DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. Food and Drug Administration

FINAL DECISION OF THE COMMISSIONER

Docket No. 2000N-1571

WITHDRAWAL OF APPROVAL OF THE NEW ANIMAL DRUG APPLICATION FOR ENROFLOXACIN IN POULTRY

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I. INTRODUCTION

Enrofloxacin is an antimicrobial drug belonging to a class of drugs known as fluoroquinolones. On October 31, 2000, the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) published a Notice of Opportunity for Hearing (NOOH) proposing to withdraw the approval of the new animal drug application (NADA) 140.828 for the use of enrofloxacin in chickens and turkeys. *Enrofloxacin for Poultry: Opportunity for Hearing (NOOH)*, 65 Fed. Reg. 64,954 (2000).[1] On November 29, 2000, Bayer Corporation (Bayer), the sponsor of enrofloxacin (sold under the trade name Baytril® 3.23% Concentrate Antimicrobial Solution), requested a hearing on the proposed withdrawal. On February 20, 2002, FDA's Acting Principal Deputy Commissioner published a Notice of Hearing (NOH) granting Bayer's request and identifying the factual issues that would be the subject of the evidentiary hearing. *Enrofloxacin for Poultry: Notice of Hearing (NOH)*, 67 Fed. Reg. 7700 (2002). On March 21, 2002, the Animal Health Institute (AHI) submitted a Notice of Participation pursuant to 21 CFR § 12.45, identifying itself in part as "the national trade association representing research based manufacturers of animal health products." AHI Notice of Participation (APE4) at 1.[2]

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[1] FDA approved two fluoroquinolones for use in poultry: enrofloxacin, the subject of this administrative proceeding, was approved on October 4, 1996 (NADA 140-828). Two applications of sarafloxacin hydrochloride, sponsored by Abbott Laboratories as SaraFlox® WSP and SaraFlox® Injection, were approved on August 18, 1995 (NADA 141-017), and October 12, 1995 (141-018), respectively. Prior to the issuance of the NOOH, Abbott Laboratories requested withdrawal of the two NADAs applicable to sarafloxacin, and in so doing waived its right to a hearing. *NOOH*, 65 Fed. Reg. 64,954 (2000). The ANADAs for sarafloxacin were withdrawn effective April 30, 2002. *Sarafloxacin for Poultry; Withdrawal of Approval*, 66 Fed. Reg. 21,400 (2001).

[2] Certain documents in the administrative record, such as ALJ orders and participants' motions and briefs are cited by the document's name and, when cited for the first time, the number assigned it in the docket (*e.g.*, motion (MO [number]), order (OR [number])). The exceptions are in the docket at EXC1 (CVM Exceptions); EXC2 (Bayer and AHI Exceptions); REX1 (CVM Reply to Bayer Exceptions); and REX2 (Bayer and AHI Reply to CVM Exceptions). The Initial Decision is in the docket as IDF1. Most documents submitted by the participants to the

The participants filed joint stipulations on September 20, 2002, and revised them in a submission on December 24, 2002. CVM submitted documentary evidence and written direct testimony on December 9, 2002, and Bayer and AHI submitted documentary evidence and written direct testimony on December 13, 2002. On December 17, 2002, the Administrative Law Judge (ALJ) granted the participants' motions to submit written direct testimony of witnesses and to move specific exhibits and documents into the evidentiary record of the hearing, subject to later motions to strike. (The ALJ handled subsequent requests concerning admission of evidence on a submission-by-submission basis.) Oral hearing for the purposes of cross-examination of witnesses was held at FDA from April 28 through May 7, 2003. Following the hearing, the participants submitted post-hearing briefs, pursuant to 21 CFR § 12.96(a).

On March 16, 2004, the ALJ issued an Initial Decision pursuant to 21 CFR § 12.120. The ALJ found, among other things, that more than a million people annually suffer from infections caused by *Campylobacter*, a genus of bacteria; that poultry is a source of *Campylobacter* infections; that the use of enrofloxacin in poultry results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*; that fluoroquinolone-resistant *Campylobacter* in poultry can be transferred to humans and "can contribute to" fluoroquinolone-resistant *Campylobacter* infections in humans; and that fluoroquinolone-resistant *Campylobacter* infections in humans "have the potential to adversely affect human health." Initial Decision at 66-67. Based on these and other findings, the ALJ determined that "Bayer has not shown Baytril use in poultry to be safe[,]" *id.* at 66, as set out in § 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 360b(e)(1)(B).

On May 17, 2004, Bayer (jointly with AHI) and CVM each filed exceptions to the ALJ's Initial Decision, pursuant to 21 CFR § 12.125(a).[3] Bayer's exceptions run to 234 pages and raise numerous legal and factual challenges to the ALJ's conclusions. CVM also filed exceptions, primarily challenging the ALJ's statements concerning evidentiary standards and burdens of proof and also seeking correction of some factual statements and findings by the ALJ. On July 16, 2004, the participants filed responses to each other's exceptions. Large portions of Bayer's exceptions do not comply with 21 CFR § 12.125(b), which provides: "Exceptions must specifically identify alleged errors in the findings of fact or conclusions of law in the initial decision, and provide supporting citations to the record." Additionally, many of Bayer's exceptions are frivolous or trivial.

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administrative record, including written direct testimony, were given exhibit numbers by the participants. These numbers were maintained throughout the proceeding and do not reflect whether the exhibit was later stricken from the evidentiary record. A guide is provided as an appendix to this Final Decision that identifies each exhibit cited herein by exhibit number and the number assigned to it in the document by FDA's Division of Dockets Management. Evidentiary citations to the record in this decision are as follows: Bayer's and AHI's exhibits (B-[number] at and A-[number] at); CVM's exhibits (G-[number] at); and transcript of cross-examination (Tr. at). The transcript cited in this Final Decision is the corrected version; it is found in the docket as TR 9 through TR 16. A breakdown of what pages of the transcript are found in each docket entry is provided in the appendix.

[3] As Bayer and AHI do in their exceptions, I will refer to them collectively as "Bayer." *See* Bayer Exceptions at 1 n. 1.

Bayer's lengthy filing contains sentences, paragraphs, and even whole pages that completely lack any citation to the record.[4]

In its exceptions, Bayer requested oral argument before the Commissioner pursuant to 21 CFR § 12.125(b). Bayer Exceptions at 1. The request did not identify any specific issues to be addressed by oral argument. There is no right to oral argument under 21 CFR § 12.125(b) and (e). Because I do not find oral argument necessary, I am denying this request.

After reviewing the evidentiary record of the hearing, I find that the record supports the ALJ's determination under § 512(e)(1)(B) of the FDCA that enrofloxacin is not shown to be safe for use in poultry under the approved conditions of use. However, my reasoning varies in several regards from that of the ALJ. I therefore am withdrawing the approval of the NADA for use of enrofloxacin in poultry for the reasons set forth more fully in this Final Decision. This Decision supplants the Initial Decision except where it is specifically adopted.

As to exceptions filed by the participants, I am required by law and regulation to address only those exceptions by the participants raising "significant" issues. *Nitrofurans; Withdrawal of Approval of New Animal Drug Applications (Nitrofurans),* 56 Fed. Reg. 41,902, 41,903 (1991); *Simpson v. Young*, 854 F.2d 1429, 1434 (D.C. Cir. 1988); 21 CFR §§ 12.120(b) and 12.130(c). Exceptions by Bayer not specifically addressed in this Final Decision are overruled. I have addressed all legal and significant factual exceptions by CVM.

II. PRELIMINARY MATTERS

A. Statutory Standard

CVM proposed to withdraw approval of enrofloxacin pursuant to § 512(e)(1)(B) of the FDCA, which provides:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) with respect to any new animal drug if the Secretary finds --
>
> . . .
>
> (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available

[4] *See, e.g.*, Bayer Exceptions at 2-6 (purporting to be an overview); 11-15 (more summary); 72 (setting out an unreferenced calculation purporting to demonstrate an increased risk of human *Campylobacter* infection in the absence of enrofloxacin as a treatment for air sacculitis); 94 ("Practically speaking, one can demonstrate that something is a confounder by removing the factor from the analysis and testing whether it changes the results."); and 190 ("Moreover, annual chicken consumption data are in evidence," followed by two unattributed figures purporting to plot per capita consumption against rates of illness). There are many more examples like these.

> to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved....

21 U.S.C. § 360b(e)(1)(B).

I address exceptions regarding the ALJ's interpretation of this standard below.

B. Burden and Standard of Proof Issues

I agree with the Initial Decision's general description of the allocation of the burdens between CVM and Bayer. *See* Initial Decision at 5. CVM, as the proponent of withdrawal of approval of the use of enrofloxacin in poultry, has the burden of making the first showing; in other words, CVM has the initial burden of production. *Hess & Clark, Inc. v. FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974); *Diethylstilbestrol*; *Withdrawal of New Animal Drug Applications (DES)*, 44 Fed. Reg. 54,852, 54,861 (1979). Once this threshold burden has been satisfied, the burden passes to Bayer, as the sponsor of enrofloxacin, to demonstrate its safety. *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980) (*per curiam*); *Hess & Clark*, 495 F.2d at 992; 21 CFR § 12.87(d).

I adopt the formulation of CVM's burden that FDA Commissioners have used in previous new animal drug withdrawal proceedings under § 512(e)(1)(B): "'...[the Center] must provide a reasonable basis from which serious questions about the ultimate safety of [the drug] and the residues that may result from its use may be inferred.'" *DES*, 44 Fed. Reg. 54,852, 54,861 (quoting *DES Initial Decision*); *Nitrofurans*, 51 Fed. Reg. 41,902, 41,903, *quoting DES*; *see also Rhone-Poulenc*, 636 F.2d at 572 ("We must therefore review the record in this case to determine whether the FDA has presented new evidence raising questions about the safety of DES that are sufficiently serious to require the manufacturers to demonstrate the drug is safe.")[5] I note that this formulation does not, as Bayer occasionally states, require CVM to "demonstrate harm to human health." *E.g.*, Bayer Exceptions at 80. That level of evidence is only required when CVM seeks to withdraw approval under § 512(e)(1)(A) of the FDCA because "experience or scientific data show that such drug is unsafe" under the approved conditions of use. 21 U.S.C. § 360b(e)(1)(A). *DES*, 44 Fed. Reg. 54,852, 54,861.

In its Exceptions, CVM challenged statements by the ALJ in the Initial Decision that the standard of proof that he was applying was preponderance of the evidence. CVM Exceptions at 1-3. CVM argues that the ALJ's findings must instead be based on "substantial evidence." *Id.* In responding, Bayer argues that CVM's burden is to show by a preponderance of the evidence that enrofloxacin is not shown to be safe; Bayer also argues that if the burden shifts, it then must show by a preponderance of evidence that enrofloxacin is safe. Bayer Reply to CVM Exceptions at 4.

I disagree with both CVM and Bayer. CVM's exceptions relate to the standard of proof (or quantum of evidence) that must support the ALJ's (and my) factual findings. Unless the substantive statute specifies otherwise, the standard of proof that the fact

[5] I overrule the Initial Decision to the extent it can be read as suggesting formulations of CVM's burden at variance with this discussion. *See* Initial Decision at 5, 6, and 54.

finder applies in administrative adjudications is the preponderance of the evidence standard. *Steadman v. SEC*, 450 U.S. 91, 96-102 (1980) (formal adjudication); *Bender v. Clark*, 744 F.2d 1424, 1429 (10th Cir. 1984) (informal adjudication). Here, I find that nothing in § 512(e)(1)(B) of the FDCA, which is the relevant substantive section, provides for a different result.[6]

Bayer's argument in its reply to CVM's exceptions deals, in part, with the burdens of production and persuasion. Bayer Reply to CVM's Exceptions at 4. CVM's initial burden of production in this withdrawal has already been well established by Final Decisions concerning prior new animal drug approval withdrawals. CVM's initial burden of production is to "provide a reasonable basis from which serious questions about the ultimate safety" of enrofloxacin can be inferred. *DES*, 44 Fed. Reg. 54,852, 54,861; *Nitrofurans*, 51 Fed. Reg. 41,902, 41,903, *quoting DES*; *see also Rhone-Poulenc*, 636 F.2d at 572.

Moreover, it is not clear why Bayer describes a standard of proof as applying to the participants' respective burdens. By arguing that the standard of proof that applies to both participants' burdens is preponderance of the evidence, Bayer also seems to be implying that CVM has the burden of persuasion. Bayer Reply to CVM Exceptions at 4-5. If that is what Bayer means, I disagree. Bayer, as the sponsor of enrofloxacin, has the ultimate burden of persuasion regarding the safety of the drug. 21 CFR § 12.87(d); *see also Rhone-Poulenc, Inc.*, 636 F.2d at 752; *Hess & Clark*, 495 F.2d at 992. Bayer must satisfy the statutory standard of showing by "adequate tests by all methods reasonably applicable" that enrofloxacin is safe, 21 U.S.C. § 360b(b)(1)(A), (c)(1), & (d)(1)(A); in other words, Bayer must come forward with evidence that is sufficient to address CVM's safety questions.[7]

In sum, with respect the various issues raised by the participants on the burden of proof and standard of proof, I conclude that:

- CVM bears an initial burden to produce evidence. CVM must show that there is a reasonable basis from which serious questions may be inferred about the ultimate safety of enrofloxacin use in poultry and any substance that may be formed in or on food as a result of such use.

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[6] CVM argues that the substantial evidence standard applies to fact finders based on the fact that it is used in § 505(h) of the FDCA, 21 U.S.C. § 355(h), which describes the standard for judicial review of findings of facts if a withdrawal is challenged by the drug's sponsor. CVM Exceptions at 1-3. However, in *Steadman*, one of the statutes at issue had a provision similar to § 505(h) of the FDCA. 450 U.S. at 96 & n.12. The Court did not consider this judicial review provision when looking to see if the statute in question specified a standard of evidence. *Id.* at 96. Under *Steadman*, then, the use of the term "substantial evidence" in a judicial review provision is not relevant to determining the standard of proof in an adjudication.

[7] Bayer's responsibility as the drug's sponsor is to show that enrofloxacin is safe; that is, that the drug is entitled to approval. This means that the substantive provisions of the FDCA that govern Bayer's showing are the approval portions of § 512, in particular §§ 512(b)(1)(A), (c)(1), and (d)(1)(A). 21 U.S.C. §§ 360b(b)(1)(A), (c)(1) & (d)(1)(A). Together, these provisions make clear that an applicant for approval must show a drug is safe by "adequate tests by all methods reasonably applicable." 21 U.S.C. § 360b(d)(1)(A).

- If CVM carries its burden of production, Bayer, as the drug's sponsor, has the burden of persuasion on the ultimate question of whether enrofloxacin is shown to be safe. Bayer must do so, as set out in § 512(d)(1)(A) with "adequate tests by all methods reasonably applicable...." 21 U.S.C. § 360b(d)(1)(A).
- As the fact finder, I must weigh the record evidence and make my factual findings based on the weight of the evidence. In other words, my findings must be supported by a preponderance of the evidence.

C. Scope of Commissioner's Review

21 CFR § 12.130(a) provides that "[o]n appeal from or review of the initial decision, the Commissioner has all the powers given to make the initial decision." 21 CFR § 12.130(b) provides that "[t]he scope of the issues on appeal is the same as the scope of the issues at the public hearing unless the Commissioner specifies otherwise." *See also* 5 U.S.C. § 557(b) ("[o]n appeal from or review of the initial decision, the agency has all the powers which it would have in making the initial decision except as it may limit the issues on notice or by rule").

In the NOH, the Acting Principal Deputy Commissioner, after reviewing Bayer's response to the NOOH, defined the factual issues that would be the subject of the hearing as follows:

> Whether new evidence shows that enrofloxacin is not now shown to be safe for use under the conditions of use upon the basis of which the application was approved. This issue includes:
>
> A. Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred, such as:
>
> 1. Whether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter spp.* [species] in poultry?
>
> 2. Whether fluoroquinolone-resistant *Campylobacter spp.* in poultry are transferred to humans and whether they contribute to fluoroquinolone-resistant *Campylobacter* infections in humans?
>
> 3. Whether fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?
>
> B. Whether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe?

67 Fed. Reg. 7700, 7701. This is an appropriate statement of the issues in this proceeding.[8]

[8] Bayer moved on April 15, 2002, for reformulation of the hearing issues. MO4. The ALJ denied this motion on April 26, 2002. OR4. Bayer's exceptions do not specifically renew objections to the formulation of the hearing issues, although they raise a number of matters excluded by the ALJ as irrelevant to the proceedings. To the extent Bayer's exceptions can be interpreted as challenging the formulation of issues, they are overruled.

D. Evidentiary Issues

Under 21 CFR § 12.94(c)(1)(i) and (d)(1)(i), the presiding officer may exclude written or oral evidence only if it "is irrelevant, immaterial, unreliable, or repetitive." *See also* 5 U.S.C. § 556(d) ("the agency as a matter of policy shall provide for the exclusion of irrelevant, immaterial, or unduly repetitious evidence."). Under 21 CFR § 12.94(c)(3), written evidence excluded by the ALJ remains in the evidentiary record of the hearing.

1. Exclusion of evidence on relevance grounds

In an order dated March 3, 2003, the ALJ, acting on motions to strike by the participants, struck in part or entirely several pieces of evidence. OR31 at 1. In this order, the ALJ held that "[r]isk/benefit evidence is relevant only to the extent it deals with human health effects, *i.e.*[,] whether the human health benefits of using the drug outweigh the human health risks from use of the drug," and stated categorically that "[e]conomic and environmental evidence is not relevant to the issues in this proceeding." *Id.*; *see also* Initial Decision at 9. In light of this ruling, the ALJ struck on relevance grounds, among other testimony and exhibits, the written direct testimony of Mr. G. Thomas Martin, B-1907 (economic benefits), Mr. Steven Woodruff, B-1918 (environmental impact of withdrawal), and Dr. Robert Harris, B-1919 (indirect human health impact of environmental impact). Bayer challenges this ruling. Bayer Exceptions at 64-72.

For the reasons set out in section IV.B.2, I agree with the ALJ that evidence concerning economic benefits of enrofloxacin use, the environmental impact of withdrawal of approval, and the human health consequences of the environmental impact are irrelevant to withdrawal of approval of a new animal drug, but disagree with the ALJ to the extent the Order of March 3, 2003, or the Initial Decision allows for the consideration of alleged human health benefits of enrofloxacin.[9] All evidence relating to any human health benefits of enrofloxacin also should have been stricken as irrelevant.[10]

I also agree with the ALJ that animal welfare is not relevant in assessing the safety of enrofloxacin. Initial Decision at 8-9 and 67 ("[i]n a NADA withdrawal proceeding, the effects of withdrawal on ... animal welfare are not relevant.... Moreover, even if it were appropriate to consider enrofloxacin's withdrawal's effects on ... animal welfare, the evidence presented in this proceeding is insufficient to warrant such a finding."). No participant took exception to this finding. *See* Bayer Exceptions at 64 (challenging ruling with respect only to economic, environmental, and human health evidence).[11]

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[9] CVM did not take exception to this finding by the ALJ. *See* CVM Exceptions at 10.

[10] As described in more detail in section IV.B.2, in addition to finding that this evidence is irrelevant to this proceeding, I have also determined that much of it is in any event unreliable.

[11] Even if Bayer had challenged these findings, I agree with the ALJ as a matter of law. As explained in section IV.B.2, no benefits of any kind are relevant when assessing the human safety of a new animal drug used in a food-producing animal. Second, under § 201(u) of the FDCA, 21 U.S.C. § 321(u), safety of a new animal drug encompasses safety to both humans and other animals. Thus, the FDCA makes clear that a new animal drug for use in a food producing animal must be found to be safe for both humans and animals before it can be approved. Any argument

2. Standards for reliability of evidence

Pursuant to 5 U.S.C. § 556(d), my findings must be "in accordance with the reliable, probative, and substantial evidence." Whether evidence meets this standard depends in part on the governing standard, which here is § 512(e)(1)(b). Here, as explained in section II.B, CVM's threshold burden under § 512(e)(1)(B) of the FDCA is to show that there are serious questions about the safety of enrofloxacin use in poultry. Contrary to Bayer's Exceptions, there is no checklist against which each individual study relied on by CVM must be evaluated to determine its reliability. *See, e.g.,* Bayer Exceptions at 27-34. Rather, the evidence offered by CVM, taken as a whole, must be sufficiently reliable to satisfy CVM's limited statutory burden.

a. Applicability of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*

As Bayer acknowledges, Bayer Exceptions at 28, the evidentiary standards set out in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and its progeny are not binding in administrative adjudications. *See Peabody Coal Co. v. McCandless*, 255 F.3d 465, 469 (7th Cir. 2001); *Sierra Club v. Marita*, 46 F.3d 606, 621-22 (7th Cir. 1995); *Stewart v. Potts*, 996 F. Supp. 668, 678 n.8 (S. D. Tex. 1998). *Daubert* is not binding in this proceeding because the Federal Rules of Evidence, which it interprets, do not apply to administrative adjudications. *E.g., Peabody Coal*, 255 F.3d at 469.[12]

As will be clear in reviewing the discussion of the evidence below, however, the principles of *Daubert* are useful to this proceeding. Furthermore, I find that consideration of those principles leads me to conclude that the epidemiologic and other research CVM presented is reliable. These studies are helpful to me in understanding and deciding on facts in issue; the evidence is relevant; there is a general acceptance within the relevant scientific communities about the process and methodologies used in these studies; the data were generated apart from this administrative proceeding; the data were developed and presented in an open, transparent process; and most of the studies were either peer-reviewed and published or were subject to an equivalent public and expert review process. *Cf.* 509 U.S. at 591-595 (listing some of these factors as useful in determining reliability).

b. The Information Quality Act

Bayer also asserts that the FDA and Office of Management and Budget (OMB) guidelines issued pursuant to the Information Quality Act (IQA), Pub. L. No. 106-554, § 515 (2000), *see* 44 U.S.C. § 3516 note,[13] provide "useful guideposts" for evaluating the

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that I must weigh the welfare of animals against the health costs to humans would run counter to that statutory mandate.

[12] By their own terms, the Federal Rules of Evidence do not apply to administrative adjudications. *Fed. R. Evid.* 101. The Federal Rules can be made applicable to administrative proceedings, either by Congress or the agency, but that has not happened in proceedings to withdraw approval of new animal drugs. *See* 21 U.S.C. § 360b(e); 21 CFR Part 12.

[13] OMB's guidelines are at 67 Fed. Reg. 8452 (2002); FDA's guidelines were announced at 67 Fed. Reg. 61,343 (2002) and can be found at http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml (accessed on April 19, 2005).

testimony and evidence relied on by CVM. Bayer Exceptions at 31. Bayer further argues that a risk assessment relied on by CVM, described in more detail below, must satisfy FDA's guidelines to be considered reliable evidence in this proceeding. *Id.* at 32.

I disagree with both arguments. The stated intent of the IQA is to ensure and maximize the quality of data "disseminated" by Federal agencies and to allow "affected persons" to request correction of such information -- not to impose new evidentiary standards in administrative proceedings.[14] Pub. L. No. 106-554, § 515. Indeed, OMB's guidelines specify that such requests for correction should serve to address the genuine and valid needs of outside parties without disrupting agency processes, 67 Fed. Reg. 8452, 8458, and information used in and findings made in adjudications are expressly exempted by the FDA Guidelines. *See* FDA Information Quality Guidelines, II.F. Furthermore, on its face, the FDA guidance makes clear that it, like all FDA guidance documents, does not "create or confer any rights for or on any person or bind FDA or the public." FDA Guidelines;[15] *see also* 21 CFR § 10.115(d). Rather, the guidance "represents [FDA's] current thinking on this topic," and the document specifies that "[a]n alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations." FDA Guidelines.

The risk assessment, like all scientific evidence before me, will be evaluated to determine its strengths and weaknesses. I conclude, however, that the IQA Guidelines provide no independent set of mandatory standards by which the risk assessment, or any other evidence, must or even should be evaluated in this context.[16] If I were to agree with Bayer's interpretation of the role of the FDA's IQA guidelines in this proceeding, I

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[14] AHI filed a request for correction concerning the risk assessment on January 23, 2003, well after this proceeding was underway. Initial Decision at 20. CVM's Director, Dr. Stephen F. Sundlof, notified AHI by letter dated March 20, 2003, that a decision on the request for correction would be made within 60 days of this final decision. *Id.* AHI appealed Dr. Sundlof's decision in a letter dated April 16, 2003, alleging that the deferral of the decision amounted to a denial of the request for correction. *Id.* By letter dated September 16, 2003, FDA Principal Associate Commissioner, Dr. Murray M. Lumpkin, stated that the questions raised by AHI concerning the risk assessment under IQA should be considered by the ALJ as part of the administrative proceeding. *Id.* at 20-21. *See* http://www.aspe.hhs.gov/infoquality/requests.shtml (accessed on June 20, 2005). This referral to the ALJ is not intended to serve as agency precedent for handling future IQA requests related to evidence being used in formal adjudications.

[15] The FDA Guidelines appear only on the HHS Website. There is, therefore, no way to cite to a specific page. Where possible, I cite to specific sections of the Guidelines.

