the Molbak paper is little more than a draft and has not been peer reviewed and/or published, the Molbak paper (G-1495) and testimony (G-1468) relying on it fails to meet the reliability threshold for admissible evidence in Federal Court as well and does not comply with the FDA Guidelines. Additionally, because the scope of the Molbak paper and testimony do not "fit" the issues of this hearing, the paper and testimony are not relevant from a scientific evidence perspective. This Administrative Hearing should exclude such scientifically unreliable and irrelevant materials as well.

IX. BAYER MOVES TO STRIKE ALL TESTIMONY AND DOCUMENTS REPRESENTING THAT CAMPYLOBACTER IS THE LEADING CAUSE OF BACTERIAL GASTROENTRITIS IN THE U.S., THAT THERE ARE 2.4 MILLION U.S. CASES OF CAMPYLOBATERIOSIS, AND ALL ESTIMATIONS OF ADVERSE HEALTH, ECONOMIC AND OTHER IMPACTS CALCULATED USING SUCH FIGURES BECAUSE THE ABOVE STATEMENT AND FIGURE IS UNRELIABLE, NOT RELEVANT AND FAILS TO MEET THE STANDARDS FOR ADMISSIBILITY OF SCIENTIFIC EVIDENCE

X.

In 1999 Meade et al (G-410) at CDC estimated that there were annually 2.4 million *Campylobacter* infections in the U.S. This estimate was based on data collected in 1996-97 and largely extrapolated from *Salmonella*. Additionally, CDC has described *Campylobacter* as the leading cause of bacterial gastroenteritis in the U.S. This statement and figure have gained

currency. Notwithstanding that rates of *Campylobacter* infection in the U.S. have markedly declined since 1996, and that campylobacteriosis is not the leading cause of bacterial gastroenteritis in the U.S., CVM has used these outdated data in their attempt to quantitate the adverse health and economic impact of campylobacteriosis on the U.S. population, including from both susceptible and resistant *Campylobacter*. The 2.4 million estimate, the statement about the "leading cause", and calculations and statements which are derivative thereof, are therefore a significant overstatement of the impacts of campylobacteriosis on the U.S. population, unreliable and irrelevant because they are outdated, inaccurate and conflict with newer data, as acknowledged by CVM.[16]

A. These Data and Statements Are Unreliable

1. The Estimate of 2.4 Million Annual U.S. Cases of Campylobacteriosis is Outdated and an Exaggeration

In 1999 CDC estimated that there were 2.4 million cases of campylobacteriosis in the U.S. annually. (G-455) The figure is derived from a combination of outdated data and is an extrapolation based upon the etiology of salmonellosis. (G-455). Some of these data were collected in 1996-97 (Angulo G-1452, P. 7, L 4-7) and much of these data are in excess of ten years old. Regardless of whether or not the figure of 2.4 million presented an accurate estimation at the time it was published it is not currently accurate, and has not been for some time. The rate of *Campylobacter* infection in the U.S. has declined markedly since 1996. CDC FoodNet reported a 19% decline in the incidence of *Campylobacter* from 1998 to 1999 in the original five FoodNet sites. From 1996 to 2001 CDC reported a 27% drop in human cases of campylobacteriosis. (Angulo G-1452, P. 5, L 15-21; *See*, Preliminary FoodNet Data on the Incidence of Foodborne Illnesses - Selected Sites, United States, 1999, MMWR Weekly, March

[16] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix F.

17, 2000/ 49(10); 201-5; Tauxe G-1475, P. 16, L 24-25.) The testimony of Angulo confirms that the correct estimated annual incidence of *Campylobacter* infections is 1.4 million cases in 1999. (Angulo G-1452, P. 7, L 10-14). 1.4 million is based on a model developed by, and first used by David Vose, in the CVM/Vose risk assessment in ***1999***. (G-953 CVM/Vose Risk Assessment; Angulo G-1452, P. 7, L 10-14.)

Notwithstanding that the estimated 2.4 million cases of campylobacteriosis is outdated, incorrect and a significant overstatement CVM has continued to use the figure and otherwise rely on it, with the effect of overstating the impact of campylobacteriosis (both fluoroquinolone susceptible and resistant) on the U.S. population. (See, *e.g.*, testimony of CVM's David G. White G-1484, P. 2, L 29-30; Tollefson G- 1478, P. 3, L. 36-38; Kassenborg G-1460, P. 2, L 12-13; Ohl G-1485, P. 6, L 6-9, P. 14, L 32-38 (relying on Barza, who extrapolates using the 2.4 million incidence rate); Tauxe G-1475, P. 2, L 10-16, P. 3, L 45-56, P. 4, L 1-2.