[16] To the extent the Initial Decision can be read as finding that the IQA does provide a standard for reliability in the context of this formal administrative proceeding, it is overruled. *See* Initial Decision at 40-41. Because I do not find that the IQA provides any independent standard for reliability, I also reject the ALJ's finding that "[i]f the withdrawal of Baytril would have an effect of $100 million or more on the economy, the CVM risk assessment would need to meet FDA's more stringent guidelines for 'influential information.'" *Id.* at 41. Thus, I do not need to reach Bayer's argument that the ALJ could not make a finding about whether the economic impact trigger for heightened scrutiny of agency dissemination of "influential" information had been met because the ALJ had excluded the written direct testimony of Bayer witness Mr. G. Thomas Martin, Jr. Bayer Exceptions at 109-10.

would in effect be ruling that in any formal administrative proceeding the IQA guidelines should replace longstanding and well-established statutory provisions and judicial doctrine about the admissibility and reliability of expert testimony and scientific evidence. Bayer's IQA argument would also require me to evaluate the evidence on which CVM relies differently from that on which Bayer relies. *See* Bayer Exceptions at 32 ("...even if the FDA Guidelines are not strictly applicable to this proceeding, they do nevertheless inform the evaluation of the reliability of CVM's testimony and evidence in this proceeding." (emphasis added)). I do not believe that Congress would have chosen such an indirect means of changing the formal adjudication provisions of the APA and drug approval and withdrawal provisions of the FDCA. The factors I look to in evaluating the reliability of the scientific evidence do not change depending on which participant is relying on it.

c. Epidemiologic evidence

Finally, Bayer presents "several principles" that it claims epidemiologic studies "must satisfy" to be "reliable." *See* Bayer Exceptions at 28-31. These purported principles, which are largely unreferenced, confuse or misstate in several instances both applicable law and science, and I reject them without extended discussion.[17] To the limited extent that Bayer provides legal references for its assertions, they consist of tort and product liability cases that do not involve the statutory standard at issue here. At best, the sweeping assertions that Bayer makes in reliance on these cases may reflect a court's position with respect to whether a particular piece of evidence might satisfy a party's burden in those actions.

That said, because much of the evidence at issue in this proceeding consists of epidemiologic data, I describe the nature of epidemiologic studies and identify some considerations helpful in evaluating the reliability of an individual study. Epidemiology is the study of "the incidence, distribution, and etiology of disease in human populations." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 590 (D.N.J. 2002) (quoting from Michael D. Green et al., *Reference Guide on Epidemiology*, in Federal Judicial Center, Reference Manual on Scientific Evidence at 335 (2d ed. 2000)); *see also* Feldman, B-1902 at 5 and 51 (Att. 1). Epidemiology is not focused on specific causation, in the sense of tracing an exposure to a particular individual's health outcome. 180 F.Supp. 2d at 590. Rather, its aim is to identify "agents that are associated with an increased risk of disease" or other outcome of interest. 180 F.Supp. 2d at 591.

Epidemiology encompasses a range of research methodologies, including both experimental and observational studies. In experimental studies, such as randomized controlled trials, subjects are randomly assigned by researchers in advance to treatments or exposures and compared with subjects who are assigned to a control or no exposure. *Id.* at 590. A clinical trial that evaluates the safety or efficacy of a therapeutic treatment is an example of an experimental study.

[17] In addition to being incorrect, the assertions made without any reference to record support are essentially testimony of counsel and may be disregarded for that reason alone.

Observational studies are done to characterize the health and other outcomes of events or exposures without intervening to change the outcomes. In analytical studies, researchers evaluate the experience of a group exposed to an agent with respect to a particular health outcome (*e.g.*, cancer), and compare it to the experience of a comparable group or groups of individuals that have not been exposed to the agent to identify and quantify associations, test hypotheses, and identify causes. This type of study often has a cohort study design, in that the experience of a cohort, or group, of exposed individuals is compared over time to the experience of a non-exposed group of individuals.

Another observational epidemiologic study design is the case-control study, in which individuals who are classified as "cases" having the disease or outcome of interest are compared with "controls" that do not have the disease or outcome of interest. Cases and controls are typically matched for similarity by age, sex, or other factors. The purpose of case-control studies is to investigate what differentiates the cases from the controls. For example, an outbreak of food poisoning linked to an event like a luncheon served at a conference can be investigated by comparing the foods the people who got sick ate with the foods the people who did not get sick ate. In this way, exposures that may differentiate the risk associated with being a case are identified.

In case-control studies involving sources of suspected foodborne illness, scientists often question cases and controls about their food intake and other exposures in the time period shortly before occurrence of symptoms in the cases. Wegener, G-1483 at 12. Limitations of this study design include the fact that no information is available beyond what was asked of the study participants and what is within their knowledge (for example, they would not know what the food handling practices were in the kitchens of restaurants in which they ate). There is also a possible difference in how well or how accurately cases and controls remember foods they ate in a particular period of time. There may be differences in the timing of questioning of cases and controls that can affect the quality of their recall. Differences in accuracy or completeness of recall between cases and controls may introduce a systematic error into the results. Feldman, B-1902 at 27; *see, e.g.*, Angulo, G-1452 at 93 (Att. 3) (discussing possible sources of bias in a case-control study of foodborne illness). Another issue with observational case-control studies is that it can be difficult to discern differences in risk when an exposure is common among both cases and controls; for example, asking subjects whether they ate chicken in a particular time period. *See* Wegener, G-1483 at 12. Measures to reduce the risk of not finding a difference in exposure between cases and controls when such a difference actually exists include increasing the size of the study, since with a very large number of cases and controls small differences between the two groups can be detected. *Id.* at 13.

In general, the design, conduct, statistical methods, and data analysis of an individual epidemiologic study should be evaluated to determine the reliability of the study's conclusions. In addition, a number of criteria may be relevant in evaluating whether an individual study or group of studies establishes an association between an exposure and an outcome. These criteria include temporal relationship; strength of the association; the existence of a dose-response relationship; whether the relationship is consistent across different studies and in different populations; whether the association is biologically plausible; whether alternative explanations have been taken into account and

eliminated or controlled for; whether the outcome changes when exposure changes; the specificity of the association; and whether the findings of the relationship are consistent with other data. *Magistrini*, 180 F.Supp. 2d at 592-593. One or more of these factors may be absent even where a causal relationship exists, and no one factor is necessary to establish an association between an exposure and an outcome. *Id.* at 592 n. 9.

Epidemiologic studies often are designed to evaluate a pre-defined hypothesis; for example, researchers may hypothesize that there is a real difference in exposure to a risk factor between cases and controls, or a real difference in the observed incidence of an event among the exposed compared with the non-exposed. An example of such a hypothesis might be that consumption of drinking water from a certain municipal well is associated with an elevated risk of cancer. Researchers use a statistical concept called "statistical significance" to quantify the likelihood that the observed differences between cases and controls could have been due to chance, rather than to a true association between exposure and health outcome. Researchers often judge the statistical significance of a study result in terms of the magnitude of the "p-value," which is derived from statistical analysis or statistical testing of the researchers' hypothesis on the data observed. Traditionally, a p-value of 0.05 or less indicates that the observed results are not likely due to chance. In general, the smaller the p-value, the more "significant" a result is, in the sense that the possibility that the association (outcome) is due to chance is lowered (because, when the p-value is 0.05, there is still a 5%, or 1 in 20, chance that the result is a false positive and does not actually reflect a difference between cases and controls). Tr. at 60.

Statistical uncertainty is also sometimes reported by researchers by a "confidence interval" or "CI," which reflects the upper and lower limits of an interval, calculated from the observed data, which is likely 95% of the time to contain or cover the true value of the mean, proportion, or rate of interest. *See* Last JM, (ed.), *A Dictionary of Epidemiology* (Third Edition), New York, Oxford University Press, 1995 at 35.[18] So, for example, when CVM witness Dr. Frederick Angulo testified that " [i]n the multivariate logistic regression model, the proportion of *Campylobacter* isolates[19] resistant to [fluoroquinolones] in 2001 ... was 2.5 times higher (95% confidence interval, 1.4 to 4.4 times higher) than the proportion of *Campylobacter* isolates resistant to [fluoroquinolones] in 1997," Angulo, G-1452 at 8, he communicated that the true value of the proportion of resistant isolates in 2001 compared with 1997, estimated to be 2.5 times higher (*i.e.*, 150% higher), had a 95% likelihood of being within the interval that was at least 1.4 times higher (40% higher) and not more than 4.4 times higher (340% higher).

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[18] Much of the evidence in this case consists of epidemiologic studies. Where helpful in defining terms from epidemiology or biostatistics, I reference the Last text, which is recognized in the field.

[19] Clinical laboratories isolate foodborne enteric bacteria, usually from diagnostic specimens collected from ill persons; these specimens, called "isolates," are then forwarded to state public health laboratories. Angulo, G-1452 at 3. Bacteria can also be isolated from retail meat products, *id.* at 12, and from other sources, as discussed more fully in this Final Decision.

Of equal importance in the evaluation of epidemiologic studies is the impact of bias on the measures of association or risk. Such bias can derive from defects or limitations in the study design, the study's conduct, data analysis, matching strategies, or interpretation of the results. These factors might impact the existence, direction (*i.e.*, positive or negative), statistical significance, or size of an association (*i.e.*, the magnitude of the association between an exposure and the health outcome). Statistical significance alone cannot be relied upon to exclude bias as a plausible explanation for a study finding. Instead, in-depth analysis and evaluation of epidemiologic studies is always necessary to support the strength of the conclusions and to understand and explain the underlying limitations.

The participants stipulated that FDA is committed to following "well recognized principles of epidemiology." Revised Joint Stipulations 28 (CR2). While the participants did not specify to what precise principles they were referring, the principles for evaluating the strength of a particular epidemiologic study described in the preceding paragraphs are well-recognized in the field of epidemiology. *See, e.g.*, Last at 77 (describing "Hill's criteria of causation").

As noted above, under § 512(e)(1) of the FDCA, I must withdraw approval if I determine that new evidence, "evaluated together with the evidence available ... when the [drug] was approved, shows that such drug is not shown to be safe...." 21 U.S.C. § 360b(e)(1)(B). In the proceeding before me, each piece of scientific evidence will have its own strengths and limitations. As a matter both of science and of law, the issue is whether a preponderance, or the weight of, the record evidence, taken as a whole, supports my decision. *Cf. Public Citizen Health Research Group v. Tyson*, 796 F.2d 1479, 1489, 1490 (D.C. Cir. 1986) (despite some limitations to each epidemiologic or animal study relied on in OSHA proceeding, cumulatively they provided "compelling" evidence of carcinogenicity).

3. Exclusion of the testimony of Dr. Louis Anthony Cox, Jr.

In the Initial Decision, the ALJ excluded the testimony of Bayer witness Dr. Louis Anthony Cox, Jr., an expert in risk analysis. Dr. Cox was one of eight witnesses cross-examined during a hearing held from April 28, 2003, through May 7, 2003. *See* Tr. at 843-1120; Cox, B-1901. The ALJ held that Dr. Cox's testimony lacked credibility and was unreliable. Initial Decision at 15.

I agree with the ALJ's determination that Dr. Cox's credibility was such that his testimony was so unreliable that it was inadmissible. The ALJ found that Dr. Cox's credibility was "severely compromised" because he intentionally misquoted published articles. Initial Decision at 15; *see* Tr. at 947-980. The ALJ found that some of Dr. Cox's quotes contained edits that went well beyond punctuation. *Id.* ("It seems that Dr. Cox edits referenced materials, prefers his versions to the originals, and quotes the edited version in his testimony.") On cross-examination, Dr. Cox acknowledged that his method of quoting from a particular research article in his written direct testimony did not comport to the standards he would have used for citing the paper in a journal article. Tr. at 967. Rather, he testified that in quoting from the article for his written direct testimony his "emphasis was on finding the supporting quote and giving it in enough detail and adequate citation so that everyone could see what I was talking about. And so that's a

somewhat different context from a journal article, for example." Tr. at 967-968. Equally disturbing, Dr. Cox similarly stated that the quotation marks in a description he wrote of CVM's risk assessment as being based on "'average exposure for an average individual,'" *see* Cox, B-1901 at 25 (Att. 1), did not necessarily reflect a quotation attributable to CVM, but rather were included because he was "pretty sure that I was using their phrase," Tr. at 1002, and that he had "stuck that in quotes in my testimony because it seemed to be an important concept." Tr. at 1003. The ALJ determined, Initial Decision at 15, and I agree, that it should not be incumbent on a fact-finder to have to compare a witness's quotes from a published research article or other source against the original to determine if it appropriately characterizes or quotes from the original.

Bayer argues that the exclusion of Dr. Cox's testimony "favors form over scientific substance." Bayer Exceptions at 44. I am disturbed by this argument, and by Dr. Cox's own explanation of his actions. FDA expects witnesses in adjudications (formal or informal) to follow basic, accepted rules of attribution (*e.g.*, when using quotation marks, the material should, in fact, be an accurate quote).

To ensure a complete record in the event of judicial review, I have nonetheless reviewed Dr. Cox's testimony, and it is discussed more fully below.

III. DISCUSSION

In this section I first describe the illness caused by *Campylobacter* infections in the United States, including how common such infections are, what the symptoms and complications are, and how they are treated. I then discuss the link between the use of enrofloxacin in poultry and human infection with *Campylobacter*, including infections that are resistant to fluoroquinolones. Finally, I discuss the impact on humans of infection with *Campylobacter* that are resistant to fluoroquinolones.

A. Human Campylobacter *infections in the United States*

1. Nature and public health impact of Campylobacter *infections*

The U.S. Centers for Disease Control and Prevention (CDC) estimated in 1999 that foodborne infections cause 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths each year. G-410 at 1; Tollefson, G-1478 at 3; Tauxe, G-1475 at 2. Foodborne illnesses may be caused by viruses, bacteria, parasites, toxins, metals, and prions. G-410 at 1; Tauxe, G-1475 at 2. CDC estimated that bacterial agents are associated with approximately 30.2% of foodborne illnesses and a majority of resulting hospitalizations (59.9%) and deaths (71.7%). G-410 at 5 (Table 3).[20]

Campylobacter is a genus of bacteria with many different species, a number of which are known to cause illness in humans, although two, *Campylobacter jejuni* (abbreviated as *C. jejuni*) and *Campylobacter coli* (*C. coli*), are identified as the cause of almost all cultured human infections. Tauxe, G-1475 at 2; Nachamkin, G-1470 at 3; G-

[20] Many witnesses included citations to record evidence in their written direct testimony. In the interests of keeping the Final Decision as streamlined as possible, my citations to written direct testimony should be understood to incorporate the cited references as well.

444 at 20-43, 85-104, and 105-136. *Campylobacter* is recognized as a leading cause of gastroenteritis[21] in many developed and developing countries. Endtz, G-1457 at 2; G-1743 at 42. In the United States, the most important, in terms of human infection, is *C. jejuni.* Tauxe, G-1475 at 2; Jacobs-Reitsma, G-1459 at 2; Nachamkin, G-1470 at 3. *C. jejuni and C. coli* are difficult to differentiate in laboratory analysis, Nachamkin, G-1470 at 3 (5-10% of *Campylobacter* infections reported as *C. jejuni* are actually caused by *C. coli*), and the exact species of *Campylobacter* may not be identified in clinical laboratory settings. Tr. at 346.

Quantifying the burden of *Campylobacter* infections in the United States population is difficult because many people who become ill with gastroenteritis do not seek medical care. Revised Joint Stipulation 20; Tauxe, G-1475 at 2; Angulo, G-1452 at 6-7. Furthermore, even if a health care provider is consulted, many patients are not asked to provide a stool sample for culture to identify the presence of disease-causing bacterial pathogens. Tauxe, G-1475 at 2; G-1790 at 7. Finally, even where a specimen is obtained and cultured, positive cultures may not be reported to public health authorities, Tauxe, G-1475 at 2; Angulo, G-1452 at 6, and, as a result, are not tracked.

Based on data from 1996-1997 (adjusted for underreporting), in 1999 CDC estimated that 2.4 million illnesses in the United States each year are caused by *Campylobacter*, of which approximately 80% were foodborne infections. G-410 at 4-5; Angulo, G-1452 at 7; Tauxe, G-1475 at 2. In that analysis, CDC estimated that about 14.2% of foodborne illness in the United States annually is caused by *Campylobacter* infection, making it the leading bacterial source of foodborne illness in this country. G-410 at 5.

Almost all cases of campylobacteriosis in the United States are sporadic, *i.e.*, they are unrelated to each other by a shared source of infection.[22] Angulo, G-1452 at 9; Wegener, G-1483 at 12; Endtz, G-1457 at 3; Tauxe, G-1475 at 6. According to CVM witness Dr. Herbert Endtz , "*Campylobacter* leading to sporadic infections can be transmitted by several different routes, the relative importance of which varies with time and location.... In developed countries poultry is often considered to be the most important reservoir of *C. jejuni*." *Id.* at 4; *see also* Wegener, G-1483 at 12-15. The role of poultry as a risk factor for human campylobacteriosis is discussed more fully below.

Annual incidence[23] of *Campylobacter* infections has declined since 1996-1997, when the data analyzed in the 1999 CDC report were collected. In a 2000 publication, Tauxe reported a decline in incidence of reported, laboratory-confirmed *Campylobacter* infections from 25.2 per 100,000 people in 1997 to 17.3 per 100,000 in 1999. Endtz, G-1457 at 2, citing G-1743 at 42. In April 2002, CDC reported that the bacterial pathogens

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[21] Gastroenteritis is inflammation of the stomach and intestine. Ohl, G-1485 at 4.

[22] An outbreak of *Campylobacter* infection is recognized "when a group becomes infected with the same organism at about the same time, following an exposure they had in common." Tauxe, G-1475 at 6; *see also* Endtz, G-1457 at 3-4; Wegener, G-1483 at 12.

[23] "Incidence" of a disease is the number of new cases over a defined period of time in a defined population. Tr. at 32-33. A related measure of disease is "prevalence," which is the number of existing cases at a point in time. *Id.* at 33.

with the highest relative incidence during 1996 to 2001 were *Salmonella*, *Campylobacter*, and *Shigella*. G-1791 at 2.[24] Over that time period, *Campylobacter* infections decreased 27% (95% CI 19-35%),[25] as did infections caused by other foodborne bacterial pathogens. *Id.* at 2-3. CDC noted that "the declines in the incidence of these foodborne infections occurred in the context of several control measures, including the implementation of the U. S. Department of Agriculture's (USDA) Food Safety Inspection Service (FSIS) of the Pathogen Reduction/Hazard Analysis Critical Control Point (HACCP) systems regulations in meat and poultry slaughter and processing plants." *Id.* at 3; *see* also G-1743 at 42. Bayer concurs that these and other food safety efforts, including "poultry safety labeling, FDA approval of poultry irradiation, improved consumer preparation and handling practices, and changes in poultry marketing and distribution" have reduced the risk of foodborne *Campylobacter* infections. Bayer Exceptions at 167-168; *see also* Minnich, G-1467 at 10-11. Using 1999 data and a simulation procedure, in the 2000 publication CDC estimated that the annual burden of foodborne *Campylobacter* infections is about 1.4 million. Angulo, G-1452 at 7 (citing an in-press publication).

Thus, although the incidence of these infections has declined in recent years, I find that the record demonstrates that *Campylobacter* infections remain a major cause of foodborne illness in the United States.

2. Symptoms and complications of Campylobacter *infections*

Campylobacter infections in humans are characterized by fever, headache, abdominal pain, and diarrhea (bloody or watery), usually 24-72 hours after ingestion of the contaminated food. Nachamkin, G-1470 at 2, Thielman, G-1477 at 2. Less frequently, patients may suffer from muscle aches and vomiting. Thielman, G-1477 at 2.

Campylobacter infection in humans can be self-limiting, *i.e.*, it may resolve without antibiotics or other pharmaceutical treatment. Revised Joint Stipulation 19; Nachamkin, G-1470 at 2; Endtz, G-1457 at 2, 6. However, in some patients the illness may be prolonged or more severe. Nachamkin, G-1470 at 2; Endtz, G-1457 at 2, 6. In addition, *Campylobacter* infections can occasionally result in significant and sometimes long term adverse health outcomes. First, extraintestinal infections, such as meningitis, peritonitis, and bloodstream infection, are possible, although rare. Nachamkin, G-1470 at 3; Thielman, G-1477 at 2; Endtz, G-1457 at 2-3; Tr. at 289-290.

More commonly, *Campylobacter* infection can cause reactive arthritis and Guillain-Barré syndrome (GBS). Thielman, G-1477 at 2; Endtz, G-1457 at 3. Reactive arthritis, with pain and joint swelling, occurs within 2 weeks of infection. Nachamkin, G-1470 at 3. Incidence of reactive arthritis is uncertain, but has been estimated to range from 10-30 per 1,000 *Campylobacter* infections. Endtz, G-1457 at 3. GBS is

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[24] The overall incidence of reported and laboratory-confirmed *Salmonella* infections for the entire reporting period was slightly higher, at 15.1 cases per 100,000 people, than the incidence of *Campylobacter* infections (13.8/100,000). G-1791 at 5, Table 1.

[25] *See* explanation of "confidence interval" or "CI" in section II.D. Thus, in this case, the estimate of the decrease in infection was 27%; the true decrease almost certainly falls somewhere between 19% and 35%.

characterized by a sudden onset of paralysis that in 20-35% of cases leaves patients unable to breathe without a respirator. Endtz, G-1457 at 3, 5-6. Most patients with GBS slowly recover within a year of onset, Endtz, G-1457 at 3; Nachamkin, G-1470 at 3, although about 20% have residual health problems and about 3-8% die from the illness. Endtz, G-1457 at 3. GBS is estimated to annually affect about 1-3 persons per 100,000 people. Endtz, G-1457 at 3; G-444 at 171. GBS is triggered by *C. jejuni* infections in 25-30% of cases in Europe and the United States, and up to 75% of cases in China and the Caribbean. Endtz, G-1457 at 3. Among people with *Campylobacter* infections, an estimated one in a thousand develops GBS. Tauxe, G-1475 at 3; Endtz, G-1457 at 3; G-444 at 174.

Finally, there is a very low possibility of death associated with *Campylobacter* infections. Mortality in the United States associated with *Campylobacter* is low, with estimates ranging from 8 per 10,000 to 24 per 10,000. Endtz, G-1457 at 2; *see also* B-205 at 7; Nachamkin, G-1470 at 3.

Campylobacteriosis cannot be distinguished clinically from illness caused by *Salmonella*, *Shigella*, and some *E. coli* bacteria; in other words, the symptoms are very similar and the causal agent cannot be ascertained without laboratory stool analysis. Thielman, G-1477 at 2. The similarity among these infections complicates diagnosis and treatment, as discussed more fully below.

I find that campylobacteriosis is a gastrointestinal illness characterized by fever, headache, abdominal pain, and diarrhea (bloody or watery). Although it usually resolves without treatment, complications occur, including secondary infections, reactive arthritis, and GBS.

3. Treatment of Campylobacter *infections*

For patients with a normal immune system who are not at the extremes of age or have other chronic diseases, antibiotic therapy is not generally indicated for treatment of mild *Campylobacter* infection. Ohl, G-1485 at 9-10. However, I find that the record demonstrates that certain groups of patients, including the very young, the elderly, the immunocompromised, and people with certain chronic diseases, should be treated, as should people with severe illness. Ohl, G-1485 at 7, 9-11; Revised Joint Stipulation 42; Endtz, G-1457 at 6; Nachamkin, G-1470 at 2; G-172 at 7.[26]

When treatment is indicated, most practicing physicians will begin empirical antibiotics without waiting for stool culture results, in order to mitigate symptoms promptly, reduce the rate of recurrence, and decrease the risk of associated

[26] The participants stipulated that "[c]ommon criteria for the antimicrobial treatment of human *Campylobacter* infection include: severe illness, severe systemic toxicity, high fever, severe symptoms of dysentery; prolonged illness; worsening and/or relapsing symptoms despite supportive therapy; underlying primary and acquired immunodeficiency states such as HIV, immunoglobulin deficiency states, allograft recipients; chronic illness; and the elderly." Revised Joint Stipulation 42 (punctuation as in original).

complications.[27] Thielman, G-1477 at 2-3; Endtz, G-1457 at 6; Ohl, G-1485 at 7-8, 10-11. There are "many obstacles to the identification of a bacterium that might be causing a diarrheal illness," Ohl, G-1485 at 8, including the inconvenience of obtaining a sample during an emergency room or physician visit, delays in culturing of the specimen in the laboratory, and the low diagnostic yield of stool cultures, *id.* As a result, many physicians do not order a stool culture at all, even for patients who present with diarrhea. Ohl, G-1485 at 8; Morris, G-1469 at 5.

Antibiotic therapy shortens the duration of illness or bacterial shedding, reduces the intensity of symptoms, and prevents complications. Ohl, G-1485 at 10-13; Thielman, G-1477 at 2-3. Treatment of gastroenteritis is more effective if begun early in the course of disease. Morris, G-1469 at 4-5; Thielman, G-1477 at 2-3; Endtz, G-1457 at 6. Early treatment may have a greater impact on resolution of symptoms than delayed treatment. Thielman, G-1477 at 2-3. In addition, if illness is prolonged, patients may be prone to further complications, including death. Thielman, G-1477 at 4-5.

I find that the record demonstrates that fluoroquinolones, such as ciprofloxacin,[28] are widely used to treat gastroenteritis, because they are generally well-tolerated, can be prescribed on an outpatient basis, and are effective against a broad range of bacteria. Nachamkin, G-1470 at 6; Thielman, G-1477 at 4.[29] Because treatment of gastroenteritis with antimicrobials begins before the results of fecal culture become available (or in the absence of a fecal culture), fluoroquinolones are the preferred antibiotics used to treat serious infections and as an empiric therapy for travelers' diarrhea and diarrhea of unknown cause. Endtz, G-1457 at 6-7; Nachamkin, G-1470 at 6; Ohl, G-1485 at 11-13; Thielman, G-1477 at 3; Morris, G-1469 at 5-6. Practice guidelines for clinicians, including the Infectious Diseases Society of America's "Practice Guidelines for the Management of Infectious Diarrhea," specifically recommend consideration of a fluoroquinolone for adults. Thielman, G-1477 at 3; *see* G-261 (IDSA guidelines) at 11-13; *see also* G-244 at 2.

4. Public health surveillance for Campylobacter

An important source of data on *Campylobacter* in the United States is the Foodborne Diseases Active Surveillance Network (FoodNet), which is a collaborative project among CDC, FDA, FSIS, and state health departments. Angulo, G-1452 at 2. FoodNet was set up "to determine the frequency and severity of foodborne diseases;

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[27] "Empiric" treatment means prescribing a drug that is effective for any number of possible causative pathogens where the actual causal agent has not been laboratory-confirmed. Thielman, G-1477 at 2.

[28] Ciprofloxacin is a metabolite of enrofloxacin that is used in human medicine. Weber, G-1482 at 7-8. Bayer is the sponsor of ciprofloxacin. Revised Joint Stipulations 49-78 (registration dates for Bayer's ciprofloxacin and enrofloxacin products).

[29] In contrast, while treatment with erythromycin, a macrolide, is effective for early *Campylobacter* infection, erythromycin is not effective for infections with *Shigella*, *Salmonella*, or pathogenic *E. coli*. Thielman, G-1477 at 2; Endtz, G-1457 at 6-7; B-1127. As a result, erythromycin is not appropriately used to treat enteric infections without a known cause. Thielman, G-1477 at 2; Endtz, G-1457 at 6-7.

determine the association of common foodborne diseases with eating specific foods; and describe the epidemiology of new and emerging bacterial, parasitic, and viral foodborne pathogens." *Id.* FoodNet uses population-based active surveillance for clinical laboratory isolations of a number of bacterial pathogens in a growing number of states and selected counties. *Id.* In 2001, the total population in the area under surveillance was more than 37 million people, or more than 13% of the United States population. *Id.*; G-1791 at 1.

The National Antimicrobial Resistance Monitoring System, or NARMS, monitors antimicrobial resistance trends in human, animal, and retail meat isolates.[30] Tollefson, G-1478 at 4-5, 14. NARMS was formed in January 1996 and also is a collaborative effort of the federal and state entities involved with FoodNet. *Id.* at 14; Angulo, G-1452 at 2-3. In part, NARMS was developed to evaluate the consequences of the approval of fluoroquinolone use in poultry. Tollefson, G-1478 at 14. Although NARMS surveillance is generally somewhat broader than the FoodNet surveillance framework, the NARMS surveillance specifically for *Campylobacter* is done within the context of FoodNet. Tr. at 296. Details about data generated through FoodNet and NARMS are discussed in the text.

B. Enrofloxacin use and Campylobacter *in poultry*

1. Approval and use of enrofloxacin in poultry

On October 4, 1996, FDA approved NADA 140-828 under § 512 of the FDCA, authorizing the use of enrofloxacin (Baytril® 3.23% Concentrate Antimicrobial Solution) to control mortality in chickens associated with *Escherichia coli* (*E. coli*) and mortality in turkeys associated with *E. coli* and *Pasteurella multocida* (fowl cholera). Revised Joint Stipulation 39.[31] FDA approved the use of enrofloxacin only by prescription and under veterinary supervision, and only for therapeutic treatment (*i.e.*, not for growth promotion). Revised Joint Stipulations 15-16. FDA prohibited the extra-label[32] use of enrofloxacin for all food-producing animals, including poultry. Revised Joint Stipulations 17, 46.

The antibiotic is administered in the drinking water provided to an entire house of broiler chickens or turkeys if there is evidence that the disease is present. McDermott, G-1465 at 6-7; A-54. The participants stipulated that "FDA has long accepted drinking water delivery as a safe and effective means to administer therapeutic animal drugs, including antibiotics, to commercially grown broiler chickens and turkeys," Revised Joint Stipulation at 18, and that for commercially grown broiler chickens and turkeys in the United States, it is not feasible or practical to administer enrofloxacin to individual birds. Revised Joint Stipulation at 36. However, this method results in the treatment of birds

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[30] *See* note 19 above.

[31] FDA previously had approved two applications of another fluoroquinolone, sarafloxacin hydrochloride, for the control of mortality caused by *E. coli* in poultry. Tollefson, G-1478 at 3; Revised Joint Stipulations 47, 48. The sponsor of sarafloxacin, Abbott Laboratories, requested that FDA withdraw the NADAs. *See* note 1 above.

[32] Any use of a new animal drug not specifically approved by FDA is an "extra-label use." Tollefson, G-1478 at 4.

that are not infected, and can also lead to underdosing of infected birds. Tr. at 29; McDermott, G-1465 at 6-7; G-52 at 28-29 (Baytril product information noting risk of underdosing). Such underdosing increases the probability of selecting for fluoroquinolone-resistant *Campylobacter* in both healthy and diseased birds. McDermott, G-1465 at 7; B-868 at 3.

FDA's approval does not limit either the proportion of annual poultry production or the number of birds that may be treated with enrofloxacin. A-54. Use varies both geographically (*i.e.*, some regions may use more enrofloxacin than others) and over time, depending on the prevalence of disease in the poultry. *See* Hofacre, A-202 at 10-11 (describing regionality/seasonality of *E. coli* infections); Wages, B-1917 at 10 (in turkeys, "[o]utbreaks of *E. coli* and *Pasteurella multocida* infections tend to be regional and can be cyclical.") Bayer estimated that, of the poultry flocks that produce the 8.5-8.6 billion broilers and 270-272 million turkeys slaughtered each year, Hofacre, A-202 at 3; Revised Joint Stipulations 43, 44, 1- 2% of broiler flocks and about 4% of turkey flocks are treated with enrofloxacin annually, Bayer Exceptions at 3, 72; *see* A-192 at 3.[33] Therefore, the relatively small proportion of treated flocks translates to consumption of a relatively large amount of poultry meat from broilers and turkeys exposed to enrofloxacin.

2. Campylobacter *colonization of poultry*

Campylobacter, in particular *C. jejuni* and *C. coli*, are commonly found in the intestinal tracts of poultry, as well as cattle, swine, and other warm-blooded animals. Wegener, G-1483 at 2; White, G-1484 at 2; Jacobs-Reitsma, G-1459 at 2. In poultry, *Campylobacter* are commensal, *i.e.*, they do not generally cause illness in the birds. Jacobs-Reitsma, G-1459 at 2; White, G-1484 at 2. Broilers usually become colonized at about two weeks of age or later.[34] Jacobs-Reitsma, G-1459 at 3-5; Newell, B-1908 at 5. Turkeys are colonized at between seven and fifteen days of age. Jacobs-Reitsma, G-1459 at 4; G-686 at 2. The source of the initial colonization is unclear, but is likely to be exposure to other animals on the farm (including poultry), wild birds, rodents, insects, or contaminated drinking water. Jacobs-Reitsma, G-1459 at 3; Newell, B-1908 at 6-10. After the initial infection, colonization of the entire poultry house occurs quickly; *Campylobacter* is generally isolated from close to 100% of the birds in flocks that test positive. Jacobs-Reitsma, G-1459 at 4; G-686 at 2. Although not all flocks are colonized by *Campylobacter*, the record shows that in the United States and elsewhere such colonization is very common. Jacobs-Reitsma, G-1459 at 3-5; Newell, B-1908 at 3; G-1724 at 3; G-385 at 1.

Once chickens and turkeys are colonized by *Campylobacter*, they excrete large numbers of *Campylobacter* in their feces until slaughter. Jacobs-Reitsma, G-1459 at 2-4,

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[33] Bayer does not cite a reference for these estimates; in its exceptions, it cites the Initial Decision, Bayer Exceptions at 72, but the ALJ also does not provide support for his assertion that "only about 2% of broilers" are treated with enrofloxacin, Initial Decision at 25. There is no precise evidence in the record on this point. Exhibit A-192 is 8 pages of a fax that appears to reflect industry survey data concerning use in broiler and breeder chickens.

[34] "Colonized" refers to the growth of bacteria in or on an animal. Jacobs-Reitsma, G-1459 at 2.

7; Newell, B-1908 at 5.[35] Birds in poultry houses are exposed to the feces of other birds through direct consumption, contaminated water, and feed in open systems. Jacobs-Reitsma, G-1459 at 4. Because poultry houses in the United States are not cleaned to the floor between flocks, Carey, G-1456 at 3, birds may be exposed to contaminated litter and manure remaining in a poultry house from previous flocks, Jacobs-Reitsma, G-1459 at 3. The concentration of *Campylobacter* on the feathers and skin of poultry and the proportion of birds contaminated may increase substantially during transportation as a result of fecal shedding and reuse of inadequately cleaned transportation crates. Jacobs-Reitsma, G-1459 at 5. *Campylobacter* from colonized birds can also cross-contaminate birds originally free of *Campylobacter* at many points during the slaughter process. Minnich, G-1467 at 7-9; Logue, G-1464 at 2.

The record demonstrates that *Campylobacter* contamination remains on poultry after slaughter. For example, FSIS periodically conducts microbiological surveys of poultry carcasses. FSIS data indicate that *C. jejuni/ C. coli* was recovered from 90% of analyzed samples taken from 1,221 young turkey carcasses collected in 1996-1997 and *C. jejuni/ C. coli* was recovered from 88% of 1,297 chicken broiler carcasses collected in 1994-1995, G-651 at 6, 15; G-652 at 6, 15; White, G-1484 at 5. FSIS estimated in 1996 that the national prevalence of *C. jejuni/ C. coli* on raw ground chicken and raw ground turkey would be 60% and 25% positive, respectively, if the total volume of all federally inspected poultry meat were analyzed. White, G-1484 at 5; G-653 at 2, 8; G-654 at 2, 8. Other data on contamination of retail poultry meat products are discussed below.

Furthermore, in the same manner in which *Campylobacter* spreads among birds and flocks, flocks in which selection for fluoroquinolone-resistant *Campylobacter* has occurred may pass along resistant bacteria to other birds exposed to contaminated litter and manure and to chickens and turkeys during transport and slaughter. Minnich, G-1467 at 7-9, 11; Jacobs-Reitsma, G-1459 at 6. Once birds are colonized with fluoroquinolone-resistant *Campylobacter*, they remain colonized until slaughter. B-868 at 3-4; Jacobs-Reitsma, G-1459 at 6; McDermott, G-1465 at 3. Thus, I find that the evidence about colonization of turkey and chicken with *Campylobacter* is relevant to the issue of fluoroquinolone-resistant *Campylobacter* as well. More specific evidence that broilers and turkeys are contaminated with fluoroquinolone-resistant *Campylobacter* is discussed more fully below.

In sum, this evidence demonstrates, with respect to both fluoroquinolone-susceptible and -resistant *Campylobacter*, that *Campylobacter* colonization of poultry is widespread, that *Campylobacter* concentrations on live poultry and carcasses may increase as a result of current transportation and slaughtering practices, and that through these practices *Campylobacter* spread to birds that were previously free of

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[35] A colonized broiler has about 10^7 to 10^9 (10 million to 1 billion) *Campylobacter* colony forming units (CFUs, a measure of the concentration of bacteria in a sample) per gram of caecal content. Jacobs-Reitsma, G-1459 at 2-3, 7. A colonized turkey has between 1.2×10^4 to 1.5×10^7 CFUs per gram of caecal content. Jacobs-Reitsma, G-1459 at 3, 7. "Caecal" or "cecal" refers to pouches, known as "caeca" or "ceca," found at the junction of the small and large intestine of chickens and turkeys.

Campylobacter. While the presence of high levels of these bacteria in live poultry and poultry carcasses is not proof in and of itself that *Campylobacter* infections in humans are associated with *Campylobacter* in poultry, it is a part of the chain of evidence leading to that conclusion.

3. Mechanism of fluoroquinolone resistance in Campylobacter *and selection of resistant bacteria in poultry*

Development of antimicrobial resistant bacteria is a hazard associated with antimicrobial drug use in both human and veterinary medicine. Tollefson, G-1478 at 2. With respect to *Campylobacter*, resistance to fluoroquinolones develops as a spontaneous genetic mutation.[36] Revised Joint Stipulation 1. In *Campylobacter*, a single point mutation in the gyrase gene (*gyrA*) occurs naturally in approximately 1 to 5 in 100 million bacterial cells. McDermott, G-1465 at 4-5; Newell, B-1908 at 12-13 (natural or spontaneous mutation). Thus, given the large numbers of *Campylobacter* present in colonized broilers and turkeys, Jacobs-Reitsma, G-1459 at 2; McDermott, G-1465 at 5, it is likely that this relatively rare spontaneous mutation will result in small numbers of resistant *Campylobacter* in the gut flora of nearly all *Campylobacter*-colonized chickens and turkeys. McDermott, G-1465 at 5. Therefore, when a *Campylobacter*-colonized chicken or turkey is treated with enrofloxacin, the antibiotic will kill susceptible target and non-target bacteria (including susceptible *Campylobacter*) in the gut flora of the treated birds, Levy, G-1463 at 7, but the few *Campylobacter* that are present that are not susceptible to fluoroquinolones (*i.e.*, that are resistant to fluoroquinolones due to the spontaneous mutation) are not killed, and instead find themselves in an environment devoid of competing bacteria that they can and do quickly take over, re-colonizing the intestinal tract of the treated birds with resistant *Campylobacter*, Levy, G-1463 at 7; McDermott, G-1465 at 5; Barrett, G-1453 at 2; G-315; B-868; G-1800. This is referred to as "selection pressure." I find the record establishes that fluoroquinolone use in chickens and turkeys acts as a selection pressure for fluoroquinolone-resistant bacteria in the chicken and turkey digestive tract. McDermott, G-1465 at 2-4; Newell, B-1908 at 12; Revised Joint Stipulations 1, 7, 45 (stipulating that fluoroquinolone use can act as a selection pressure); *see also* Bayer Exceptions at 211.

Laboratory research conducted after fluoroquinolone use in poultry was approved show that fluoroquinolone treatment at therapeutic levels quickly selects for fluoroquinolone-resistant *Campylobacter*. When this selection occurs in a live bird, the fluoroquinolone-resistant bacteria quickly come to dominate. In one study, McDermott and colleagues investigated the impact of enrofloxacin (used according to label directions) on the development of fluoroquinolone resistance in the gut of broiler chickens. McDermott, G-1465 at 2-3; B-868. They found that within 24 hours of treatment with enrofloxacin, *C. jejuni* in the chickens became seven times more resistant

[36] Resistance traits may also be passed to human pathogenic bacteria by mechanisms that allow the exchange of the bacteria's genetic material. The participants stipulated that the data do not indicate that fluoroquinolone resistance can be transferred between *Campylobacter* or to non-*Campylobacter* bacteria. Revised Joint Stipulation 40; *see also* Tr. at 69-70.

to ciprofloxacin and enrofloxacin than they were before treatment.[37] *Id.* Furthermore, the researchers found that resistance persisted through the life span of the flock. McDermott, G-1465 at 3; B-868 at 3-4. In a control group of chickens also inoculated with *C. jejuni* but not treated with enrofloxacin, no fluoroquinolone-resistant *Campylobacter* were detected (that is, the resistant *Campylobacter* resulting from spontaneous mutation were below the level of detection), McDermott, G-1465 at 3; B-868 at 2-3, indicating that the dominance of resistant microflora resulted from their exposure to enrofloxacin. This work is consistent with earlier research by Dr. Jacobs-Reitsma. Jacobs-Reitsma, G-1459 at 7; G-315 at 2-3.

In another study, Newell and colleagues found that resistance to enrofloxacin and ciprofloxacin increased 7-8 times in *C. jejuni* recovered 48 hours after starting enrofloxacin treatment of the chickens in the study. McDermott, G-1465 at 4, 25 (unnumbered attachment).

Zhang, Luo, and colleagues at Ohio State University investigated the effect of dosing in evolution of enrofloxacin treatment, also finding that resistance emerged within 24-48 hours after treatment in both the group treated at 25 parts per million (ppm) enrofloxacin and the group treated at 50 ppm, and persisted after treatment ended. McDermott, G-1465 at 4; G-1800 at 2-3.[38] They did not find fluoroquinolone-resistant *Campylobacter* in the treated group of chickens before treatment or in a control group of chickens, *id.*, which, as noted above, is an indication that it is the selection pressure of exposure to enrofloxacin that allows for the resistant *Campylobacter* to proliferate.

Research in live poultry demonstrates that the development of fluoroquinolone resistance on poultry farms is consistent with these controlled laboratory data. NARMs surveillance data from broiler carcass rinse samples that were analyzed to determine the prevalence of fluoroquinolone-resistant *Campylobacter* showed that 9.4%, 9.3%, 10.4%, and 17.6% of *Campylobacter* from broilers were resistant to ciprofloxacin in 1998, 1999, 2000, and 2001 respectively. Tollefson, G-1478 at 12. Dr. Catherine Logue's research shows that 8.8% of the *Campylobacter* isolates at one turkey processing plant she investigated were resistant to ciprofloxacin, as was a majority of the *Campylobacter* (65.2%) at a second plant. Logue, G-1464 at 6. Bayer witness Dr. Diane Newell described data on the prevalence of fluoroquinolone resistance in chicken at slaughter in a number of countries; the levels of resistance cited were 6% in Denmark (2001, *C. jejuni* only); 19% in Germany (1998); 32% in Japan (2001), and 99% in Spain (2000). Newell, B-1908 at 14.

One final note: cross-resistance in *Campylobacter* occurs throughout the fluoroquinolone drug class. Barrett, G-1453 at 2; Weber, G-1482 at 7-8. In other words, resistance to one fluoroquinolone may compromise the use of any fluoroquinolone to treat a particular bacterial infection. Tollefson, G-1478 at 4. Thus, *Campylobacter*

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[37] Resistance in these studies was measured as the minimum inhibitory concentration, or MIC, which is the lowest concentration of the drug that it takes to completely inhibit the growth of a bacterium. White, G-1484 at 7. *See* discussion in section III.D.5 below.

[38] This published article was admitted into the evidentiary record by the ALJ in an order dated April 8, 2003. OR36. Exhibit A-190 is a briefer report on these data. McDermott, G-1465 at 4.

resistant to enrofloxacin (the animal antibiotic) are cross-resistant to ciprofloxacin (the human antibiotic). Weber, G-1482 at 7-8. *Campylobacter* that are resistance to precursor compounds (quinolones), such as nalidixic acid, are also cross-resistant to fluoroquinolones. Barrett, G-1453 at 2; Tollefson, G-1478 at 9-10; *see also* Bayer Exceptions at 213 n. 55 ("in the case of *Campylobacter*, because of cross-resistance, 'quinolone resistance' is essentially equivalent to 'fluoroquinolone resistance.'").

In conclusion, I find that commercially produced chickens and turkeys in the United States are frequently colonized with *Campylobacter*, and that the colonization of *Campylobacter* persists until slaughter. I further find that the selection for fluoroquinolone-resistant *Campylobacter* occurs rapidly in poultry following initiation of fluoroquinolone treatment, and that fluoroquinolone-resistant *Campylobacter* persist until slaughter.

In contrast, I find the absence of fluoroquinolone treatment of poultry to be associated with a very low level of fluoroquinolone resistance in such untreated poultry, despite the fact that the actual mutation occurs spontaneously. This is important evidence linking the use of enrofloxacin in poultry to the emergence of resistant *Campylobacter* infections in poultry and exposure of humans to resistant *Campylobacter*.

C. Poultry consumption as a risk factor for human Campylobacter *infection*

1. Introduction

In addition to the data on persistent colonization of live poultry with susceptible *Campylobacter* and resistant *Campylobacter*, the presence of susceptible and resistant *Campylobacter* in and on broilers and turkeys presented for slaughter, and the frequency of contamination of poultry carcasses with susceptible and resistant *Campylobacter*, there is substantial other evidence supporting my determination that, in the United States, poultry consumption is a primary risk factor for human infections with *Campylobacter*, including fluoroquinolone-resistant *Campylobacter*. This evidence, described more fully in this section, comes from data on contamination of retail meat in the United States; epidemiologic studies conducted in the United States and other countries; and microbiologic and molecular data linking poultry contamination with human *Campylobacter* infections.[39] Each of these additional groups of scientific evidence is discussed in turn.

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[39] There is no dispute that other exposures have been found to be significantly associated with human campylobacteriosis in epidemiologic investigations in the United States and elsewhere. Such exposures include consumption of unpasteurized milk, consumption of milk from bottles pecked by birds, contact with pets and other animals, contact with animal feces, consumption of contaminated, untreated drinking water, taking certain medication, having an underlying disease, eating pork, eating meat prepared at a barbeque, and eating raw seafood. Revised Joint Stipulation 32 (stipulating to "sources of *Campylobacter* infection other than poultry"); Wegener, G-1483 at 13, 15; Angulo, G-1452 at 10 and 92 (Att. 3); G-1488 at 23; Tauxe, G-1475 at 8. The fact that there are other ways in which individuals might become exposed to *Campylobacter* does not refute the data showing poultry to be a primary source of exposure in sporadic cases of infection.

I note at the outset of this discussion that there is no dispute that poultry is a source of *Campylobacter* infections in humans. *See* Bayer Exceptions at 37 n.12 ("Bayer has never claimed that poultry is not a source of *Campylobacter*"). Bayer does, however, challenge CVM's assertion that poultry is a predominant source of campylobacteriosis in the United States. *Id.* I find that the evidence supports CVM's position that poultry is a primary source in the United States of both susceptible and fluoroquinolone-resistant *Campylobacter* infections.

2. Retail meat studies

I find that *Campylobacter* contamination has been found on retail poultry products in every pertinent study in the record; that the presence of *Campylobacter* contamination is much more common on retail poultry than on other retail meat products; and that fluoroquinolone-resistant *Campylobacter* is now commonly found on retail chicken and turkey products. Significant investigations of retail poultry meat contamination include the studies discussed below.

In a study of 825 poultry and non-poultry meat samples randomly collected from retail stores in the Washington, D.C. area from June 1999 to July 2000, researchers from the University of Maryland examined 184 chicken carcasses and 172 turkey breasts, finding that the prevalence of *Campylobacter* in retail chicken was 70.7% and the prevalence in turkey was 14.5%. Meng, G-1466 at 2; G-727. In contrast, 1.7% of the pork samples and 0.5% of the beef samples were positive for *Campylobacter*. White, G-1484 at 3; G-727. Most (91%) of the 59 stores, from 4 different supermarket chains, had *Campylobacter*-contaminated chicken. *Id.* In the study, 722 *Campylobacter* isolates (595 from chicken, 112 from turkey, 11 from pork, and 4 from beef) were typed. About half of the isolates (53.6%) were identified as *C. jejuni*, 42.3% as *C. coli*, and 5.1% as other species. Meng, G-1466 at 3. *C. coli* was recovered more often from retail turkey samples than *C. jejuni*. *Id.* Eighteen chicken carcasses and 12 turkey breasts had more than one *Campylobacter* species present, and on two occasions three different species of *Campylobacter* were found in a single sample. *Id.*

More recently, the University of Maryland researchers evaluated the *in vitro* antimicrobial susceptibilities of 378 *C. jejuni* and *C. coli* isolates from 159 contaminated retail raw meat products (130 chicken, 25 turkey, 3 pork, 1 beef). Meng, G-1466 at 3-4; G-1778. They found 41% of the isolates were resistant to nalidixic acid and 35% were resistant to ciprofloxacin. *Id.* *C. coli* isolates had significantly higher resistance rates to ciprofloxacin than *C. jejuni* isolates. *Id.* Turkey isolates, from either *Campylobacter* species, showed significantly higher resistance rates to ciprofloxacin than did *Campylobacter* isolates from retail chickens. *Id.*

In 2002, NARMS began a pilot surveillance of retail meats to determine the prevalence of antimicrobial resistance among *Salmonella*, *Campylobacter*, *E. coli*, and *enterococci* isolated from samples of chicken, ground turkey, ground beef, and pork chops purchased from selected grocery stores in the United States. White, G-1484 at 3-4. As of November 2002, preliminary data indicated that 58% of 365 chicken breasts tested, 8% of 372 ground turkey samples, 3% of 373 ground beef samples, and 2% of 343 pork chop samples were positive for *Campylobacter*. White, G-1484 at 4.