2. *The Statement That Campylobacter jejuni is the Leading Cause of Bacterial Gastroenteritis in the U.S. is Incorrect and an Overstatement.*

Campylobacter jejuni is not infrequently described as "the leading cause of bacterial gastroenteritis in the U.S." (Nachamkin G-1470, P. 2, L 31-32; Tauxe G-1475, P. 1, L 2-43, P. 2, L 10-11; Kassenborg G-1460, P. 2, L 11-12; Morris G-1469, P. 3, L 18-20; Ohl G-1485, P. 4, L 41-42). In fact according to CDC *Campylobacter* incidence rates have declined markedly in the past five years and *Campylobacter* is no longer, and has not been for some time the leading cause of bacterial gastroenteritis in the U.S. Statements that campylobacteriosis is the "leading cause" are therefore, inaccurate, a significant overstatement, and unreliable. Notwithstanding the fact that the statement that *Campylobacter* is the leading cause of bacterial gastroenteritis in the US is outdated, incorrect and a significant overstatement, CVM has continued to use this statement and otherwise rely on it with the effect of overstating the impact of campylobacteriosis

(both fluoroquinolone susceptible and resistant) on the US population. (See, e.g., Testimony of Tauxe G-1475 P. 18, L 22-37).

B. These Data and Statements Are Irrelevant

1. *The Estimate of 2.4 Million Annual U.S. Cases of Campylobacteriosis is Outdated and an Exaggeration.*

The rate of *Campylobacter* infection in the U.S. has declined markedly since 1996, and as Angulo confirms the correct estimated annual U.S. incidence of *Campylobacter* infections is 1.4 million cases in 1999, not 2.4 million. (Angulo G-1452, P. 7, L 10-14.) The focus of this hearing, in part, is whether (and if so, the extent) human fluoroquinolone-resistant *Campylobacter* infections, caused by the use of enrofloxacin in chicken or turkey, causes harm. Data that purports to represent the annual incidence of campylobacteriosis, that is inaccurate and a significant overstatement, and data derived therefrom, can not possibly be relevant to this question.

2. *The Statement That Campylobacter jejuni is the Leading Cause of Bacterial Gastroenteritis in the U.S. is Incorrect and an Exaggeration.*

Campylobacter jejuni is not infrequently described as "the leading cause of bacterial gastroenteritis in the U.S. According to CDC *Campylobacter* is no longer, and has not been for some time the leading cause of bacterial gastroenteritis in the U.S. The focus of this hearing, in part, is whether (and if so, the extent) human fluoroquinolone-resistant *Campylobacter* infections, caused by the use of enrofloxacin in chicken or turkey, causes harm. Statements that *Campylobacter* is the leading cause of bacterial gastroenteritis in the U.S., frequently used with figures purporting to show the rate and adverse impact of fluoroquinolone-resistant and susceptible campylobacteriosis, are used by CVM to attempt to present the adverse impact of campylobacteriosis on the U.S. population. Statements and figures that purport to represent the

annual incidence and impact of campylobacteriosis, that are inaccurate and a significant overstatement, and data derived therefrom, can not possibly be relevant to this question.

C. These Data, Statements, and Information Derived Therefrom Do Not Meet The Criteria For Admissibility Of Scientific Evidence

All testimony and evidence referencing Mead et al (G-410), or any other source that states, implies or otherwise represents that (a) *Campylobacter* is currently the leading cause of bacterial gastroenteritis in the U.S., or (b) causes 2.4 million *Campylobacter* infections in the U.S. annually, including all testimony and evidence that relies in whole or in part on 2.4 million annual *Campylobacter* infections as a basis for calculating the mortality or morbidity of campylobacteriosis, whether from a fluoroquinolone sensitive or resistant organism do not meet the scientific standard for admissibility and FDA Guidelines because CVM has admitted that these statements are inaccurate and a significant overstatement. As such, all testimony and evidence either making this claim, using this figure, or making calculations based on this figure is unreliable, irrelevant and inadmissible as evidence

XI. BAYER MOVES TO STRIKE ALL OTHER CVM TESTIMONY AND EVIDENCE THAT IS IRRELEVANT, IMMATERIAL, UNRELIABLE OR REPETITIVE

Beyond what is described above, much of CVM's testimony does not meet the standards of admissible evidence in FDA administrative hearings. As noted above, admissibility of evidence in FDA proceedings is governed by 21 C.F.R. § 12.94. "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). Both testimony and written evidence are deemed admissible unless the administrative law judge excludes it. *Id.* §§ 12.94(c), (d). Under the Administrative Procedure Act, 5 U.S.C. § 556(d), an agency *shall* exclude irrelevant,

immaterial, or unduly repetitive evidence. Bayer specifically moves to strike all CVM testimony and exhibits from the evidentiary record that are irrelevant, immaterial, unreliable or repetitive.[17]

Respectfully submitted,

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[17] A list of testimony and exhibits subject to this part of Bayer's Motion to Strike is listed in Appendix G.

CERTIFICATE OF SERVICE

I hereby certify that an original and one copy of Bayer's Motion to Strike CVM's Written Direct Testimony and Evidence was hand-delivered this 27th day of January, 2003 to:

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

I also certify that a copy of the foregoing Motion was e-mailed this 27th day of January 2003 to:

The Office of the Administrative Law Judge
Food And Drug Administration
Room 9-57, HF-3
5600 Fishers Lane
Rockville, MD 20857

I also certify that a copy of the foregoing Motion was e-mailed and mailed via first-class mail, postage pre-paid, this 27th day of January 2003 to:

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Counsel for Bayer

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

ORDER

UPON CONSIDERATION of Bayer's Motion to Strike CVM's Written Direct Testimony and Evidence; it is hereby

ORDERED that Bayer's Motion is GRANTED.

DATED this the ___ day of _____, 2003.

_____
Daniel J. Davidson
Administrative Law Judge