Smith and colleagues conducted a survey of retail chicken products in Minnesota in 1996 as part of a larger study they conducted on quinolone-resistant[40] *Campylobacter* infections of humans. Smith, G-1473 at 5-6, 13; G-589 at 1, 5. They found *Campylobacter* on 88% of the 91 retail chicken products they tested, including *C. jejuni* (74%) and *C. coli* (21%), and both species on some products. *Id.* Ciprofloxacin-resistant *Campylobacter* (MIC > 32 μg/mL) was isolated from 20% of these poultry products. *Id.*

There are several other retail meat studies in the record, which CVM witness Dr. David G. White described. *See* White, G-1484 at 3-8. These and other data in the record establish that a substantial proportion of the raw retail chicken products in the United States are contaminated with *Campylobacter* in general and also with fluoroquinolone-resistant *Campylobacter*.[41]

Bayer argues that, even if these data establish the presence of *Campylobacter* on poultry, these *Campylobacter* are for various reasons not capable of causing human illness, either because they are the wrong strains of *Campylobacter* or because they are present in insufficient amounts to cause human illness. I discuss Bayer's challenges to the molecular and genetic evidence linking poultry contamination and human illness in the next section. I address below Bayer's dose-response argument, which is also a substantial part of its challenge to CVM's risk assessment (*see* section III.D.4 below).

a. Dose-response

In the context of its challenge to the retail meat studies and elsewhere in its exceptions, Bayer argues that evidence concerning the presence of *Campylobacter* on retail poultry meat is insufficient to show a risk of harm without evidence that the amount of bacterial contamination present is sufficient to cause illness. *See, e.g.,* Bayer Exceptions at 185. I disagree.[42]

First, the evidence in the record linking consumption of poultry and human campylobacteriosis is sufficient without calculating the precise amount of bacteria (which the participants refer to as "bacterial load") found on particular products, and without knowing exactly how much *Campylobacter* a person must consume to become ill. As

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[40] As noted above, *see* pp. 26-27, quinolones, such as nalidixic acid, are precursor compounds to fluoroquinolones. Barrett, G-1453 at 2.

[41] Investigators have also identified *Campylobacter* contamination of retail poultry in Europe. *See* White, G-1484 at 8.

[42] Bayer also argues generally that the studies on which CVM relies use inaccurate criteria to define resistance. This argument is addressed in section III.D.5, *infra*.

In its post-hearing brief, Bayer argues that the retail study resistance results are unreliable because of bias introduced by the isolation methods for *Campylobacter*. Bayer Post-Hearing Brief (CR3) at 46-47. Although Bayer's exceptions do not raise this argument, *see* Bayer Exceptions at 185-188, I nonetheless have reviewed Bayer's argument and the testimony of Bayer witness Dr. Peter Silley, B-1913, that commonly used isolation methods introduce bias. I find Dr. Silley's testimony and Bayer's argument speculative and unsupported by evidence in the record. I find the use of a pre-enrichment step allows *Campylobacter* in food samples to flourish and that the use of antimicrobials in selective media is intended to eliminate other competing microorganisms that would hamper identification of the bacteria at issue. Meng, G-1466 at 2-3.

described above, there is abundant evidence in the record establishing that *Campylobacter* and fluoroquinolone-resistant *Campylobacter* are found on poultry carcasses and retail meat. *See, e.g.*, White, G-1484 at 2-3, 4, 7; Meng, G-1466 at 3. The epidemiologic studies described below make clear that poultry consumption is a primary risk factor for sporadic *Campylobacter* infections in the general population in the United States. Furthermore, the molecular data support the epidemiologic data, because these genetic and other "fingerprinting" studies demonstrate that bacterial strains found in retail poultry meats are also isolated from human patients. These data support a finding that, with respect to *Campylobacter*, the bacterial load to which people are exposed when they consume or prepare poultry is sufficient to make at least some exposed people sick at least some of the time, such that, as discussed above, public health experts estimate that there are more than a million cases of campylobacteriosis each year in the United States, a large proportion of which are associated with poultry and chicken handling and consumption.

In addition, although in general the retail meat studies do not quantify bacterial load on the products tested, there are FSIS data on the prevalence and levels of bacteria (including *Campylobacter*) on turkey and chicken carcasses in the United States; these data indicate that broilers and turkeys carry a higher carcass and ground product load of *Campylobacter* than do other food animal carcasses/products. G-651; G-652; *see also* G-1656 (1987 report of small investigation in England that found high bacterial load on 82 chickens purchased at 11 retailers).

Finally, I find that the very limited research in the record on the infective dose, *i.e.*, the amount of bacteria needed to make someone ill, supports a finding that the dose needed to cause illness can be very low, although the precise dose-response[43] relationship between exposure to *Campylobacter* and human illness has not been established.

The participants stipulated that the risk that a given meal will cause campylobacteriosis depends at least in part on the number of colony-forming units (CFUs)[44] of *Campylobacter* ingested. Revised Joint Stipulation 27. However, this is not the same as stipulating that there is a dose at which no effect can occur in at least some exposed people.[45]

There are only two studies in the record investigating the infective dose of *Campylobacter*. One is a case report, published in 1981, about an experiment in which the researcher (Robinson) ingested one dose of 500 CFUs of *C. jejuni* and then became ill. G-1816. The second is a study by Black in which 111 healthy young adult volunteers

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[43] A "dose-response relationship" is a "relationship in which a change in amount, intensity, or duration of exposure is associated with a change--either an increase or a decrease--in risk of a specified outcome." Last at 49.

[44] As explained in note 35, colony forming units, or CFUs, are a measure of the concentration of bacteria in a sample.

[45] Indeed, although I do not rely on it as evidence, I note that Bayer witness Dr. Anthony Cox, whose stricken testimony concerned in part risk modeling he had done based on dose-response data, admitted on cross-examination that there is no evidence in the record of a dose at which no effect occurs. Tr. at 1048-1049.

were exposed to one of two different strains of *C. jejuni* in a range of doses from 800 CFUs to 2 x 10^9 CFUs. G-67; *see* Tauxe, G-1475 at 5. Black found that rates of infection increased with dose, "but development of illness did not show a clear dose relationship." G-67 at 1. One strain was more likely to cause illness and caused more severe illness. *Id.* One person in the Black study developed illness at the lowest dose administered in the study (800 CFUs). G-67 at 4. Thus, neither the Black nor Robinson study identifies the minimal dose needed to cause illness, although they suggest it is lower than the lowest doses ingested in these studies. CVM witness Dr. Robert Tauxe testified that in his expert opinion, based on data from a study in the United Kingdom (U.K.) that estimated a thousand to a million *Campylobacter* per chicken (G-1656), "a drop of raw chicken juice would often include an infectious dose of 500 organisms [*i.e.*, CFUs]." G-1475 at 10. Dr. Tauxe also testified about the ease of cross-contamination of other foods with *Campylobacter* from raw poultry through improperly cleaned cutting boards or other kitchen surfaces and utensils. *Id.* This evidence suggests that even minimal spread of contaminated "chicken juice" can result in illness.[46]

In sum, the record shows that illness can occur at very low levels of exposure to *Campylobacter*. I find that there is no scientific justification for disregarding the retail meat studies because they do not provide a measure of bacterial load. The retail meat studies show that the contamination of poultry meat persists to and after the point of purchase, providing further evidence in the link between fluoroquinolone use in poultry and fluoroquinolone-resistant *Campylobacter* infections in humans. We know from these studies that, in different areas of the country and over a range of recent years, all researchers investigating retail meat contamination have found that a large proportion of retail poultry products is contaminated with *Campylobacter*. Moreover, recent studies consistently have shown that a large proportion of the products is contaminated with *Campylobacter* that are resistant to fluoroquinolones. This is important evidence linking human infections to poultry consumption. In the section above, I described evidence that demonstrated how common *Campylobacter* colonization of poultry is and how that contamination persists until slaughter. The evidence described in this section establishes that sufficient contamination persists on poultry carcasses and retail poultry meat products at the point of consumer purchase to be a hazard to human health.

The next links in the chain, discussed in sections III.C.3 and 4 below, are the epidemiologic and microbiologic studies showing that handling raw poultry, eating undercooked chicken and turkey meat, and cross-contamination from raw poultry to other food products, are major risk factors for campylobacteriosis.

3. Epidemiologic evidence

a. Introduction

Several case-control studies from the United States and elsewhere have shown that the risk of *Campylobacter* infection is significantly elevated with respect to: consumption of poultry generally; poultry consumption in restaurants; consumption of

[46] The dose-response issue is also raised in the context of risk modeling relied on by Bayer, discussed in section III.D.6 below, in which 500 CFUs is assumed to be the lowest dose of *Campylobacter* that can cause illness in humans.

undercooked or raw poultry; handling of raw chicken; and failure to clean food preparation or cutting board surfaces. The association between poultry and *Campylobacter* infections in humans is generally consistent across studies, despite broad differences in size, methodology, and sample population. Angulo, G-1452 at 89-90 (Att. 3) (prior to the FoodNet study described in his testimony and below, "at least 14 previous epidemiologic investigations of sporadic *Campylobacter* infections implicate exposure to poultry as a major risk factor.") Estimates of the proportion of human campylobacteriosis cases attributable to poultry range from 28%, *id.* at 10, 101, to 70%, Endtz, G-1457 at 4.

b. United States case-control studies

Early case-control research from the 1980s in the United States linked chicken consumption and *Campylobacter* infections soon after identification of campylobacteriosis as a common human enteric disease. Harris and colleagues identified 218 cases of confirmed *C. jejuni* or *C. coli* infections diagnosed through a health maintenance organization in Washington State and matched them to 526 controls by age and month of interview. G-268. They found that consumption of chicken and Cornish game hen was associated with more than a double risk of infection, and that consumption of raw chicken was even more strongly associated with illness. *Id.* at 4.[47] The researchers estimated that 48% of the cases would not have occurred had chicken not been consumed. G-268 at 4. The Harris study also found processed turkey meat was significantly associated with illness. G-268 at 4; Tauxe, G-1475 at 9.

In a small study of risk factors for *C. jejuni* enteritis among college students in Georgia, Deming and colleagues found, comparing 45 cases to 45 controls, that eating fully cooked chicken, eating chicken reported to be raw or undercooked, and contact with a cat or kitten were all significantly associated with illness. G-162. Those data indicated that 66.7% (95% CI 20.2-86.1) of cases were attributed to eating chicken. *Id.* at 6; *see* G-953 at 53 (calculating percent attributed to chicken based on reported data). *See also* G-299 and B-412 (small studies from Colorado in 1981 and 1982 linking raw or undercooked chicken and illness); G-564 (small study in Iowa of campylobacteriosis occurring from April 1982 to March 1983 found no link between infection and chicken consumption, but noted that "large numbers of chicken carcasses at retail stores were contaminated with *C. jejuni*, the seasonal distribution of disease onset and percentages of chicken carcasses that were positive was similar, and serotyping did not differentiate patients' strains from chicken strains of *C. jejuni*. Thus, in our study, poultry remains a possible, but unproved, source of human infection." *Id.* at 4; G-1644 at 10 (review article).

The largest case-control study of sporadic *Campylobacter* infections in the United States was conducted in the FoodNet sites in 1998 and 1999. Angulo, G-1452 at 9-10 and 79-107 (Att. 3). The study, by Friedman and colleagues, matched 1316 cases with culture-confirmed *Campylobacter* infections to 1316 controls of the same age. *Id.* Cases

[47] For chicken, the relative risk was 2.4 (95% CI 1.6, 3.6); for game hen, the relative risk was 3.3 (95% CI 1.1, 9.8). G-268 at 3 (Table 2). Relative risk (RR) is the ratio of the risk of disease in the exposed group (*i.e.*, the cases) to the risk of disease in the non-exposed group (*i.e.*, the controls). Last at 145.

and controls were asked about foreign travel, food and water exposures, and food handling practices in the seven days before the case became ill. *Id.* The 164 cases (13%) that reported travel outside of the United States in the seven days prior to onset of illness were excluded, along with their matched controls, from the final statistical analysis performed to identify risk factors for domestically acquired *Campylobacter* infections. *Id.*

In a statistical analysis that included a number of risk factors associated with campylobacteriosis, Friedman found that cases were more than twice as likely to have eaten chicken or turkey in a restaurant than were controls. Angulo, G-1452 at 10.[48] Friedman calculated that the population attributable fraction[49] of illness associated with chicken prepared at a restaurant was 24% (95% CI 17%-30%), and the population attributable fraction of illness associated with turkey prepared at a restaurant was 4% (95% CI 1%-6%). Angulo, G-1452 at 10, 101 (Att. 3); G-1488.[50] In other words, in their analysis, 24% of the campylobacteriosis cases in the study population may be attributable to eating chicken in restaurants and 4% to eating turkey in restaurants.

The Friedman analysis found no increased risk of illness for cases who reported having eaten poultry at home; in that analysis, controls were more likely to report having eaten chicken or turkey prepared at home. Angulo, G-1452 at 90, 101 (Att. 3).[51]

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[48] Stated more specifically, the analysis calculated the adjusted odds ratios associating consumption of chicken, turkey, or other meat in a restaurant with illness as follows: 2.2 (95% CI 1.7, 2.9); 2.5 (95% CI 1.3, 4.7); and 1.7 (95% CI 1.3, 2.2), respectively. Angulo, G-1452 at 9-10 and 81 (Att. 3); Tr. at 269-270.

[49] "Population attributable fraction" (PAF) refers to the proportion of cases in a population that can be attributed to a particular risk factor. *See* Last at 10; Angulo, G-1452 at 10. Contrary to Bayer's assertion, the fact that in the Friedman study the PAF for turkey is 4% and the PAF for chicken is 24% does not support a statement that "[t]his translates into a risk six times less for turkey than for chicken." Bayer Exceptions at 230 (emphasis in original). The PAF depends in part on the amount of exposure to each risk factor. The fact that a greater proportion of *Campylobacter* cases in the Friedman study population was attributable to chicken consumption than to turkey consumption likely reflects in part that more people reported eating chicken than turkey in restaurants.

[50] Friedman also found that drinking untreated surface water, drinking raw milk, eating undercooked poultry, eating raw seafood, having a pet puppy, contact with farm animals, and contact with animal feces were also each associated with an elevated risk of infection. Angulo, G-1452 at 10 and 92 (Att. 3).

[51] More specifically, the "adjusted odds ratio" (AOR) for eating chicken prepared at home was 0.7 (95% CI 0.6, 0.9), and the AOR for eating turkey prepared at home was 0.5 (95% CI 0.4, 0.8). *Id.* at 101 (Att. 3). The Initial Decision adopts the suggestion by CVM witness Dr. Herbert Endtz that repeated contact with contaminated poultry provides an acquired immunity to infection. Initial Decision at 32, *citing* Endtz, G-1457 at 4; this possible explanation of this outcome is also discussed by Friedman and colleagues, Angulo, G-1452 at 90 (Att. 3). Assuming this acquired immunity occurs, however, there is no evidence on the record that would provide a clear explanation for why people who eat chicken in restaurants would not similarly acquire immunity. Such acquired immunity could affect the ability of any study to accurately identify poultry consumption as a risk factor for *Campylobacter* infections. Thus, I decline to adopt the ALJ's

As the authors acknowledge, there are limitations to the Friedman study. Angulo, G-1452 at 93-94 (Att. 3). In addition to the potential for bias inherent in observational case-control research, this investigation was a screening study that encompassed hundreds of independent and overlapping exposure factors, some of which were included in the final multivariate analysis (*e.g.*, "Ate chicken prepared at a restaurant," "Ate undercooked or pink chicken," "Ate fried chicken"). *Id.* at 101. Because of the large number of variables analyzed in the study, many of which were interrelated, *see* Angulo, G-1452 at 98 (Att. 3), the relationship between particular risk factors and the outcome of interest (campylobacteriosis) is best analyzed in the context of the entire body of research on risk factors for *Campylobacter* infection.

In light of these limitations, it is noteworthy that the Friedman study is consistent with other studies that also identified *Campylobacter* risk associated with poultry consumption in restaurants. Indeed, this consistency with other, smaller studies may be more meaningful than the actual values estimated through the statistical model.

Bayer argues that the findings of the Friedman study show that "some factor other than poultry consumption must be affecting the risk of infection with *Campylobacter*." Bayer Exceptions at 184, 196. Bayer suggests that "[r]estaurant workers ...or veal ... could easily be additional sources of restaurant cross contamination of many other foods. CVM has not shown otherwise." *Id.* at 184 (citations omitted).

I do not agree. First, CVM does not have to disprove, and in fact does not contest, that there are other sources of *Campylobacter* infection. *See* Revised Joint Stipulation at 32 ("[s]ources of *Campylobacter* infection other than poultry, such as domestic pets, are known"). The burden on CVM in this proceeding is to show that poultry is a risk factor for fluoroquinolone-resistant *Campylobacter* infection. As discussed in this Final Decision, CVM's evidence shows that poultry is a primary risk factor with respect to both fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter*.

Second, Bayer does not provide sufficient evidence to support its allegations that restaurant workers, veal, or flies or rodents are plausible sources of sporadic

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reasoning on this point. It is at least equally possible that the findings with respect to poultry prepared at home are associated with study design issues as discussed in the text. The Friedman draft notes other possible factors, including different methods of preparing chicken at home and away from home (*e.g.*, barbecued chicken may pose a higher risk if prepared away from home, possibly due to undercooking), improvements in awareness and use of safer poultry handling practices in the home, and possibly lower risk of cross-contamination. *Id.* at 91-92. As Dr. Angulo testified, in a home or restaurant kitchen, hands, utensils, and work surfaces contaminated by raw poultry can quickly cross-contaminate cooked poultry and other foods just before consumption. *Id.* at 9, 12-13; Tauxe, G-1475 at 9-10, 15-16. While this cross-contamination can occur in a home setting, the evidence suggests that food handling practices in commercial settings may increase risk. One possible common sense explanation may be that multiple meals are present in a commercial setting at any given time at all stages of preparation, while in a home it is less likely that both raw chicken and chicken and other foods ready to be served are being handled at or near the same time. I note that in finding unconvincing the acquired immunity Bayer raises, I specifically am not considering Bayer's wholly unsupported argument about the science of acquired immunity. *See* Bayer Exceptions at 184.

Campylobacter infections in humans. Exhibit G-22, cited by Bayer in support of its "veal" (and fly and rodent) claim, is a review article; neither the article nor the underlying research support Bayer's claim. As support for the "restaurant worker" claim, Bayer cites to a statement in an attachment[52] to the stricken written direct testimony of Dr. Anthony Cox, which in turn cites the testimony of CVM witness Dr. Frederick Angulo. I find that Dr. Angulo's full testimony and other evidence in the record do not support Dr. Cox's interpretation.[53] Thus, even if Dr. Cox's testimony were not stricken, I would find Bayer's argument with respect to veal and vermin entitled to little weight, and the evidence on food handlers simply unreliable. This testimony plainly does not refute the evidence that poultry, and cross-contamination due to poultry contamination, are a primary source of *Campylobacter* infections in the United States.

Finally, because of the way the study was designed, the Friedman analysis provides information about risk associated with poultry consumption in restaurants, as explained above, but it cannot support any conclusions about the independent risks posed by poultry, other meats and foods, food handlers and handling practices, or by restaurants. Furthermore, there is plenty of evidence in this record demonstrating an association between consumption of poultry and acquiring campylobacteriosis; the same cannot be said about data linking eating in a restaurant with the illness. While there may be some lower risk of campylobacteriosis associated with consuming other meats in a restaurant setting, *see* Angulo, G-1452 at 10-11 and 89, 92 (Att. 3), most of the evidence in the record linking food consumption and sporadic campylobacteriosis involves consumption of chicken and turkey and probable cross-contamination of other foods with bacteria originating from raw poultry. Angulo, G-1452 at 12-13; Tauxe, G-1475 at 7-10.

In a smaller recent case-control study, Effler and colleagues investigated indigenous exposures contributing to the high incidence of sporadic *C. jejuni* infections in Hawaii, which has the highest rate of *C. jejuni* infections in the United States. G-185 at 1. The study involved 211 cases with confirmed *Campylobacter* infection, each matched to one age-and telephone-exchange matched control. Effler found that people who ate chicken prepared by a commercial food establishment in the seven days before

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[52] The attachment is called "Report of Summary and Discussion of Cox Findings--12-13-02." *See* Cox, B-1901 at 9 (Att. 1). There is no explanation in the sworn testimony about why this document is not part of the sworn testimony of this witness: it is not a journal article, abstract, or other similar document more commonly attached to expert witness testimony in this proceeding.

[53] Dr. Cox stated in the attachment: "We propose that transmission from asymptomatic but shedding food workers in restaurants and institutions also occurs, with unknown frequency...." Cox, B-1901 at 57 (Att. 1), citing in support a sentence in the written direct testimony of CVM witness Dr. Frederick Angulo that "transmission from ill food handlers occurs occasionally but is not common," *id.*, *see* G-1452 at 9. However, Dr. Angulo was testifying about food-handler transmission associated with outbreak events, not sporadic *Campylobacter* infections, and his testimony, along with other evidence in the record, is that such transmission is rare. Angulo, G-1452 at 9. CVM witness Dr. Hubert Endtz testified human-to-human transfer of *Campylobacter* infections is rare and "probably of no epidemiological importance." Endtz, G-1457 at 4; *see also* Tauxe, G-1475 at 5 (discussing human transfer as a rare source of outbreak); G-1644 at 8 ("Transmission from ill food handlers occurs occasionally [as a source of outbreaks] but is not common.").

case illness onset were just under twice as likely to become ill as controls (AOR 1.8; 95% CI 1.1-2.9).[54]

In sum, I find that the research conducted in the United States, described in this section, provides solid and reliable evidence that the consumption of poultry is a primary risk factor for campylobacteriosis. Research from other nations supporting the conclusions of the United States studies is discussed below.

c. Non-U.S. studies

European studies also support the link between chicken consumption and risk of campylobacteriosis. I find that these studies provide information that is useful and relevant to the United States. Tr. at 408; Endtz, G-1457 at 7 ("Twenty-five years of study of the epidemiology of *Campylobacter* infections in the U.S. and Europe has not come up with data that refute the hypothesis that epidemiology of *Campylobacter* in the two continents is in essence very comparable. Therefore, data from outside the U.S. include valuable information that may be extrapolated to the U.S. situation."). Studies of risk factors for *Campylobacter* infections are available from Denmark, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom. *See* Wegener, G-1483 at 14 (table of case-control studies from 1979-1998). Consumption of poultry is identified as a risk factor in studies in Sweden, G-602 at 1; the United Kingdom, G-1686 at 1; Switzerland, G-1718 at 1; Norway, G-334 at 1; and the Netherlands, G-474. In Denmark, Neimann identified eating undercooked chicken as a risk factor for illness, Wegener, G-1483 at 13, and in England, Rodrigues identified eating chicken in a restaurant as a risk factor, G-1711 at 2.

Similar findings can be seen in studies conducted in Canada and New Zealand. Michaud and colleagues (Canada) found in a case control study conducted in Canada in 2000-2001 that eating undercooked poultry and failing to clean kitchen surfaces were each risk factors for campylobacteriosis. G-1681; Tauxe, G-1475 at 9. A study in New Zealand found that eating undercooked poultry was a risk factor for illness, as was eating chicken in a restaurant, G-182, while a second New Zealand study found that eating undercooked chicken, eating poultry at a barbeque (a risk the authors hypothesized may be associated with inadequate cooking, lack of refrigeration, or cross-contamination), and eating poultry at a friend's house (a risk the authors suggested might be associated with catering to larger numbers than usual) were risk factors for infection, G-307 at 3.

Thus, I find, with respect to the record evidence concerning epidemiologic studies conducted in the United States and other developed nations to determine risk factors for sporadic *Campylobacter* infections, that, "[a]lthough these studies differed in location, technique, and sample size, they consistently indicate several dominant sources of infection, including contact with and consumption of chicken and turkey." Angulo, G-1452 at 9.

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[54] An odds ratio in a case control study is the ratio of the odds of exposure in the cases to the odds of exposure in the controls. Last, at 118. An odds ratio is adjusted if the effects of differences in the populations being compared (*i.e.*, the cases and controls) have been minimized in the statistical analysis. *Id.* at 4 (definition of "adjustment").

d. Intervention studies

I find that further epidemiologic evidence of the link between Campylobacter and poultry consumption is found in studies of the impact on *Campylobacter* infections of changes in a population's poultry consumption, referred to by the participants as "intervention studies." Wegener, G-1483 at 18.

One such situation occurred in Belgium in 1999, when domestic poultry and eggs were taken off the market for a month because dioxin had been detected in animal feed (imported poultry and other meat products were still available to consumers). *Id.* The incidence of human *Campylobacter* infections dropped in Belgium almost 40% in the month that domestic poultry was unavailable (based on a model generated from data for the period from 1994 to 1998). Endtz, G-1457 at 4; Wegener, G-1483 at 18; G-672. Researchers hypothesized that the fact that 41% of poultry sold in Belgium is imported (and remained available to consumers) could explain in part the cases of campylobacteriosis that did occur during that period. *Id.*

Similarly, Iceland experienced an increase in *Campylobacter* infections from 1997 to 1999, a period of time that coincided with the introduction of fresh, rather than the traditionally available frozen, chicken products on the market. Wegener, G-1483 at 18. After the country imposed stringent control measures to test poultry for *Campylobacter* at slaughter and to process and market contaminated poultry meat differently from uncontaminated meat, incidence of domestically acquired campylobacteriosis in Iceland was reduced by about 70%. Wegener, G-1483 at 19. Norway has implemented a similar program and early results showed after 39 weeks an almost 50% reduction in domestically acquired campylobacteriosis. *Id.*

e. Fluoroquinolone-resistant *Campylobacter* infections

The epidemiologic studies I have described thus far identified risk factors for acquiring *Campylobacter* infections, without consideration of the susceptibility or resistance of the bacteria to fluoroquinolones. However, the record demonstrates, and I find, that there are no significant biologic reasons that transmission of fluoroquinolone-resistant *Campylobacter* infections from animals to humans is different from transmission of fluoroquinolone-susceptible infections. Wegener, G-1483 at 20. As a result, it can be expected that when resistance to fluoroquinolones emerges in *Campylobacter* in animals, resistant *Campylobacter* will be transmitted to humans, *id.*, and investigations have shown temporally that this in fact occurs, *id.* at 21.

Not surprisingly, then, research focused specifically on identifying risk factors for fluoroquinolone-resistant *Campylobacter* infections confirm that consumption of poultry is a risk factor. Using the FoodNet *Campylobacter* case-control data, Kassenborg and colleagues evaluated risk factors associated with fluoroquinolone-resistant *Campylobacter* infections. They interviewed 646 of 858 (75%) cases for whom information on resistance to fluoroquinolones was known. Kassenborg, G-1460 at 6; G-

337.[55] Of these 646 cases, 64 had infections that were resistant to fluoroquinolones and 582 had infections that were sensitive to fluoroquinolones. *Id.*

Although Kassenborg found that some of the cases with fluoroquinolone-resistant *Campylobacter* infections had likely become infected outside of the United States, I find it noteworthy that a majority of the 64 cases with fluoroquinolone-resistant infections (37 out of 64, or 58%) had infections that were domestically acquired (in other words, the cases had no history of travel outside of the United States in the week before they became ill).[56] Furthermore, domestically acquired fluoroquinolone-resistant *Campylobacter* infections were reported in all of the FoodNet surveillance sites. Kassenborg, G-1460 at 7. These data are consistent with the NARMS data, described below, indicating that an increasing proportion of human *Campylobacter* infections are resistant to fluoroquinolones and refuting Bayer's arguments (*see* section III.D.2. below) that these cases can be attributed to *Campylobacter* infections acquired outside of the United States. Together with the data from retail food sampling demonstrating the presence of fluoroquinolone-resistant *Campylobacter* on poultry products in the United States, this research supports a conclusion that poultry is the dominant source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the United States. *Id.* at 9.

In a statistical analysis that incorporated a number of risk factors, Kassenborg found that the 37 cases with domestically acquired fluoroquinolone-resistant infections were ten times more likely to have eaten chicken or turkey at a commercial establishment than were their age-matched controls (95% CI 1.3-78). Kassenborg, G-1460 at 8; G-337 at 15.[57]

Despite certain methodologic and statistical limitations, such as the high degree of correlation among certain of the study variables (*e.g.*, 75% of cases reported "eating in a non-fast food restaurant" and 55% reported "eating chicken or turkey at a commercial establishment," G-337 at 15) and the limitations inherent in any questionnaire-based case-control research, I find that the Kassenborg study provides valuable information about domestically acquired fluoroquinolone-resistant *Campylobacter* infections.

f. Temporal data on human fluoroquinolone-resistant *Campylobacter* infections

I also find that data from several countries, including the United States, indicate that a rise in human *Campylobacter* infections that are resistant to fluoroquinolones has

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[55] G-337 is the final draft of the study. The tables and graphs of the study were revised prior to publication and the final draft version is attached to Dr. Kassenborg's written direct testimony. Kassenborg, G-1460 at 3, 14-15; Tr. at 575.

[56] The role of foreign travel is discussed more fully in section III.D.2 below.

[57] The final model was a forward stepwise multivariate logistic regression. Kassenborg, G-1460 at 8. Bayer makes much of Dr. Kassenborg's testimony that when she and her colleagues tried a backward stepwise regression on the data none of the risk factors remained significant, and yet they did not mention this analysis in their publication. Bayer Exceptions at 183; Tr. at 603. (For purposes of this discussion, it is not necessary to understand what these statistical methods are or the difference between them.) I find no evidence of bias in Dr. Kassenborg's decision to look at the data using different approaches to model fitting.

consistently followed the introduction of enrofloxacin in poultry production in that country. As noted in the discussion of epidemiologic evidence in section II.D.2.c above, an indication that an exposure precedes the outcome of interest is consistent with a causal association.

(i) Data from the United States

Veterinary use of sarafloxacin and enrofloxacin was approved in the United States in August 1995 and October 1996, respectively. Revised Joint Stipulations 39, 47. If there is evidence that *Campylobacter* isolates from human stool samples had higher levels of resistance to fluoroquinolones after approval than they had before approval, and that the level of resistance continued to increase following approval, this evidence would support a finding that the use of enrofloxacin in poultry has resulted in increased resistance to fluoroquinolones in human *Campylobacter* infections.

As described below, the participants each provided a set of studies intended to show what the pre-approval "baseline" of fluoroquinolone resistance was among *C. jejuni* and *C. coli* in the United States. I find that fluoroquinolone resistance was very low (*i.e.*, less than 5% of human *Campylobacter* isolates) prior approval and use of enrofloxacin in poultry in the United States. In so finding, I disagree with Bayer that the evidence shows that as early as 1995 fluoroquinolone resistance in *Campylobacter* was as high as 20%. I also find that the longer enrofloxacin has been in use, in the United States and elsewhere, the more resistance to fluoroquinolones has been found in human *Campylobacter* isolates.

At the outset, it is important to understand the role of nalidixic acid with respect to fluoroquinolone resistance in *Campylobacter*. Nalidixic acid is a precursor to fluoroquinolones, Barrett, G-1453 at 2, and fluoroquinolone-resistant *Campylobacter* are typically also resistant to nalidixic acid. *Id.* Thus, data on resistance to nalidixic acid are relevant to understanding how common fluoroquinolone resistance was prior to the approval of enrofloxacin and sarafloxacin. Fortuitously, these data are available because, throughout the 1980s, resistance to nalidixic acid was used in the laboratory to distinguish *C. jejuni and C. coli*, which were almost universally susceptible to nalidixic acid, from *C. lari*, which is not (for reasons that are not germane to this proceeding). Barrett, G-1453 at 2-3. Published research using resistance to nalidixic acid to distinguish among *Campylobacter* species found in human stool isolates shows that, before the introduction of enrofloxacin, *C. jejuni* and *C. coli* were almost entirely susceptible to nalidixic acid, and by implication, also susceptible to fluoroquinolones. In one such study, Barrett and colleagues reported in 1988 that only 2 of 42 *C. jejuni* isolates, and 0 out of 25 *C. coli* isolates (from human stool samples) were resistant to nalidixic acid, while all (23 out of 23) *C. lari* isolates were resistant. *Id.* at 3; G-1609 at 5.[58]

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[58] Bayer argues that the Barrett study supports a pre-approval estimate of 5% quinolone resistance in *C. jejuni* isolated from humans, and that "[t]his 5% resistance level from surveillance studies was likely *underestimated* in this timeframe." Bayer Exceptions at 149 (emphasis in original). The Barrett study does not provide adequate support for a quantitative estimate of prevalence of resistance, however, because the study did not attempt to include samples that were

In Minnesota, Smith and colleagues observed an increase in quinolone-resistant[59] *Campylobacter* infections in humans from 1.3% in 1992 to 10.2% in 1998. Smith, G-1473 at 7; G-589 at 6. Part of that increase can be explained by foreign travel and quinolone use by the patients prior to collection of stool specimens. *See* Revised Joint Stipulations 8, 9. However, in an analysis of data from 1996-1998 that excluded patients with a history of foreign travel, Smith found that there was still a statistically significant increase in resistance to quinolones in domestically acquired *C. jejuni* infections between 1996 and 1998. Smith, G-1473 at 12. Smith estimated that only a maximum of 15% of quinolone-resistant *Campylobacter* infections could have been due to prior quinolone therapy in the patient. G-1473 at 15; G-589 at 6.[60]

In 1989, Tenover and colleagues analyzed 332 *C. jejuni* isolates and found only one to be resistant to ciprofloxacin. Barrett, G-1453 at 3. The resistant isolate later proved to be *C. lari* (and as a result the resistance can be presumed to be a characteristic of the bacteria rather than a result of exposure to fluoroquinolones). Barrett, G-1453 at 3; Nachamkin, G-1470 at 6. Dr. Barrett testified that the 1989 data by Tenover is appropriately considered a "baseline" from which to evaluate the later emergence of resistance in *C. jejuni* and *C. coli*. Barrett, G-1453 at 3.

Nachamkin and colleagues tested 132 *C. jejuni* isolates from patients with gastroenteritis at the University of Pennsylvania Medical Center between 1982 and 1992. Nachamkin, G-1470 at 6. During this ten-year period, none of the isolates was resistant to ciprofloxacin. In a follow-up study, Nachamkin found that among 297 *C. jejuni* isolates collected from patients (most of whom were outpatient) between 1995 and 2001 within the University of Pennsylvania Health System, 8.3% of the isolates were resistant to ciprofloxacin in 1996 and 40.5% were resistant in 2001. Nachamkin, G-1470 at 6. All but one of the resistant isolates had a ciprofloxacin MIC $\geq$ 32 μg/mL. *Id.*

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representative. However, even if a quantitative estimate were possible, the figure would be 3%, not 5% (2/67); there is no reason to exclude the *C. coli* isolates from the calculation.

[59] *See* note 40 above and discussion in the text concerning cross-resistance. Dr. Smith testified that for the population of isolates he and his colleagues studied, "nalidixic acid resistant, quinolone-resistant, ciprofloxacin-resistant, and fluoroquinolone-resistant can all be considered equivalent terms" (with "very rare" exceptions). Smith, G-1473 at 3. He explained further that while few isolates from the earlier years of the study (1992-1994) were available to be tested for fluoroquinolone resistance as well as nalidixic acid-resistance, for the rest of the study "virtually all of the nalidixic acid isolates were actually tested for resistance to fluoroquinolones (and were found to indeed be resistant to fluoroquinolones)." *Id.* at 3. In describing the Smith research, I use the terminology used by the researchers with this clarification in mind.

[60] Bayer argues that although the Smith paper does not report resistance levels for 1995, a figure in G-589 suggests that resistance in 1995 was at between 5 and 6%. Bayer Exceptions at 150; *see* G-589 at 3 Fig. 1. However, there is no analysis of the source of infection (*i.e.*, domestically acquired versus associated with foreign travel) for the years prior to 1996, and it is possible, and consistent with the later data, that foreign travel during the early 1990s is responsible for at least part of the apparent increase from 1.3% in 1992 to about 5% in 1995. *See, e.g.*, G-589 at 6 (noting seasonal peaks in quinolone resistance between 1992 and 1998 "that were primarily related to foreign travel during winter.").

In sum, I agree with the Initial Decision's finding that "[i]t is not clear what was the exact pre-approval level of fluoroquinolone resistance in the United States. Nevertheless, those levels appear significantly higher post-approval as compared to preapproval." Initial Decision at 52. Indeed, I would state this even more strongly: I find that the weight of evidence in the record establishes that post-approval levels of quinolone-resistance in human *Campylobacter* isolates are substantially higher than pre-approval levels of such resistance.

In so finding, I disagree with Bayer that the weight of the evidence is to the contrary. Bayer Exceptions at 149. I also find that Bayer's additional challenges to research relied on by CVM with respect to this issue are not based on evidence deserving of much weight.

First, Bayer cites to research by Kiehlbach and colleagues comparing *Campylobacter* isolation on selective media to that obtained by filtration. B-39. Fecal specimens collected between 1992 and 1995 were cultured, and 97 *Campylobacter* isolates obtained. *Id.* at 2-3. Forty of these were identified as *C. jejuni* and three as *C. coli*. The report notes that 88% of the *C. jejuni* isolates were susceptible to ciprofloxacin. *Id.* at 3. It does not, however, identify how susceptibility was defined and it does not define the proportion that was resistant, and I find that it is inappropriate to assume, as Bayer does, Bayer Exceptions at 149-150, that a reported susceptibility of 88% means a resistance rate of 12%.[61]

Exhibit B-67, which Bayer also cites, is an abstract describing 181 *Campylobacter* isolates collected during an outbreak of enteritis at a nursing home in New York in 1993, 6 (3.3%) of which were found to be resistant to nalidixic acid. B-67; DeGroot, A-200 at 6. In this outbreak, the percentage of infections that was resistant was less than 5%, so to the extent the abstract is relevant (since it concerns an outbreak, not sporadic infections), these data are consistent with my findings about baseline levels of quinolone resistance.

Finally, Bayer cites a draft paper by Nachamkin and colleagues (G-1517) reporting on an increase in fluoroquinolone resistance in *Campylobacter* isolates from the University of Pennsylvania Health System. Bayer Exceptions at 150. That study, which looked at 297 case isolates collected from 1995 to 2001, reported an increase over time from 8.3% (1996) to 40.5% (2001). G-1517 at 4-5. The draft does not report the proportion of isolates resistant for the other years covered by the study (1997 to 2000), but indicates them graphically at Figure 1. G-1517 at 11. Bayer cites this figure because it indicates about 20% resistance for 1995. There is no information in this study or

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[61] First, there is an "intermediate" category in which bacteria that have some measured resistance (and thus might not have been reported as susceptible) are not classified as resistant. Walker, G-1481 at 4. Second, many of the cases reported in B-39 may have been the result of campylobacteriosis outbreaks, rather than from sporadic cases. DeGroot, A-200 at 59. In an outbreak, there is a common exposure. If the outbreak were with a resistant strain of *Campylobacter*, the proportion of isolates that were susceptible would be much lower than would be the case if only isolates from sporadic infections were included. In the Smith study, where cases were known to be associated with an outbreak, only the initial case in each identified outbreak was included in the analysis. *See* G-589 at 3.

elsewhere in the record that allows for an understanding of why the 1995 isolates for this one year within this population were elevated, but a number of epidemiologic variables may have made this study population unrepresentative of the general population. Therefore, I decline Bayer's invitation to give this one data point extraordinary weight, as it is clearly out of line with Nachamkin's other data and the other evidence on this issue. *E.g.*, G-589; G-440; Barrett, G-1453 at 3, G-1609.[62]

I conclude that the totality of Dr. Nachamkin's research shows that from 1982 to 1992, there was no resistance to ciprofloxacin in *Campylobacter* isolates collected in the University of Pennsylvania Health System; that in 1996, the proportion that was resistant was 8.3%, and that in 2001 the proportion that was resistant was 40.5%. G-440; G-1517. I also find that, as described in this section, there is evidence in the record, in particular the data about which Dr. Barrett and Dr. Nachamkin testified, that fluoroquinolone resistance rates in the United States were low before August 1995, when fluoroquinolones were first approved for veterinary use, and that they have increased significantly since fluoroquinolones were approved for veterinary use in the United States.

I also find that the NARMS and other data show that the proportion of human *Campylobacter* isolates that was resistant to ciprofloxacin increased significantly in the period following approval of fluoroquinolones for veterinary use. NARMS data show that the percentage of *Campylobacter* isolates that was resistant to ciprofloxacin was 13% (28/217) in 1997, the first year of such testing; 14% (48/345) in 1998, 18% (58/319) in 1999, 14% (46/324) in 2000, and 19% (75/387) in 2001. Angulo, G-1452 at 8, 74-78 (Att. 2). The NARMS analysis found a modest but statistically significant increase over the time period from 1997 to 2001. Angulo, G-1452 at 7-9, 74-78 (Att. 2); Molbak, G-1468 at 8. The proportion of human *Campylobacter* isolates that was resistant to ciprofloxacin (adjusting for site variation and age) was 2.5 times higher in 2001 (95% CI 1.4-4.4) than it was in 1997. Angulo, G-1452 at 8-9, 74-78 (Att. 2). These data parallel the findings from Minnesota in which resistance among human *Campylobacter* isolates rose from 1.3% in 1992 to 10.2% in 1998. G-589 at 6.

Bayer raises several challenges to these temporal data. First, Bayer argues that the human NARMS data for *Campylobacter* are not nationally representative. Bayer Exceptions at 156-160. Bayer's specific arguments are that the sampling scheme does not produce a nationally representative sample, because only one sample per month per state is collected, and that data from Connecticut skew the analysis because of "an unexplained one-year spike in resistance from Connecticut." Bayer Exceptions at 158; *see* Molbak, G-1468 at 8 (in 1999, the number of resistant isolates from Connecticut was high).

While no surveillance system is without limitations, *see* Tr. at 358-359, I find that the NARMS data provide reliable information about the prevalence of fluoroquinolone-

[62] It would have been helpful if Dr. Nachamkin had addressed this anomaly in his written direct testimony, or in the article itself, but there is no discussion of it on the record. It is also unfortunate that there are no data available for isolates from 1993 and 1994, *see* G-1517 at 4; Nachamkin, G-1470 at 7; I agree with Bayer that having such information would strengthen our understanding of the 1995 data. *See* Bayer Exceptions at 151.

resistance in *Campylobacter* infections in the United States. Because the sampling scheme has not changed over time, any bias will affect all years. As a result, a statistically significant increase in prevalence over time is sufficiently robust, even if the exact figures are not perfectly correct. Tr. at 437. Furthermore, CVM witness Dr. Frederick Angulo testified that CDC had investigated the sampling basis of NARMS and that as a result he was "confident that the prevalence that we're measuring in NARMS is a close approximation of the national prevalence of fluoroquinolone-resistant *Campylobacter*." *Id.* at 438; *see also* Tr. at 135.

Bayer argues that, because there is seasonal variability in some states with respect to infections with *Campylobacter* and resistant *Campylobacter*, *see* Tr. at 124-128, 381-83, including only one isolate per week per participating state laboratory skews the data toward resistance. Bayer Exceptions at 157-158. Dr. Angulo's testimony recognized that there are variations from month to month on the proportion of *Campylobacter* infections that is resistant to fluoroquinolones; the proportion varies from state to state and in some, but not all, states it can be seasonal, although in general, there is seasonality across FoodNet sites. Tr. at 381-82. However, there is evidence in the record that CDC periodically evaluates the FoodNet surveillance system to confirm the "generalizability," or external validity, of the data it generates. Tr. at 311, 315, 320-325. Inasmuch as NARMS operates under the general umbrella of FoodNet, it is likely that its sampling scheme produces data that likewise can be generalized to the general population. Tr. at 358. Furthermore, even with respect to Minnesota, a state in which seasonal variation is apparent, Tr. at 382, AHI witness Dr. Bradley DeGroot testified that any seasonal bias "explains only a small proportion of the number of resistant isolates submitted by Minnesota to the Human NARMS program, beyond what can be expected based on overall resistance measured for the state," DeGroot, A-200 at 24. Dr. DeGroot testified that he believed that the seasonal selection bias inflated estimates from all contributing sites. I find that any bias created by seasonal fluctuation in resistance is minimal and does not affect the general conclusion, supported by the evidence in the record, that the proportion of human *Campylobacter* infections that is resistant to fluoroquinolones is increasing even as human *Campylobacter* infections decline.

Bayer also argues that at the time it was drafting the NOOH, CVM could only have known the NARMS results for 1998 and 1999, and that the increase shown in resistance prevalence in those years (14% in 1998 to 18% in 1999) was due to data from Connecticut. Bayer Exceptions at 159. Since no one is claiming that CVM based its NOOH solely on this evidence, the argument is not material. However, I disagree in any event with Bayer's suggestion that because the removal of the Connecticut data removes the statistical significance of the trend in increased prevalence of resistance over time, the data show no increase. *Id.* at 159-60. Between 1997 and 2001, the prevalence of fluoroquinolone resistance increased significantly (prevalence ratio 1.98; 95% CI 1.23-3.19, p= 0.008). Molbak, G-1468 at 8; *see* Angulo, G-1452 at 8-9. In other words, there was an almost 100% increase in the prevalence of resistance. When the Connecticut data are excluded, the trend in resistance remains, although statistical significance at a 95% confidence level is lost, probably due to the small sample size involved (prevalence ratio 1.61; 95% CI 0.95-2.73). Molbak, G-1468 at 8. Despite the lack of statistical significance, this analysis is informative because the upward direction of the trend (*i.e.*, a finding that resistance increases over time) remains the same, even without the

Connecticut data. Angulo, G-1452 at 8-9. With respect to the statistical analyses, Dr. Angulo testified that "[n]o remarkable changes were observed in either multivariate model when the cases from Connecticut were excluded from the analysis." Angulo, G-1452 at 8. In sum, I do not believe that Bayer has shown a reasonable scientific basis for excluding the Connecticut data, but even excluding the Connecticut data, the trend in increasing resistance over time in this data set, while not statistically significant, is apparent and is consistent with the totality of the trend data.

In conclusion, with respect to temporal data from the United States, I find that there is reliable evidence that in the United States there was little or no quinolone resistance in *Campylobacter* prior to the 1995 and 1996 approvals of sarafloxacin and enrofloxacin for use in poultry. In so finding, I give more weight to studies that involved relatively large samples and studies that evaluated characteristics of the study population and controlled for common-source infections. Because I find that there was little resistance pre-approval of enrofloxacin and sarafloxacin, I find there is no need to speculate, as Bayer invites me to do, about alternative explanations for the rates of ciprofloxacin resistance Bayer argues were prevalent prior to 1995.[63]

Bayer also challenges the temporal data by arguing that the incidence of *Campylobacter* infections that are resistant to fluoroquinolones has declined. Bayer Exceptions at 154-156. Bayer's argument is that "this declining incidence of fluoroquinolone-resistant campylobacteriosis cases reflects a decreased risk in acquiring a resistant *Campylobacter* infection after enrofloxacin's 1996 approval." Bayer Exceptions at 156. Even if there were sufficient evidence to support Bayer's incidence estimates, however, the issue before me, as I have noted before, is not whether there are more *Campylobacter* infections currently than in previous years, but rather whether the proportion of those infections that is resistant to fluoroquinolones has increased since the approval of the use of fluoroquinolones in poultry.

There is no dispute that the overall incidence of *Campylobacter* infections (*i.e.*, not specifically susceptible or resistant), measured as new cases per 100,000 per year in the United States, has declined in recent years. *See* section III.A.1. Based primarily on this trend, Bayer argues that "in absolute numbers, the U.S. population has experienced steadily decreasing fluoroquinolone-resistant *Campylobacter* infections since enrofloxacin's 1996 approval." Bayer Exceptions at 13. Bayer concludes: "If enrofloxacin were a substantial source of such infections, one would think that post-approval, the number of such infections would have increased, especially as poultry consumption has increased since 1996."[64] *Id.*

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[63] Bayer cites a study showing elevated *Campylobacter* infections among HIV-positive persons in the Los Angeles area in 1983-1987. Bayer Exceptions at 153; G-22 at 3. Bayer cites no evidence in the record linking this study with data on resistant *Campylobacter* infections pre- or post-approval.

[64] I note that Bayer cites to no evidence in the record that poultry consumption has significantly increased since 1996, despite its reference to these data. *See, e.g.*, Bayer Exceptions at 161, 190. There is evidence in the record that supports this assertion, however. *See, e.g.*, G-953 at 69 (chicken consumption data used in CVM risk assessment). Because I reject Bayer's effort to re-define the relevant risk, I do not address this point at length.

While an estimate[65] of the incidence of fluoroquinolone-resistant infections in the United States is possible, such an estimate cannot support a conclusion that there are significantly fewer new cases of fluoroquinolone-resistant *Campylobacter* infections each year than there were before approval of enrofloxacin.

Even if Bayer could support these statements, however, I reject its argument that "CVM lacks a reasonable basis to claim an increased risk and therefore fails to raise a serious question about enrofloxacin's safety." *Id.* at 156. First, even though the overall risk of *Campylobacter* infections has gone down since 1997 (which no party alleges is related to the approval in 1996 of enrofloxacin), the number of cases is still large and the risk that any *Campylobacter* infection that does occur will be resistant to fluoroquinolones has increased significantly since 1997. As discussed in this section, the record in this proceeding supports a finding that this increase in the proportion of fluoroquinolone-resistant *Campylobacter* infections is due in large part to the approval of enrofloxacin, and, as described later, I find that such infections are a significant public health concern. Although I find that there is an increasing risk over time that a case of campylobacteriosis will be resistant to treatment with a fluoroquinolone, I note that I need not base my decision to withdraw approval on a finding that the risk is increasing temporally: the relevant statutory question is whether the animal drug "has been shown to be safe," 21 U.S.C. § 360b(e)(1), which, as explained earlier, has been interpreted to require that CVM show that there are serious questions about the safety of enrofloxacin. Thus, even if the proportion of resistant infections were not increasing, or if the absolute number of resistant infections were to remain constant or to decline over time, this risk could still raise serious questions about the safety of enrofloxacin.

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[65] CVM witness Dr. Linda Tollefson acknowledged that the data suggest that the number of fluoroquinolone-resistant *Campylobacter* infections per 100,000 people in the United States had gone down between 1997 and 2001 for every year except 1999. Tr. at 143-144. Dr. Tollefson explained that the surveillance data on fluoroquinolone-resistant *Campylobacter* infections were prevalence data, not incidence data. Tr. at 129-137. To support its estimate of incidence, Bayer asked Tollefson to multiply the resistance rates estimated by CDC (*i.e.,* the proportion of all human *Campylobacter* isolates submitted by participating state health departments to CDC in a year that are fluoroquinolone-resistant) by the overall *Campylobacter* incidence rates per year. Tr. at 137-139. However, Dr. Tollefson was clear that while doing this calculation afforded an "approximation" of an incidence rate, she, "wouldn't call it an incidence rate, the problem being that FoodNet is an active surveillance system, that's more statistically robust, to get new cases of disease as they arise in the population. NARMS [the National Antimicrobial Resistance Monitoring System, is not." Tr. at 139. The words "good estimate" that Bayer attributes to Dr. Tollefson are actually those of Bayer's counsel. For example: "Q: So we could get a good estimate by your testimony, a good estimate of the number of fluoroquinolone resistant *Campylobacter* infections per 100,000 people by taking 14 percent of 21.4, couldn't we? A: Approximately, yeah." Tr. at 140. Dr. Tollefson qualified "good estimate" in her answer and in her testimony was otherwise clear about the limitations of such an estimate.

(ii) Data from other countries

The experience of a number of other nations has been similar to that of the United States: fluoroquinolone resistance in *Campylobacter* isolates from humans has increased following approval of fluoroquinolone use in poultry.[66]

Until the licensing and use of enrofloxacin in poultry in 1987 in the Netherlands, Revised Joint Stipulation 61, fluoroquinolone resistance was absent from poultry isolates, Endtz, G-1457 at 7; G-190. Resistance increased from 0% to 11% in humans and to 14% in poultry by 1989. *Id.* It is unlikely that human use of quinolones in the Netherlands was the source of most resistant infections in humans: before 1987, only norfloxacin was approved, for urinary tract infections, and it was used on a very small scale and most likely not used off-label. Endtz, G-1457 at 7-8. Ciprofloxacin was not introduced in the Netherlands for use in humans until October 1988. *Id.* at 7. Dr. Endtz testified that he and his colleagues concluded that fluoroquinolone resistance in *Campylobacter* from poultry must be the result of the use of fluoroquinolone drugs in animal husbandry and that it was "more probable that the use of enrofloxacin in poultry contributed significantly to the resistance problems in humans" than that the limited use in the Netherlands of fluoroquinolones in humans could have led to the development of resistant *Campylobacter* strains in humans. *Id.* at 8. Moreover, Dr. Endtz testified that he had reviewed the literature on the question in the intervening years (1991-2002) and that in his expert opinion the conclusions reached in his earlier research remained "sound and valid." *Id.* Research reported by Smith and colleagues found that in 1997 the proportion of human isolates in *Campylobacter* in the Netherlands that was resistant to fluoroquinolones had risen to 29%. G-586 at 2.

Spain saw a sharp increase in resistance following licensing of enrofloxacin. Endtz, G-1457 at 8; G-529; G-532; G-671; G-557; G-544. Before enrofloxacin was licensed for veterinary use there in 1990, Revised Joint Stipulation 63, the prevalence of fluoroquinolone resistance in human *Campylobacter* infections was 0% to 3%. Endtz, G-1457 at 8. In 1990, 9% of human isolates were resistant, and in 1991, 39% of isolates were resistant. G-586 at 2. In another study, Sanchez and colleagues found that ciprofloxacin resistance in human *Campylobacter* isolates jumped from 8.6% in 1990 to 50.7% in 1991. G-557 at 3. Similarly, Reina and colleagues found an increase in resistance to ciprofloxacin in *C. jejuni* isolates from a pediatric population from 2.3% in 1988 to 48.8% in 1993. G-532 at 1. Ruiz and colleagues found in tests of isolates from stool samples collected from outpatients with diarrhea at a Barcelona clinic that ciprofloxacin resistance rose from 47.5% of 55 *C. jejuni* isolates tested in 1991 to 88% of 76 *C. jejuni* isolates tested in 1994. G-586 at 2, *citing* G-544. Perez-Trallero and colleagues reported that in 1996 resistance to ciprofloxacin among human *Campylobacter*

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[66] As with the United States data, I find that the temporal evidence is strong despite the fact that human travel and import and export of food of animal origin inevitably result in human infections that did not originate within domestic borders. *See* Aarestrup, G-1451 at 2 ("[the] evolving resistant bacterial population does not respect traditional boundaries between countries. People travel and food of animal origin is traded worldwide. Thus, the development of resistance in any country is an impending problem for all countries.").

isolates collected in a city in Spain was at 81.6% (534/654 samples). G-734. Other support for this finding of a temporal link between the introduction of enrofloxacin in Spain and fluoroquinolone resistance in human isolates includes G-491, G-549, and G-671.

In the United Kingdom, enrofloxacin was registered for poultry use in November 1993 and ciprofloxacin was registered for human use in February 1987. Revised Joint Stipulation 65. Although fluoroquinolone resistance to *Campylobacter* in humans was first reported in 1991, resistance in the early 1990s remained low, at 1.9 to 4.1%, despite the use of ciprofloxacin in human medicine. Endtz, G-1457 at 8; G-77; G-240; G-407. In the early U.K. studies, the researchers associated fluoroquinolone resistance with either foreign travel or imported chicken. For example, Gaunt and Piddock reported that in 1991, 4.1% of 2209 *Campylobacter* isolates collected in a Public Health Laboratory were resistant to ciprofloxacin; of the 91 cases with resistant infections, none had taken a quinolone, but 33% (33/91) had traveled abroad, 16 of these to the Iberian peninsula, in the preceding three months. G-240 at 1. McIntyre and Lyons reported that in 1991, 1.9% of 311 *Campylobacter* isolates from fecal samples were ciprofloxacin-resistant, and of these 67% (4/6) were acquired abroad. G-407. During the first 11 months of 1992, the researchers found that of 347 *Campylobacter* isolates, 4.9% were ciprofloxacin resistant and of these only 35% (6/17) were acquired abroad. *Id.* As the authors noted, these findings suggest both a trend toward greater resistance in *Campylobacter* species and increasing acquisition of such infections within the U.K. itself. *Id.* *See also* Endtz, G-1457 at 8; G-634 at 2-3; G-1772.[67]

In contrast, nations that have not approved the veterinary use of fluoroquinolones have not experienced comparable increases in resistance among human *Campylobacter* isolates. In Australia, where fluoroquinolones are not registered for use in food-producing animals but are registered for use in humans, there are only "extremely" low

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[67] Bayer argues that Denmark's experience indicates that, in that country, enrofloxacin use in poultry was not followed by high resistance in humans and that this experience shows that poultry use is not responsible for resistance in humans. Bayer Exceptions at 166 ("Even as late as 2000, Denmark was reporting only 8 and 10% fluoroquinolone resistance in broiler chicken *C. jejuni* and *C. coli*, respectively. [G-151 P.25] In humans, fluoroquinolone resistance in domestically-acquired cases in Denmark was 22%. [G-151 P.27]."). However, G-151 does not support this assertion; rather it indicates that use of enrofloxacin in Denmark is limited and that resistance is linked to use, a fact Bayer acknowledged in an email admitted into evidence. B-454 ("Resistance rates in Denmark are low because relatively few [sic] Baytril is being used"); *see* Initial Decision at 53 n. 13. In G-151, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) noted that the use of fluoroquinolones in food animals increased marginally from 1999 to 2000 but was at "much lower levels" than in 1998, G-151 at 6; use of fluoroquinolones in humans exceeds the use in animals but also had declined, *id.* The report noted an increase in resistance in *C. jejuni* isolates from broilers. *Id.* at 7. Importantly, the report noted that "The high level of quinolone resistance in *C. jejuni* from domestically acquired cases of campylobacteriosis and a level of tetracycline resistance not seen in isolates from food animal reservoirs is an indication that there are reservoirs of *Campylobacter* infection not included in the DANMAP programme, probably imported poultry. The presence of quinolone resistance in about 25% of *Campylobacter* isolates is worrying because of the possible adverse implications for human health." *Id.*

levels of fluoroquinolone resistance in humans, and these levels are associated with foreign travel. Endtz, G-1457 at 8-9. Finland and Sweden also have low levels of fluoroquinolone-resistant *Campylobacter* among domestically acquired human infections. Hanninen, G-1458 at 3-4.

Bayer cites the data from Finland and Sweden as indicating the presence of fluoroquinolone resistance in *Campylobacter* before the approval of fluoroquinolones for human or animal use in those countries. Bayer Exceptions at 162-166. I find, however, that the research cited by Bayer and other evidence in the record support a finding that the levels of fluoroquinolone resistance in Finland and Sweden are largely explained by foreign travel, and that despite the role of foreign travel in the occurrence of resistant *Campylobacter* in these populations, this research supports the finding of an increase over time of fluoroquinolone resistance following introduction of fluoroquinolones into veterinary medicine. For example, in Finland, Rautelin and colleagues compared ciprofloxacin and other antimicrobial resistance in 102 human *Campylobacter* isolates collected from 1978-80 and 100 strains isolated in 1990. G-524. They found no ciprofloxacin-resistant strains in the early years and 9% resistance in 1990. The authors noted that "[n]one of the resistant strains were known for certain to be of domestic origin" and that the majority (80%) of all campylobacteriosis in Finland is acquired abroad. G-524 at 4. Other evidence in this case also shows a connection between fluoroquinolone-resistant infections in Finland and foreign travel. Hanninen, G-1458 at 3-4.

In the 1981 Swedish study cited by Bayer, Svedhem and colleagues obtained what they reported as *C. jejuni* isolates from patients at a hospital for infectious disease in Sweden and from chickens and tested them for susceptibility to various antimicrobials, including nalidixic acid. They found very high levels of resistance (39% in the poultry and 11% in humans). B-1851 at 3 (table). Because there is no information provided about the possible sources of this resistance (*e.g.*, whether it resulted from prior treatment or from some other mechanism), it is difficult to evaluate the significance or relevance of this study. Accordingly, I cannot give it much, if any, weight.

4. Microbiologic/molecular data

Microbiologic and molecular research[68] is used to evaluate whether bacterial strains in possible exposure sources and in human cases are related. Detecting the same types of bacteria in animals, food, and human patients is evidence of a "chain of transmission," although it does not by itself provide evidence about the direction of the transmission. Wegener, G-1483 at 16. Before reviewing some of the microbiologic research linking *Campylobacter* and fluoroquinolone-resistant *Campylobacter* in poultry with isolates from humans, I will briefly describe for each the laboratory techniques used in these investigations.

[68] The term "microbiologic data" refers to data that describe or characterize a bacterium or other microorganism and its properties. The term "molecular data" refers, in the context of microbiologic data, to information derived from a microorganism's genetic material (DNA or RNA).

Serotyping is a diagnostic test that classifies microorganisms such as bacteria by looking at the surface for antigens. Wegener, G-1483 at 16. Although serotyping is useful in distinguishing bacterial strains of public health importance, much of the data in this proceeding has been generated using genetic tools. Serotyping studies in the Netherlands in the late 1980s observed that the five most prevalent human serotypes of *Campylobacter* were also frequently found in isolates from poultry. Endtz, G-1457 at 5. A Danish study found a large overlap between the serotype distribution of human isolates and cattle and broiler isolates. G-459 at 10.

Diagnostic tests can also be based on the genetic makeup of the microorganism. Genetic methods look at the chromosome of the bacterium, in a manner similar to "genetic fingerprinting" used in forensic medicine. Wegener, G-1483 at 16. Bacteria generally contain a single chromosome of DNA. Differences in the order of the base constituents of the DNA, called nucleotides, allow for comparisons. Nachamkin, G-1470 at 7. Methods used to fingerprint bacteria include pulsed-field gel electrophoresis (PFGE), restriction-fragment length polymorphism (RFLP) or amplified fragment-length polymorphism (AFLP), ribotyping, multilocus sequence typing (MLST), and restriction end nuclease digestion analysis (REA). *Id.*; *see also* Wegener, G-1483 at 16. PFGE and RFLP analyses in particular have been widely used to study *C. jejuni*. Nachamkin, G-1470 at 8. Overall, Dr. Nachamkin testified that "[e]ach fingerprinting method has strengths and weaknesses, and are best used in combination, or interpreted in light of information taken from epidemiologic investigations." *Id.*

Dr. Wegener testified that typing for investigation of *Campylobacter* epidemiology is "not without problems." G-1483 at 17. One problem is that there are many different strains of *Campylobacter*. As a result, "when strains isolated from animals, food and humans are typed, most strains will appear as unique and different, with only a few identical strains from animals, food and humans." *Id.* Dr. Wegener explained that while the detection of identical types indicates that transmission takes place, detecting different strains does not rule out any particular source as a cause of illness. *Id.*

A number of studies from different countries have shown that *Campylobacter* from broiler chickens or turkeys and human patients in the same geographic location "can show a high degree of similarity or be identical as determined by their PFGE or AFLP." Wegener, G-1483 at 16; *see also* Nachamkin, G-1470 at 8; Besser, G-1455 at 10; Barrett, G-1453 at 6-7. Bayer argues that to the extent these studies were conducted outside of the United States, they provide no information about risk factors for campylobacteriosis in the United States. Bayer Exceptions at 178. I disagree. What the non-U.S. genetic subtyping studies show is that *Campylobacter* can be transmitted from poultry to humans. Wegener, G-1483 at 17.

There has also been research specifically focused on genetic subtyping of fluoroquinolone-resistant *Campylobacter*. Between 1996 and 1998, in Taiwan, Wu and colleagues collected 140 human and 75 poultry isolates of *Campylobacter* resistant to nalidixic acid and analyzed them by two molecular typing methods, PFGE and *flaA* RFLP (RFLP for the *flaA* gene). They found that 40% of the types of quinolone-resistant *Campylobacters* from human isolates were shared with types from isolates from poultry products. G-1775; Wegener, G-1483 at 17; Endtz, G-1457 at 5. The study concluded

that, in Taiwan, domestic poultry products were an important, but not the only, source of fluoroquinolone-resistant *Campylobacter* infections in humans. Wegener, G-1483 at 17.

In the study by Dr. Kirk Smith and his colleagues in Minnesota, 45 subtypes were identified among 269 human *C. jejuni* isolates from 1996-1997. Twelve of these subtypes were also identified among *C. jejuni* isolates from 13 positive chicken products. Of the 7 subtypes of quinolone-resistant *C. jejuni* recovered from retail chicken products, 6 were also identified among the quinolone-resistant *C. jejuni* isolates from humans. Smith, G-1473 at 13. This link between retail chicken products and human infections is even clearer when the human patients from just 1997 (the year retail products were collected) were examined, excluding those patients who took a quinolone before culture. Among that group of patients, 12 of 13 patients with domestically acquired quinolone-resistant *C. jejuni* had a subtype that was also found among quinolone-resistant strains acquired from the chicken products. Smith, G-1473 at 13. As Dr. Smith testified, "[t]he fact that identical subtypes/DNA fingerprints of quinolone-resistant *C. jejuni* were found in domestically acquired human cases and domestic retail chicken products is extremely strong evidence supporting chicken as a source of quinolone-resistant *C. jejuni* for humans in Minnesota." *Id.* at 13-14.

When this evidence is compared with typing of isolates from the comparison group (*i.e.*, the group of people that were also "cases," but with susceptible infections), it is even more compelling. The Smith study found that cases with domestically acquired resistant *C. jejuni* infections were 15 times more likely to have a *C. jejuni* subtype that was also found among resistant *C. jejuni* isolates from domestic chicken products than were cases with domestically acquired, quinolone-sensitive isolates. *Id.* at 14. The study also found that cases with domestically acquired resistant *C. jejuni* infections were 22.3 times more likely to have a *C. jejuni* subtype that was also found among resistant *C. jejuni* isolates from domestic chicken products than were patients with foreign travel-associated quinolone-sensitive isolates.[69] *Id.* It was Dr. Smith's expert opinion that these data strongly support a link between domestically acquired cases of quinolone-resistant *Campylobacter* infections and retail chicken products. *Id.* at 14.

Bayer criticized the use by Smith of PCR-RFLP of the *fla*A gene, arguing that it is "an older technique, of low discriminatory power...." Bayer Exceptions at 177.[70] Dr.

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[69] Possibly because of the small size of the populations included in this sub-analysis (13 resistant infections and 90 susceptible infections), these odds ratios are very uncertain [95% CIs are 1.9, 322 and 2.5, 508]. However, in both cases the results are statistically significant.

[70] The testimony of Dr. Irving Nachamkin, cited by Bayer in support of this argument, *see* Bayer Exceptions at 177-178, is not contrary to this evidence. Dr. Nachamkin testified that the usefulness of the *fla* typing arises from the fact that the gene is highly variable, and, as a result, it can be used to discriminate between strains. Nachamkin, G-1470 at 8. He testified that he believes "that RFLP analysis is a good typing method.... When two strains have different RFLP types, there is a high probability that the strains are indeed different. However, strains with similar RFLP types may or may not be similar, and often need to undergo additional 'subtyping' testing." *Id.* at 8 (citations omitted). I find Dr. Smith's data to be reliable despite the lack of more discerning subtyping, although the method used does affect the weight that I give the evidence. I note that the molecular analysis in the Smith study is only a small part of the

Smith testified that the subtyping method used provided a level of discrimination among the isolates that was appropriate for epidemiologic purposes. Indeed, the record indicates that if every single isolate was typed to the level of detail that each was unique, it would have no epidemiologic value. Smith, G-1473 at 14; Tr. at 556-57; Besser, G-1455 at 8. CVM witness Dr. Timothy J. Barrett testified that *fla*A-RFLP is adequately discriminating and had been used successfully in *C. jejuni* outbreak investigations and in measures to understand and control *Campylobacter* in poultry. Barrett, G-1453 at 5. Furthermore, Dr. Barrett testified that the primary problem with *fla* typing is that there is a potential for recombination with *fla* genes from other strains of *C. jejuni*. *Id.* at 7. However, if this recombination were to occur, it would be more likely to result in increased, rather than decreased, diversity; as a result, the Smith study likely under-identified common genotypes of ciprofloxacin-resistant *C. jejuni* in isolates from chicken samples and human patients. *Id.*

Bayer also argues that "Smith inappropriately relies only on genetic typing to try to establish the causal link." Bayer Exceptions at 176. This argument misrepresents the Smith study. The genetic typing does not stand alone in making a strong association between resistant infections in humans and chicken products. Rather, what Smith and his colleagues showed was: 1) a statistically significant increase from 1992 to 1998 in the percentage of *C. jejuni* isolates from humans that were resistant to quinolones, most but not all of which could be explained by foreign travel and the use by patients of quinolones before stool specimens were obtained; 2) a statistically significant increase between 1996 and 1998 in the proportion of human quinolone-resistant *C. jejuni* infections that were domestically acquired; and 3) a statistically significant association between resistant *C. jejuni* strains from chicken products and domestically acquired infections in Minnesota residents. *See* G-589. Only the third finding was derived from the use of genetic typing, and these data simply provide a level of external support, or validity, for the epidemiologic findings. Indeed, on cross-examination Dr. Smith denied considering the molecular evidence as establishing a causal link, explained that the molecular data was "one piece of evidence that has to be considered with everything else" in evaluating a causal link. Tr. at 537-38.

Next, Bayer argues that Dr. Smith should have, but did not, consider the possibility that there might be a "third source": *i.e.*, that the chicken and the humans both were exposed to fluoroquinolone-resistant *Campylobacter* through some common source. Bayer Exceptions at 181. Bayer does not provide any evidence that there is a common source, but suggests in a footnote, without citations, that the overlap between chicken and human isolates may be "due to common environmental sources, such as contaminated water." Bayer Exceptions at 181 n. 48. In the absence of any evidence supporting a shared source of infection, I disagree with the Initial Decision that there is such evidence. *See* Initial Decision at 48.[71] Dr. Smith explained in his cross-examination why, when he

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laboratory evidence in the record linking poultry and human *Campylobacter* isolates, and an even smaller part of the fuller body of scientific evidence in the record.

[71] The ALJ cites in support of this finding Tr. at 533-534, which is testimony by Dr. Smith that he did not look for such a common third source, and a discussion by Dr. Cox that "reverse causation" (man to chicken) or common third sources are possible, Cox, B-1901 at 27-28 (Att. 1).

found molecular evidence linking the retail chicken and humans, he did not then look into whether the chickens and humans were exposed to a common, third source. Tr. at 557-558 ("In my opinion, it's not likely at all that there's a common third sources. You have to kind of use common sense to go by what's logical -- that resistant *Campylobacter* is on the chicken and people are eating the chicken. So that's by far -- that's the most likely explanation. You don't necessarily need to be looking for some proposed third sources when a direct link is available.").

Bayer cites in particular to two relatively recent studies, one by Dickins and colleagues, G-1785,[72] and a second by Nadeau and colleagues, B-553.[73] These studies do not support, or even discuss, the possibility of the existence of a common source of *Campylobacter* exposure for both poultry and humans. What they show is that there is extensive genetic variability among *Campylobacter* and that contamination of poultry with multiple strains is common.

Bayer also argues generally that not all *Campylobacter* strains present on retail turkeys and chickens are capable of both colonizing humans and causing human illness. Bayer Exceptions at 186-87. Yet Bayer does not cite any evidence that supports its suggestion that a relevant proportion of *Campylobacter* isolates on poultry are incapable of causing human disease; rather, all of the data it cites support a finding that some proportion of the *Campylobacter* on poultry are capable of causing human illness.[74]

Because it was stricken, I am puzzled by the ALJ's reliance on Dr. Cox's testimony on this point. In any event, neither citation is sufficient to support Bayer's argument.

[72] Dickins and colleagues obtained 72 fresh chicken samples over a year and isolated *Campylobacter* strains from 82% of the carcasses. G-1785 at 2. Seventy strains were defined based on their PFGE pattern, and most (67%) of the carcasses from which *Campylobacter* species were isolated had more than one PFGE-distinguishable strain on them, with up to 6 strains found on a single carcass. *Id.* at 5. The authors concluded: "In summary, the data indicate extensive variability in the PFGE patterns of *Campylobacter* [species] isolated from humans and from poultry carcasses. The diversity of PFGE patterns is consistent with the fact that most cases of campylobacteriosis are sporadic and that the variation of PFGE patterns present on possible sources of infection (*e.g.*, retail poultry carcasses) makes traceback studies difficult. In spite of such difficulties, PFGE provides a useful tool for linking a particular strain of *Campylobacter* to its source." *Id.* at 5.

[73] Nadeau and colleagues sampled cecal material from several lots of broiler chickens in two slaughterhouses in Quebec to, among other things, evaluate using PFGE the genotypic diversity and the distribution of *Campylobacter* strains isolated from colonized broiler flocks; they also evaluated the relationship between isolates from poultry and sporadic human campylobacteriosis cases within a defined geographic region. B-553 at 1. They found 20% of the human isolates from sporadic infections were genetically and phenotypically related to poultry *Campylobacter* *Id.* at 5.

[74] The evidence cited by Bayer on this point is G-589, the Minnesota study by Smith and colleagues, in which molecular subtyping linked resistant *C. jejuni* strains from retail products with strains from domestically acquired human infections; G-1785, described in n. 72 above; and the testimony of Dr. Diane Newell, B-1908 at 35 (35-80% of the strain types found in poultry are the same as the types of strains recovered from humans with infection when techniques such as serotyping are used, but more discriminatory tests result in a lower proportion of matches

Finally, Bayer argues that if poultry were a major source of human *Campylobacter* infections, then *Campylobacter* isolates from retail poultry samples and from human stool samples would have comparable levels of resistance to erythromycin, Bayer Exceptions at 187, a macrolide antibiotic, Meng, G-1466 at 3. In support of this argument, Bayer compares the University of Maryland retail chicken data, in which *Campylobacter* isolates from 54% of sampled retail products were resistant to erythromycin, Meng, G-1466 at 3, with the NARMS data on human isolates, which has not reported erythromycin resistance of more than 3%, Bayer Exceptions at 187, citing Angulo, G-1452 at 74-79 (Att. 2). I agree with the ALJ that "Bayer has not shown the relevance and comparability between erythromycin-resistant and enrofloxacin-resistant *Campylobacter*." Initial Decision at 55. For example, there is no evidence in the record before me on the mechanisms by which *Campylobacter* acquire erythromycin resistance or the impact this resistance has on the bacteria. Nor is there any indication that these two sets of data can be compared in the manner suggested by Bayer. Bayer introduced no witness and identified no other evidence to demonstrate the scientific significance, if any, of its comparison of these two unrelated data sets with respect to the issues before me.[75]

In sum, I find that the microbiologic and molecular research supports the epidemiologic evidence that poultry is a primary source of human infection with *Campylobacter* and fluoroquinolone-resistant *Campylobacter*.

D. Impact of fluoroquinolone-resistant Campylobacter *infection on human health*

1. Risk to individuals of compromised treatment

Having found that the use of fluoroquinolones in poultry results in the selection of fluoroquinolone-resistant *Campylobacter*, and that poultry consumption is a primary means by which people are exposed to and made ill by such resistant bacteria, I now describe the evidence in the record demonstrating that human infections with fluoroquinolone-resistant *Campylobacter* have a greater potential to adversely affect human health than infections with fluoroquinolone-susceptible *Campylobacter*.

As described more fully in this section, I find there are three mechanisms by which resistant infections pose an increased health risk to people beyond the risks posed by *Campylobacter* infections generally. First, despite treatment with fluoroquinolones, fluoroquinolone-resistant infections result in a longer duration of illness, measured by the

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between human and poultry isolates). What these data show is that in general there is overlap between the strains of *Campylobacter* in poultry isolates and those found in human case isolates, but that the more discerning the genetic analysis, the less clear the match looks because of the variability among *Campylobacter* strains

[75] There is evidence that multiple antibiotic resistance occurs in *Campylobacter* (*i.e.*, that *Campylobacter* can be resistant to antimicrobials in different classes) and that such multiple drug resistance, especially when it involves fluoroquinolones and erythromycin, is of particular concern since it increases even further the risks associated with *Campylobacter* infections. *See* Meng, G-1466 at 4; G-1778; Logue, G-1464 at 6. I did not use the issue of multiple antibiotic resistance to support my conclusion that approval of enrofloxacin for use in poultry should be withdrawn.

participants as days of diarrhea. Second, as a consequence of prolonged illness, fluoroquinolone-resistant infections may result in increased incidence of serious complications of *Campylobacter* infection, such as reactive arthritis and GBS. Third, an increase in the prevalence of fluoroquinolone-resistant *Campylobacter* infections may lead practitioners to abandon the use of fluoroquinolones for the empiric treatment of enteric bacterial infections, despite the fact that no other empiric treatment is currently available; the resulting failure to treat at all or at least until the causal agent has been identified through laboratory analysis may lead to an increase in the proportion of cases that results in prolonged illness and complications. In so finding, I concur generally with the conclusions of the ALJ in this regard. *See* Initial Decision at 56-59, 65-68.

2. Duration of illness

The record shows that duration of illness, measured as duration of diarrhea, is significantly longer after treatment with fluoroquinolones in patients with fluoroquinolone-resistant *Campylobacter* infections than in patients with susceptible infections. Ohl, G-1485 at 14; Angulo, G-1452 at 108-131 (Att. 4); Smith, G-1473 at 20; G-589 at 5; Molbak, G-1468 at 19-20.

As part of their investigation of *Campylobacter* in Minnesota, Smith and colleagues recruited cases (successfully enrolling 130 of 135, or 96%) of Minnesota residents who had fluoroquinolone-resistant infections in 1996 and 1997, and matched them to a comparison group, composed of 260 Minnesota residents with fluoroquinolone-susceptible infections. Cases and comparisons were matched by age (within 10 years); residence in the same region of the state; and proximity with respect to date of stool collection. Smith, G-1473 at 5. Study participants answered a standardized questionnaire asking about risk factors including use of antibiotics, food consumption, contact with animals, travel history, and swimming.[76] *Id.* at 4. The 1996 data were collected retrospectively and the 1997 data were collected prospectively. Tr. at 505. Both foreign travel during the seven days before illness and use of a quinolone antibiotic before collection of the stool specimen[77] were significantly associated with resistant infections. Smith, G-1473 at 9. Smith and colleagues found that, among cases from 1997 who were treated with a fluoroquinolone after the collection of stool specimens, the duration of diarrhea was longer for 69 cases with quinolone-resistant *C. jejuni* infections

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[76] Although Dr. Smith and his colleagues asked study participants about consumption of foods, he testified that it turned out that a very high proportion of both the cases (quinolone-resistant infections) and comparisons (quinolone-sensitive infections) had eaten chicken. Tr. at 523-524. Dr. Smith explained that because both the case group and the comparison group had Campylobacter infections, and because poultry is an established risk factor for such infections, he would not expect to see a significant difference between the groups with respect to chicken consumption as a risk factor for infection. Tr. at 522-523, 534.

[77] Even where the infection is with a susceptible organism, treatment of the infection with a quinolone can result in passage of resistant bacteria in the stool because the bacteria can develop a resistance to the human quinolone used for treatment. Smith, G-1473 at 10. As a result, if this prior treatment is not controlled for by excluding these cases from analysis, the number of infections reported as resistant may be artificially inflated. Dr. Smith testified that this phenomenon could account for a maximum of 20% of resistant infections during 1996-1997.

(median, 10 days) than for 115 comparisons with quinolone-sensitive *C. jejuni* infections (median, 7 days), a difference that was statistically significant (p=0.03). *Id.* at 10; G-589 at 5.[78]

Nelson and colleagues used FoodNet data in a multivariate analysis to identify whether persons with ciprofloxacin-resistant *Campylobacter* infections had a longer duration of diarrhea than persons with ciprofloxacin-susceptible *Campylobacter* infections. Angulo, G-1452 at 108-131 (Att. 4).[79] They interviewed 2,093, or 52%, of the 4,025 cases with culture-confirmed *Campylobacter* infections in the FoodNet sites during the 12-month study period. *Id.* at 116 (Att. 4). Isolates were available and tested for susceptibility for 858 (41%) of the cases; of the isolates tested, 94 (11%) were resistant to ciprofloxacin. *Id.* Limiting the study population to exclude cases who reported not having diarrhea (15), cases who still had diarrhea at the time of the interview (68), and cases who could not estimate the duration of their diarrhea (35), a total of 740 cases were available for analysis; as with the larger group, 11% of these 740 cases had a ciprofloxacin-resistant infection. *Id.* at 117 (Att. 4). Most of the cases with culture-confirmed *Campylobacter* infections (83%) had taken an antimicrobial agent for their illness, and of those, 53% took fluoroquinolones. *Id.* at 116 (Att. 4). In the four weeks before illness, 173 (20%) had taken an antacid. *Id.* at 116-17 (Att. 4). Six percent (55 people) reported underlying conditions that could weaken their immune systems. *Id.* at 117 (Att. 4). Twelve percent (92 people) were hospitalized for a median of 3 days (range: 1-21 days). *Id.* Mean duration of diarrhea was 8 days for the 82 people with a ciprofloxacin-resistant infection and 7 days for the 658 people with a susceptible infection, but the difference was not significant (p=0.1). *Id.* Of the 740 cases, 421 (57%) did not take an antidiarrheal medication. *Id.* at 118 (Att. 4). In this sub-group of 421 cases, the mean duration of diarrhea was 9 days for the 39 cases with a ciprofloxacin-resistant infection and 7 days for the 382 cases with a ciprofloxacin-susceptible infection, a difference that was statistically significant (p=0.05). *Id.* Among the 128 persons who only took fluoroquinolones and no other antimicrobial agent or antidiarrheal medication, people with ciprofloxacin-resistant infections experienced a longer mean duration of diarrhea than people with ciprofloxacin-susceptible infections, but the difference was not statistically significant (8 versus 6 days, p=0.08). *Id.* at 118-19 (Att. 4).

Nelson and colleagues used the group of 858 cases in a statistical model that included use of an antimicrobial agent, use of an antidiarrheal medication, having an underlying medical condition, and age. *Id.* at 16, 119 (Att. 4). Controlling for those factors, they found that the mean duration of diarrhea in persons with ciprofloxacin-resistant infection was 9 days, and the mean duration of diarrhea in persons with a

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[78] Considering only the eighteen domestically acquired cases of campylobacteriosis in the Minnesota data set, the association between resistant infection and duration of diarrhea was not statistically significant. Tr. at 545. However, as discussed in the text, in an analysis of duration of diarrhea there is no reason to exclude *Campylobacter* infections associated with foreign travel.

[79] Angulo, G-1452 at 108-131 (Att. 4) is also in the record as G-1489. At the time of the hearing in this proceeding, this draft paper had not been accepted for publication. Tr. at 399.

ciprofloxacin-susceptible infection was 8 days (p=0.05).[80] *Id.* Among the 67 people who had not taken any antibiotic or antidiarrheal medication, resistant infections lasted 12 days and susceptible infections lasted 6 days, a difference that was statistically significant (p<0.01). *Id.* at 15, 118 (Att. 4); Tr. at 462-465.[81]

In sum, I find that the research by Nelson and colleagues shows that the duration of diarrhea is longer for infections with fluoroquinolone-resistant *Campylobacter* than for infections with fluoroquinolone-susceptible *Campylobacter* when the use of antidiarrheal medication and prior quinolone treatment is controlled for. While the statistical significance varied depending on the variables included in a particular analysis, this fact affects the weight of the evidence, not its admissibility. However, the trend in the direction of increased duration of illness associated with fluoroquinolone-resistant campylobacteriosis is clear. *See* Molbak, G-1468 at 19 ("Although the results from these studies are not all statistically significant, the estimates point in the same direction, and hence suggest that there is a longer duration of diarrhea in patients infected with resistant strains.").

Neimann and colleagues compared the duration of diarrhea in 41 cases with ciprofloxacin-resistant *Campylobacter* infections and 327 comparisons with susceptible infections. G-455; B-561 at 61, 151, 200.[82] They found that the median duration of illness in the fluoroquinolone-resistant cases who received fluoroquinolone or other unknown antibiotic treatment was 5 days longer (9 vs. 14 days) than the median duration

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[80] Bayer argues that the Nelson analysis is flawed because it did not account for source of infection, immune status of host, or prior use of fluoroquinolones. Bayer Exceptions at 111. I find no evidence in the record that the source of a resistant infection affects the duration of diarrhea. I also find that the Nelson statistical analysis did appropriately adjust for the medical condition of the study population. G-1489 at 12. Bayer's point about prior use of fluoroquinolones is that some of the resistant cases may be due to prior use by the case of a fluoroquinolone antibiotic (rather than poultry consumption) and that prior use may reflect poor health. Since medical conditions are controlled for in Nelson's analysis and since for purposes of evaluating the health impacts of resistant infections it is irrelevant how they are acquired, I also reject this argument. Finally, I do not agree with Bayer that Nelson's analysis constitutes "data dredging." Bayer Exceptions at 108. Nelson and her colleagues were careful to explain the rationale behind the exclusion and inclusion of data in their analyses.

[81] There are three other exhibits on which Nelson is the lead author. Two, G-780 and G-1367, are brief undated research abstracts. These abstracts appear to be duplicative of the data and analysis contained in the longer draft report. Angulo, G-1452 at 108-131 (Att.4). The third, G-1679, is Ms. Nelson's masters degree thesis. In her thesis, Ms. Nelson used a Cox proportional hazards model to evaluate differences between fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections. Dr. Angulo, who served as Ms. Nelson's advisor on the thesis, Tr. at 452, testified that the thesis reflected a "very naive analysis," *id.* at 454, the purpose of which was to see if the statistical method used would contribute to CDC's "understanding" of the data, *id.* Dr. Angulo testified that her analysis showed that the methodology was unhelpful and, as a result, CDC did not use the Cox proportional hazard model in further analyses of the data. Tr. at 454-455. I find that the evidence in the record does not support the reliance by any participant on this thesis.

[82] Exhibit G-455 is an abstract of a "poster" presented at a scientific workshop; Dr. Kare Molbak corrected the poster in his testimony. G-1468 at 19. Exhibit B-561 is Dr. Neimann's thesis.

of illness in the susceptible cases, but the difference was not statistically significant ($p=0.109$). G-455 at 1. While this result may, as Bayer suggests, Bayer Exceptions at 119, indicate that fluoroquinolone resistance does not affect duration of infection, it is equally or more likely that the study was too small to achieve statistical significance, or that the *Campylobacter* infections in the small study population were responsive to treatment with antibiotics other than fluoroquinolones.[83]

There is also limited research suggesting that resistant infections cause a longer period of diarrhea than susceptible infections even when there has been no treatment (of either group) with fluoroquinolones, which suggests that resistance may result in more virulent infection. Angulo, G-1452 at 16 (citing research on severity of illness associated with fluoroquinolone-resistant *Salmonella*). Nelson and colleagues examined a small subgroup of their overall population that had taken no antimicrobial drug or other medication, and found, comparing the experience of 6 patients with fluoroquinolone-resistant *Campylobacter* infections with that of 61 patients with susceptible infections, that the mean duration of diarrhea was 12 days in cases with resistant infections versus 6 days in cases with susceptible infections. Angulo, G-1452 at 118 (Att. 4). This difference was statistically significant ($p<0.01$). *Id.*

In conclusion, the Nelson, Smith, and Neimann research shows that people infected with *Campylobacter* are commonly treated with fluoroquinolones, and that among persons with campylobacteriosis treated with fluoroquinolones, those people with ciprofloxacin-resistant infections had a longer duration of diarrhea than those people with susceptible infections, even when other factors affecting duration of diarrhea were taken into account, such as use of antidiarrheal medication, underlying medical condition, and age. *See* Angulo, G-1452 at 16. This evidence is sufficient to provide further support for my conclusion that CVM has shown by a preponderance of the evidence that there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred.

a. Foreign travel

Researchers estimate that in the United States about 5-10% of *Campylobacter* infections are associated with foreign travel. Endtz, G-1457 at 4, and references cited therein. As a result, foreign travel is identified as a risk factor in many studies. *E.g.*, Angulo, G-1452 at 10 (in Friedman study, about 12% of the sporadic cases of campylobacteriosis due to travel outside of the United States). However, I believe that it is more accurate to say that these are foreign-acquired infections associated with foodborne and other exposures, since there is no evidence that anything about the act of traveling itself results in infection. *See* Tr. at 45.

Because of the risk that *Campylobacter* infections acquired in certain regions of the world may be resistant to fluoroquinolones, *see, e.g.*, G-586 at 4-5, researchers who are focused on identifying domestic sources of resistant infections need to take steps to exclude people with a recent history of foreign travel from their analyses. *See, e.g.*, G-589. However, researchers investigating whether *Campylobacter* infections that are

[83] The participants do not dispute that *Campylobacter* infections respond to treatment with other non-fluoroquinolone antibiotics. *See* discussion at section III.A.3 above.

resistant to fluoroquinolone treatment result in longer illnesses than infections that are susceptible to such treatment would need to exclude cases (and comparisons) with a recent history of foreign travel from the analysis only if foreign-acquired *Campylobacter* infections are materially different from domestically acquired infections. Bayer is adamant that foreign travel is a "confounder" in the association between resistance of *Campylobacter* infection and duration of diarrhea. *E.g.*, Bayer Exceptions at 83. I disagree. There is no reason to exclude foreign travel from the analyses comparing the duration of fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* illnesses, because foreign travel is not a "confounder" as that term is generally used by epidemiologists. *See* Tr. at 462-463.

In epidemiologic studies, confounding occurs when a third variable is independently associated with both the exposure of interest and the disease or health outcome of interest. Tr. at 35-38 and 284-285; Feldman, B-1902 at 147 (Att. 1); B-1935 at 21-23; Last at 35 (definitions of "confounding" and "confounding variable"). For example, although twice as many people per 100,000 residents died in Arizona than in Alaska in 1988, one cannot conclude that Arizona is a more dangerous part of the country. Rather, age is a confounding variable in the association between state of residence and mortality, because age is associated with increased risk of death, and it is also associated with residence, since Arizona's population is older than Alaska's. Feldman, B-1902, at 147-148 (Att. 1).[84]

The researchers who have investigated the impact of resistance on duration of diarrhea have appropriately evaluated their data to determine whether foreign travel was a confounder, and have determined that it was not. For example, Smith and colleagues found that foreign travel was not significantly associated with duration of diarrhea in an analysis looking only at whether length of diarrhea was significantly associated with international travel, without controlling for other variables. Tr. at 559. Similarly, in their analysis of FoodNet data, Nelson and colleagues found that when use of antidiarrheal medication was included in multivariate analysis, international travel was not associated with the outcome. Tr. at 462-463, 466. Regardless of whether foreign travel is a confounder or whether it otherwise modifies the effect of an association between two or

[84] Bayer's expert supplied this example and Bayer agreed with this definition of confounding, Bayer Exceptions at 93, 94 n. 19, yet its attorneys and experts repeatedly misstate it, *see, e.g.*, Bayer Exceptions at 29 ("In scientific terms, the alternative cause is known as a 'confounder' or a 'confounding factor'"); Tr. at 35 ("Q: Would you agree that confounding is the distortion of an exposure/disease association by the effect of some third factor?"); Feldman, B-1902 at 8 (a third factor may be a confounder if it distorts the exposure/disease relationship and is independently associated with the outcome or the exposure). As Dr. Tollefson's testimony makes clear, there must be independent association with both disease and exposure for confounding. Tr. at 35-38. Neither is Bayer correct in its assertion that a practical way to identify a confounder is to see whether its removal changes the results of an analysis. Bayer Exceptions at 94. While that may be one way to deal with a confounder, *see* Feldman, B-1908 at 157 (Att. 1), adjustments may be necessary for any third variable that affects the interpretation of an association between a risk factor and an outcome, even if the variable is not itself associated with the risk factor and thus is not a confounder, *see* Tr. at 45; Feldman, B-1908 at 149 (Att. 1) (discussion of effect modification).

more variables, stratifying the data by the variable or otherwise controlling for it is an appropriate way to evaluate whether it has a significant impact on the estimation of the effect. Feldman, B-1908 at 147-149 (Att. 1); Last at 52 (definition of "effect modifier" and 35 (definition of "confounding variable").

In support of its argument that duration of diarrhea is not different between fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections, and that foreign travel is a confounder in the association between fluoroquinolone-resistant *Campylobacter* infections and duration of disease, Bayer largely relies on testimony by Dr. Gregory A. Burkhart, B-1900, and, to a lesser extent, testimony by Dr. Roger A. Feldman, B-1902, that reports on re-analysis of data underlying research relied on by CVM. *See, e.g.,* Bayer Exceptions at 83, 85-87, 94-97, 99-100, 105-109, 116. However, for the reasons discussed below, these re-analyses lack transparency and reliability, and are thus entitled to little, if any, weight.

Dr. Burkhart obtained and re-analyzed the dataset reflected in Dr. Smith's testimony and publication, G-1463, G-589, as well as the FoodNet case-control data analyzed by Drs. Friedman and Kassenborg and their colleagues, Angulo, G-1452 at 79 (Att. 3); G-337. Burkhart, B-1900 at 16-22, 24-40. Dr. Feldman also obtained data and re-analyzed the FoodNet data, as well as the data underlying the thesis of Dr. Neimann, G-561, Feldman, B-1902 at 4-5, 36-39. I find that these re-analyses by Drs. Burkhart and Feldman fail to include information that is critical to understanding and evaluating their reported results. For example, Dr. Feldman references the Kassenborg study but reports that in his re-analysis of the data from that study he eliminated an unidentified number of cases and that his analysis of the remaining data revealed no statistically significant difference in duration of diarrhea. *Id.* at 37. Since Dr. Kassenborg did not analyze duration of diarrhea in her analysis, *see* Kassenborg, G-1460 at 3; Burkhart, B-1900 at 25 ("Kassenborg does not appear to have conducted an analysis of the morbidity question"), this is not a refutation of Dr. Kassenborg's analysis, but rather a new use of these data, without sufficient information to evaluate the reliability of the new analysis. For example, the testimony does not make clear how Dr. Feldman dealt with cases in the FoodNet dataset who reported having diarrhea at the time of the interview or who could not recall the duration of their diarrhea; this information is necessary to evaluate whether lack of complete information on duration of diarrhea affected (created a bias in) the estimate of duration of illness. Feldman, B-1902 at 37. Nor is any information provided about Dr. Feldman's analytic methods with respect to the Kassenborg or Smith datasets. Feldman, B-1902 at 37-39.

Dr. Burkhart's testimony concerning his re-analysis is more detailed than that of Dr. Feldman, but it also suffers from flaws. He states that in analyzing the FoodNet data he used "[u]nconditional logistic regression for adjustment," Burkhart, B-1900 at 33, but he does not specify the analysis or the variables adjusted for. Since the outcome of interest is a continuous variable, it is not clear how a logistic regression would be appropriate (since those are used for binary outcome variables such as high/low, where there are only two possible outcomes). Neither Dr. Burkhart nor Dr. Feldman consistently reports statistical significance, and when it is mentioned there is often no measure of significance (*e.g.*, p-value or confidence interval). *See, e.g.*, Burkhart, B-1900 at 33-40; Feldman, B-1902 at 38. Such reporting is basic to evaluating the strength

of a reported association between an exposure and an outcome. Thus, the testimony of these two witnesses does not provide a sufficient basis on which I can conclude that flaws in the Smith and FoodNet analyses are such that the evidence on duration of diarrhea is unreliable.

Bayer's reliance on G-1772 as additional support for its position that foreign travel is a confounder is misplaced. *See* Bayer Exceptions at 87, 95, 101, 118-19. G-1772 is a report by a group referred to as the "*Campylobacter* Sentinel Surveillance Scheme Collaborators," based on surveillance in England and Wales, on risk factors for acquisition of ciprofloxacin-resistant *Campylobacter* infections. G-1772 at 1-2. That study found, in keeping with the FoodNet and Smith studies discussed above, that the risk of acquiring a resistant *Campylobacter* infection was strongly associated with foreign travel. *Id.* at 3-4. This paper reports on analyses of data within two distinct groups: cases associated with foreign travel, and domestically acquired cases. First, the researchers found that, among the cases associated with foreign travel, there was no difference between cases infected with ciprofloxacin-resistant strains of *C. jejuni* and cases infected with strains sensitive to all antimicrobials with respect to mean length of illness (12.7 days versus 13.5 days, p=0.56) or admission to hospital (both 6%, p=0.9). G-1772 at 3. Separately, the researchers found that, among the domestically acquired cases, there was no difference between ciprofloxacin-resistant *C. jejuni* infections and those infected with *Campylobacter* susceptible to all antimicrobials (mean length of illness 11.8 versus 11.2 days, p=0.66) or admission to hospital (14% versus 12%, p=0.39). G-1772 at 4. The researchers did not themselves compare the duration of illness in travel-associated fluoroquinolone-resistant cases and domestically acquired fluoroquinolone-resistant cases and they did not provide sufficient information for a reader to do so. While it may be tempting to pull data from within these two separate analyses and compare them, it is not appropriate to do so. Without identifying and controlling for the effect of antidiarrheal medication or antibiotics, for example, and without understanding what between-group difference would be statistically significant, no reliance can be placed on the apparent facial difference between these two groups of cases with respect to duration of illness.

Bayer also argues that people with resistant infections and foreign travel-acquired infections experience longer infections because they wait longer to seek treatment. Bayer Exceptions at 106-107. Bayer bases this argument on Dr. Burkhart's re-analysis of FoodNet data, and in particular his discussion about the questionnaire used in collecting those data. Burkhart, B-1900 at 34. However, although Dr. Burkhart reports that "[t]he questionnaire asked for the total days of diarrhea, the total days of illness before the doctor visit and total days of illness after the doctor visit," *id.*, the actual questionnaire, which is included as Appendix A to Ms. Nelson's thesis (G-1679 at 102-140) does not ask for this information. Dr. Burkhart's conclusion that "resistant cases tended to have longer illnesses before the first doctor visit and that foreign travel seemed to be associated with more diarrhea and illness," Burkhart, B-1900 at 34, was based on the responses to these non-existent questions. As a result, the record does not support Bayer's assertions that on average, resistant cases in the dataset "sought treatment later,"

Bayer Exceptions at 131, and that people who acquired infections during foreign travel wait longer to seek medical help, Bayer Exceptions at 97.[85]

Finally, I also agree with the ALJ that there is no evidence that fluoroquinolone-resistant *Campylobacter* infections acquired abroad are more virulent than domestically acquired fluoroquinolone-resistant *Campylobacter* infections. Initial Decision at 58. Bayer's argument is that "unless the domestic and foreign-acquired strains of *Campylobacter* are identical, a near impossible occurrence given the wide diversity in *Campylobacter* [G-444, P.52, P.369, P.532], the domestically acquired infecting strain may express itself differently regardless of whether the resistance develops by cell division or is plasmid mediated." Bayer Exceptions at 90-91. This is pure speculation, however. Bayer cites no evidence that fluoroquinolone-resistant *Campylobacter* from the same species, isolated in different geographic locations, express themselves differently in any way relevant to the human health impacts of exposure.

I find that foreign travel is not a confounder in the association between fluoroquinolone-resistant *Campylobacter* infections and duration of illness. I find that research that includes persons whose infections may have been acquired internationally is relevant to understanding this relationship, as long as important variables such as use of antidiarrheal medications are factored into the analysis. I find that the evidence relied on by CVM appropriately evaluated the role of foreign travel and appropriately handled the possible impact that variables such as use of medications and age might have on duration of diarrhea in cases of fluoroquinolone-resistant infections. Accordingly, as set out above, I find that a preponderance of the evidence shows that many people infected with *Campylobacter* are treated with fluoroquinolones, and that, among those persons with campylobacteriosis treated with fluoroquinolones, those people with fluoroquinolone-resistant infections are more likely to experience a longer illness (measured as days of diarrhea) than people with fluoroquinolone-susceptible infections when other factors that can influence the length of diarrhea (such as medication use) are controlled for.

3. Risk of complications

There is limited evidence that at least some of the more serious complications of *Campylobacter* infections are associated with longer duration of illness. While the evidence is not definitive and further research is needed, CVM witness Dr. Robert Tauxe testified that it suggests that, because antibiotic treatment may shorten the duration of illness, such treatment could prevent some complications of *Campylobacter* infections by

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[85] There are two other pieces of evidence in the record that provide some limited evidence contrary to Bayer's argument. First, as noted above, the FoodNet dataset included a group of 67 people who did not take *any* antidiarrheal or antimicrobial medication, and in this group there was a marked and statistically significant difference in duration of illness that cannot be explained by delayed treatment. Angulo, G-1452 at 118 (Att. 4). Second, in the *Campylobacter* Sentinel Surveillance study, 6% of all foreign-travel associated campylobacteriosis cases (*i.e.*, fluoroquinolone-resistant and -susceptible) were hospitalized, while a larger proportion (12-14%) of the domestically acquired cases were hospitalized, G-1772 at 3-4. While, as noted above, because of the likely impact that medication had on duration of illness, these data cannot be relied on to support a finding that domestically acquired cases cause more serious illness than travel-associated cases, they do undermine the argument that the converse is true.

decreasing the risk that the infection could trigger an adverse immune system response. Tauxe, G-1475 at 4. Thus, treatment failure may result not only in longer duration of diarrhea, but also in increased risk of serious complications. *Id.*

Neal and Wright described the results of a mailed questionnaire sent to people with culture-confirmed foodborne infections from October 1999 to June 2000. *Id.* at 50 Neal Att. Of the 268 responses from people with confirmed *Campylobacter* infections, 34 reported reactive arthritis-like symptoms. *Id.* As compared to short duration of illness (0-4 days), risk was significantly linked to the severity of the initial illness (> 15 days). *Id.* Because the record contains only an abstract of the Neal and Wright research, *id.*, and because it reports on preliminary and unpublished data, and does not provide information about certain aspects of the study design, including definitions of terms, *see* Tauxe, G-1475 at 4, I give this research very limited weight. However, contrary to Bayer's argument, *see* Bayer Exceptions at 128-129, I find that the Neal abstract was not the sole basis for Dr. Tauxe's testimony that, because it may shorten the duration of illness, antibiotic treatment could prevent some complications of *Campylobacter* infections by decreasing the risk of triggering an adverse immune system response. Tauxe, G-1475 at 4. Dr. Tauxe is a recognized expert in his field, and he himself testified that the Neal study findings needed to be "fully published and confirmed." *Id.* However, he also testified that, in his expert opinion, the Neal data, combined with other data on complications of *Campylobacter* infections, suggested to him that effective antibiotic treatment could help prevent some complications by shortening the duration of illness and thus decreasing the stimulation of the immune system. Tauxe, G-1475 at 4.

I find that this limited evidence on increased risk of complications is sufficient to raise serious questions about the safety of enrofloxacin, especially when combined with other data on duration of illness.

4. Rates of treatment failure

To counter CVM's evidence, described above, that people with fluoroquinolone-resistant *Campylobacter* infections who are treated with fluoroquinolones experience a longer duration of illness than do people with fluoroquinolone-susceptible infections, Bayer argues that rates of treatment failures are similar with respect to fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections. Bayer provides very little evidence to support this assertion. Exhibit B-50, relied on by Bayer in support of this argument, is an abstract in which Dr. Laura J.V. Piddock noted that "[p]reliminary data showed that only 1/39 patients with ciprofloxacin-resistant *Campylobacter* enteritis did not respond to ciprofloxacin therapy, suggesting that many bacteria classified as resistant by laboratory tests may nevertheless be amenable to antimicrobial therapy." *Id.* at 2. Because it is not clear whose research Dr. Piddock is describing (the abstract mentions a number of studies) or what the clinical significance it has, if any, *id.*, because it is preliminary, and because there is only sketchy information about the data, I give very little weight to this exhibit.[86]

[86] Dr Piddock followed the quoted statement, and concluded the abstract, as follows: "However, the clinical relevance of these data are [sic] unclear as enteric infections are rarely treated with antibiotics due to their self-resolving nature. In conclusion, exposure to antibiotics gives rise to antibiotic-resistant bacteria, and any use of antimicrobials will allow such strains to proliferate,

Bayer also cites B-1920, a "cross sectional observational study" of 22 patients in Thailand with fluoroquinolone-resistant *Campylobacter* infections, 19 of whom were treated with ciprofloxacin. B-1920 at 1. Of the 19 treated patients, 11 (58%) "achieved a cure," defined as resolution of diarrhea within 72 hours of initiating therapy. B-1920 at 4. Assuming three patients lost to follow-up also meet the study criteria for a cure, the proportion of this small group that recovered within 72 hours was 75%. While this seems high, there was no control or relevant comparison group[87] and there is no information about the point in the course of illness at which the patients sought treatment; as a result, there is no way of knowing which of the cases achieved a cure despite ineffective ciprofloxacin treatment. Indeed, underscoring the difficulty of drawing conclusions from this research in the absence of a control or comparison group, the authors noted that the overall cure rate was lower than that found in early studies in which a smaller proportion of the *Campylobacter* isolates were fluoroquinolone-resistant. *Id.* at 4-5.[88]

5. Loss of empiric treatment

I also find that, as fluoroquinolone resistance increases, the value of fluoroquinolones as an empiric treatment of severe enteric infections, described in section III.A.3 above, will be compromised. The only treatment guidelines in the record recommend empiric treatment with fluoroquinolones, G-244 at 3,[89] and it is well-established in the record that if *Campylobacter* infections are treated, they are commonly treated without obtaining stool culture confirming the nature of the bacterial infection. *See* section III.A.3, above. The evidence shows that, because of the length of time it takes to identify *Campylobacter* in a stool sample, and then to document resistance (if

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many of which will cause difficulties in treating infections in man. Any reduction in antibiotic use in any environment will have beneficial effects upon reducing the incidence of antibiotic resistance." B-50 at 2.

[87] A comparison population was used "to assess the significance of microbiologic findings," made up of persons reporting to medical units for complaints other than diarrhea or fevers. B-1920 at 1. Exclusion criteria included diarrhea, fevers, or use of microbials other than malaria prophylaxis in the previous week. *Id.* The researchers did not attempt to match this group with the case group. *Id.* Thus, this comparison group is not relevant to the findings for which Bayer relies on this study.

[88] A third study cited by Bayer (G-354) was designed to evaluate the efficacy of azithromycin as an alternative to ciprofloxacin when treating fluoroquinolone-resistant *Campylobacter* infections in Thailand and it does not shed much light on the issues in this proceeding. Defining clinical failure as continued diarrhea more than 72 hours after initiation of treatment, 5% of the ciprofloxacin group (2/37) experienced clinical failure, and 1 of these failures had a resistant infection. *Id.* at 3. The authors noted that "[c]iprofloxacin was effective in eradicating Campylobacter species from all nine patients infected with susceptible strains but was not effective in eradicating resistant strains." G-354 at 4-5. Among 14 patients infected only with *Campylobacter* species who were treated with ciprofloxacin, 4/7 (57%) with susceptible isolates recovered by 48 hours, compared with 2/7 (29%) with resistant isolates (p=0.2), and the mean duration of illness was also longer (48.3 hours vs. 59.6 hours) but not statistically significant (p=0.8). *Id.* at 3.

[89] Bayer cites guidelines published by the Infectious Disease Society of America (IDSA). Bayer Exceptions at 143. These guidelines are not part of the record.

resistance testing is done at all), it would take about a week to know whether a particular infection is resistant to fluoroquinolones. Thielman, G-1477 at 4. During that time, the illness may well resolve on its own. However, as noted in section III.A.3, it may also progress with complications, particularly in immunocompromised patients. Thielman, G-1477 at 4-5 ("Failure of *Campylobacter* infections to respond to a fluoroquinolone antibiotic can be devastating; not only may the illness be prolonged, but patients may then be prone to further complications, including death."). Similarly, Dr. Endtz testified that "with the introduction of quinolone resistance in *Campylobacter* species[,] empirical treatment of patients with quinolones may result in treatment failures." Endtz, G-1457 at 7, *citing* G-589. He explained that, "with increasing levels of fluoroquinolone resistance, empirical treatment with these drugs will become hazardous. Most patients with *Campylobacter* diarrhea are not hospitalized and one has therefore to rely on oral drugs. No other oral drug with comparable activities and toxicity profile is currently available as an alternative to treatment." *Id.*

Bayer argues that there is a new, commercially available test allowing for identification of *Campylobacter* within hours, thus making empiric, and possibly ineffective, treatment unnecessary. Iannini, B-1905 at 6. However, the evidence about this test is insufficient to show that this test is available, in use, and accurate, and thus insufficient to refute the evidence before me that the effectiveness of fluoroquinolones as an empiric treatment for *Campylobacter* infections is reduced by the increasing proportion of such infections that is resistant to fluoroquinolones.

I also reject Bayer's argument that, in weighing the safety of enrofloxacin, I should consider "the mild nature of most campylobacteriosis, with only very rare occurrences of potentially serious complications." Bayer Exceptions at 80.[90] Even assuming to be correct Bayer's rough calculation that only about 9% of campylobacteriosis patients are treated with fluoroquinolones, or "less than 0.05% of the U.S. population," this estimate leaves many people at risk each year of ineffective empiric treatment, putting them at greater risk both of duration of illness and of complications associated with longer illness.[91]

Having found that the use of fluoroquinolones in poultry results in the selection of fluoroquinolone-resistant *Campylobacter*, and that poultry handling and consumption are primary routes of human exposure to and illness from fluoroquinolone-resistant *Campylobacter*, I also find that the record demonstrates that human infection with resistant *Campylobacter* pose an increased health risk to people beyond the risks posed by *Campylobacter* infections generally, because: 1) despite treatment with fluoroquinolones, fluoroquinolone-resistant infections result in a longer duration of illness, measured by the participants as days of diarrhea; 2) as a consequence of prolonged illness, fluoroquinolone-resistant infections may result in increased incidence of serious complications of *Campylobacter* infection, such as reactive arthritis and GBS;

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[90] Bayer also appears to be suggesting that additional days of diarrheal illness should not be considered harm. Bayer Exceptions at 80. I disagree. *See Olestra Final Rule (Olestra),* 61 Fed. Reg. 3118, 3158 (1996).

[91] This calculation uses, as does Bayer, 1999 Census data reporting the U.S. population at 272,690,813. Bayer Exceptions at 143; G-953 at 26.

and 3) an increase in the prevalence of fluoroquinolone-resistant *Campylobacter* infections may lead practitioners to abandon the use of fluoroquinolones for the empiric treatment of enteric bacterial infections, which may lead to an increase in the proportion of cases that results in prolonged illness and complications.

6. Estimation of public health impact: CVM's risk assessment

CVM introduced into evidence a quantitative assessment of the human health impact of fluoroquinolone-resistant *Campylobacter* infections attributed to the consumption of contaminated chicken. G-953; Vose, G-1480. The question the risk assessment addresses was whether the use of fluoroquinolones in poultry introduced a significant human health burden associated with a specific prevalence of fluoroquinolone resistance in poultry carcasses, and, if so, whether any action by CVM would significantly reduce that burden. Vose, G-1480 at 5. Using the risk assessment model, CVM estimated that in 1998 about 8,678 people (95% CI 4,758-14,369) and in 1999 about 9,261 people (95% CI 5,227-15,326) were expected to be infected with fluoroquinolone-resistant *Campylobacter* from consuming chicken, receive fluoroquinolone treatment, and experience a longer duration of illness because of the decreased effectiveness of the antibiotic. G-953 at 64; 15-16.

I concur with the ALJ that "[o]verall, the CVM Risk Assessment is reliable and presents valuable information regarding poultry as a major source of fluoroquinolone-resistant campylobacteriosis." Initial Decision at 41.[92] In this section, I describe CVM's risk assessment and address Bayer's numerous challenges to its reliability.

a. CVM's methodology

A risk assessment is a decision-support tool that uses observations about what is known to make predictions about what is not known. Vose, G-1480 at 2. As Dr. Vose noted (quoting from the Society for Risk Analysis Principles for Risk Analysis), "'[b]ecause decisions about risks are usually needed when knowledge is incomplete, risk analysts rely on informed judgment and on models reflecting plausible interpretations of the realities of Nature,'" making sure to assess and disclose the basis for such judgments and to identify uncertainties. *Id.*

The foundation of the CVM risk assessment is a mathematical model that relates epidemiologic surveillance data on annual, culture-confirmed *Campylobacter* illnesses and per capita chicken consumption data to generate estimates of human health risk. The model estimated separately for the years 1998 and 1999: 1) the probability that a person would be affected by the risk in question for various U.S. subpopulations; 2) the nominal

[92] Bayer argues that because the risk assessment was developed to "'relate[ ] the prevalence of fluoroquinolone-resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone resistant *Campylobacter* in chickens,'" G-953 at 6, and because of assumptions made in the model, the Initial Decision "*assumes*, but does not show, that poultry is a source of fluoroquinolone-resistant campylobacteriosis." Bayer Exceptions at 189. A fair reading of the Initial Decision makes clear that the ALJ understood the purpose and methodology of the risk assessment. The use of the vague term "regarding poultry as a major source" likely reflects the use of the same phrase in the caption to the section under which this discussion falls. *See* Initial Decision at 24.

mean number of *Campylobacter* cases in the U.S. population; 3) the nominal mean number of fluoroquinolone-resistant *Campylobacter* illnesses attributable to chicken; 4) the nominal mean number of fluoroquinolone-resistant *Campylobacter* infections attributed to chicken consumption that were treated with fluoroquinolones; and 5) total consumption (in pounds) of boneless, domestically reared chicken contaminated at slaughter with fluoroquinolone-resistant *Campylobacter* in the United States. G-953 at 12.

CVM stated in the risk assessment that it had adopted an innovative approach in its model, rather than following the steps of a microbial food safety risk assessment. G-953 at 8. In the final risk assessment, CVM explained its approach and described advantages and disadvantages of its chosen method. *Id.* at 8-10. Notwithstanding the novelty of CVM's general approach, the CVM risk assessment model employs mathematical and statistical methods commonly used in the risk assessment field. Much of the model uses statistical distributions to capture and communicate the uncertainty of model parameters.

CVM's risk assessment calculated two values referred to as "K" values. These values are defined as "the probability that a pound of *Campylobacter*-contaminated chicken meat (in general, and resistant) will result in a case of campylobacteriosis (in general and resistant)." G-953 at 12. The first parameter is calculated by dividing the nominal mean number of *Campylobacter* cases attributable to chicken by the estimated amount of *Campylobacter*-contaminated chicken meat consumed; the second parameter is the subset of the nominal mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken by the estimated amount of fluoroquinolone-resistant *Campylobacter*-contaminated chicken meat consumed. *Id.* at 13. The model assumes that the distribution of the total number of *Campylobacter* on carcasses is the same for both resistant and susceptible bacteria, and also assumes that resistant and susceptible *Campylobacter* have similar survivability and virulence. G-953 at 12-13. The risk assessment notes that the model likely underestimates the probability of resistant human illness because, among other possible reasons, it used unweighted analysis of NARMS chicken isolate test results, and because, if a sampled carcass had both fluoroquinolone-susceptible and fluoroquinolone-resistant bacteria present, the isolate selected from a culture dish might be susceptible, although a large proportion of the bacteria on the carcass itself were, in fact, fluoroquinolone-resistant. G-953 at 13.

The CVM risk assessment contains a sensitivity analysis that evaluated the effect that varying the numerical value of a parameter within the probable range would have on the final risk estimate. G-953 at 84. Sensitivity analysis is useful for identifying those parameters with the greatest influence on risk and those sections of the assessment in which additional information or research would decrease uncertainty and thereby improve the risk estimate. CVM concluded that there was more combined uncertainty associated with human health variables than with respect to variables representing chickens. To clarify, for example, the probability that a stool sample would be collected from patients with non-bloody diarrhea, and probability of a confirmed culture are both human health variables; prevalence of fluoroquinolone-resistant *Campylobacter* on chicken carcasses is a chicken variable. *Id.* at 84-89.

CVM states that one of its goals was that the risk assessment be "transparent." G-953 at 8. In furtherance of this goal, CVM highlighted critical assumptions, detailed the mathematical equations and relationships in the model, described and referenced the data used, and in discussion sections within the document, articulated the limitations of some of the data used for certain parameters. G-953 at 102-106 (App. B); Vose, G-1480 at 15.

The risk assessment was not published in a peer reviewed journal. It was, however, subject to extensive public review and layers of expert review within and outside of FDA. The process began with draft guidance to industry in November 1998 on antimicrobial use in food-producing animals. G-953 at 6. In December 1998, CVM issued a discussion document called "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food Producing Animals." G-953 at 6. FDA also developed the quantitative risk assessment model used in the CVM risk assessment, which was released publicly in December 1999. At that time the draft risk assessment document, as well as two spreadsheet models -- one for use with Microsoft Excel and a second version, in an Microsoft Excel spreadsheet, for use with the software package @Risk (Palisades Corp, NY) -- were posted on the FDA-CVM website. Vose, G-1480 at 6. CVM held a public conference exclusively to discuss and present the risk assessment that included panel discussions involving food safety and risk assessment experts. *Id.* Comments collected at the conference and submitted in writing were organized, assembled, and summarized by CVM, and were addressed in the final version of the model and the report. *Id.* Thus, the conference offered an opportunity for peer review of the document by providing critical evaluations of the science, data and information, and methodologies used to develop the risk assessment. *Id.*

b. Challenges to the CVM risk assessment

Bayer argues that the risk assessment is flawed because it does not adhere strictly to the four-step risk assessment paradigm described by the National Research Council (NRC) in a series of influential publications[93] on the use of risk assessment by the federal government and because CVM did not use a "farm-to-fork" model. Bayer Exceptions at 197-198, 207. Bayer also argues that the risk assessment was required to, but does not, comport with FDA and OMB guidelines issued pursuant to the Information Quality Act. *See* Section II.D. Bayer argues that the model CVM used is "invalid on its face," because it "assumes that cases increase in proportion to contaminated chicken consumed, and hence in proportion to total chicken consumed," and that the risk assessment did not use reliable data. Bayer Exceptions at 190; *see also id.* at 192. Finally, Bayer presented its

[93] Although these publications are not in the administrative record, they are widely referenced and used by government agencies and are cited by all participants. They are: National Research Council, Risk Assessment in the Federal Government, National Academies Press, Washington, DC (1983), http://books.nap.edu/catalog/776.html (accessed on July 14, 2005); NRC, Science and Judgment in Risk Assessment, National Academies Press, Washington, DC (1994), http://books.nap.edu/catalog/2125.html (accessed on July 14, 2005); and NRC, Understanding Risk: Informing Decisions in a Democratic Society, National Academies Press, Washington, DC (1996), http://books.nap.edu/catalog/5138.html (accessed on July 14, 2005). I agree with Bayer that I can appropriately take official notice of these publications. *See* Bayer Exceptions at 198 n. 50.

own quantitative assessment of the risk of fluoroquinolone-resistant *Campylobacter* in chicken, referred to as the "Cox model." I will address each of these contentions in turn.

As a threshold matter, I note that, unless there is some statutory obligation to prepare the risk assessment in a certain way (and there is none here), the initial question is not whether the risk assessment relied on by CVM could have been done differently, but rather, whether the risk assessment relied on by CVM meets the criteria for admissibility under the APA, 5 U.S.C. § 556(e), as well as 21 CFR § 12.94(c)(1).

(i) NRC publications on risk analysis

I agree with the ALJ that the NRC publications do not impose any binding obligations on FDA. Initial Decision at 38. No statute requires FDA to follow the NRC guidelines, and FDA has not adopted the NRC guidelines by rulemaking. Moreover, the guidelines themselves are clear that they are not intended to be applied inflexibly in all situations. *E.g., Science and Judgment in Risk Assessment* at 4 ("Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing and analyzing scientific knowledge and information for potentially hazardous activities or for substances that might pose risks under specific conditions."); *Understanding Risk* at xii ("The committee stresses to the readers of this report our conviction that no set of guidelines or procedures can ever substitute for scientific rigor, fairness, and flexibility in coping with dynamic risk situations.").[94] To the extent the NRC publications, which focus on toxicologic risk analysis, outline an approach to risk assessment that is generally accepted in the scientific community,[95] I find that CVM appropriately used the NRC approach to aid in the development of its risk assessment.

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[94] *See* n. 93 for full cites.

[95] The NRC identifies four elements in a toxicologic risk assessment: hazard identification, dose-response assessment (sometimes referred to as hazard characterization), exposure assessment, and risk characterization. Travis, G-1479 at 3-4. Hazard identification is "[t]he determination of whether a particular hazard is causally related to a particular effect." Travis, G-1479 at 3. Generally, this step involves reviewing scientific data on the question of "whether a particular hazard is known to cause a particular effect." *Id.* While FDA's Center for Food Safety and Applied Nutrition (CFSAN) has used this general approach in the context of an assessment of a microbial risk, *see* A-34 at 5 (draft assessment of the risk from foodborne *Listeria monocytogenes* in certain categories of ready-to-eat foods), there is no requirement that it be used inflexibly in all contexts. Furthermore, there are clear differences in complexity between a straightforward microbial risk assessment and CVM's assessment of the human health impacts associated with the use of fluoroquinolones in chickens.

Bayer's primary issue[96] with the risk assessment is with CVM's decision not to estimate a precise dose-response relationship. *See* section III.C.2 above. According to Bayer, the absence of such an estimate resulted in deficiencies in the hazard identification, dose-response, exposure assessment, and risk characterization steps of the risk assessment, *see* n. 95, that would have been present had CVM followed (as Bayer argues it should have done) a traditional NRC toxicological risk assessment paradigm. *Id.* at 199-206. Bayer argues that CVM could have, but did not, use the number of organisms ingested (microbial load) in a dose-response calculation. Bayer Exceptions at 202. Again, the question is not whether or not CVM could have done such modeling, but rather whether the scientific approach it took was reasonable under the circumstances. I find that it was. CVM's risk assessment assumes that there is a positive, linear relationship between the amount of *Campylobacter*-containing poultry meat produced in a year and resulting human campylobacteriosis cases. Vose, G-1480 at 7; G-953 at 81-83. However, nothing in the record supports Bayer's argument that the only way to measure exposure would be to use a microbial load measurement. For the reasons discussed in section III.C.2 above, there are strong arguments against using the type of dose-response modeling Bayer proposes, because there are only limited data available to estimate the relationship between exposure and associated illness. Therefore, any dose-response relationship generated would lead to highly uncertain estimates of *Campylobacter* illness and outcomes.

In his stricken testimony, Bayer witness Dr. Anthony Cox testified that "[d]ose-response data for *Campylobacter* in human volunteers are readily obtainable and have been used to create several published dose-response models." Cox, B-1901 at 18. However, each of the "several" models referenced by Dr. Cox relies only on the Black study (G-67) described in section III.C.2, in which 111 volunteers were given doses from 800 CFUs of *Campylobacter* up to 200 million CFUs. In this study, there was no clear dose response relationship shown and the minimum infective dose -- *i.e.*, the lowest dose of bacteria that would result in illness--could not be determined. *See, e.g.*, G-1788 at 4-5 ("[o]nly a few studies describing the human response to a known dose of *Campylobacter* exist"); B-748 at 3 (relying on Black's data)[97]; B-517 (relying on Black's data); B-147 at 5 ("The lack of a relationship between dose of *C. jejuni* and symptoms [in the Black study] confounds extrapolation of illness...").[98] As these models make clear, this lack of

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[96] Bayer raises several arguments against CVM's alleged failure to satisfy the NRC guidelines. *See* Bayer Exceptions at 197-207. Because these arguments raise substantive issues addressed elsewhere in this Final Decision, I will not address them in detail here. Bayer argues, for example, that the "hazard characterization" was inadequate because the risk assessment "does not identify any specific toxic outcome of ineffective therapy of [fluoroquinolone]-resistant *Campylobacter*," by, for example, assessing "whether, or to what extent, such resistant *Campylobacter* might result in more severe or longer illness." *Id.* at 199. This issue is addressed in detail in section III.D.1-5 of this Final Decision.

[97] Exhibit B-748 is also in the record as G-629.

[98] I am among the "other noted risk assessors" Bayer cites as having used a dose response model in an assessment of the impact of fluoroquinolone-resistant *Campylobacter jejuni* derived from cattle. Bayer Exceptions at 202. B-147 is a paper that I wrote with others while at the Center for Food and Nutrition Policy, Georgetown University, with funding through AHI. This study

suitable, high-quality data on exposure (dose) linked to the percentage of adverse effects or illnesses observed (response) hampers efforts to develop a robust dose-response approach capable of accurately estimating the true risk with reasonable precision. *See* G-1788 at 14. As CVM witness Dr. Mary Bartholomew testified, "the data describing the complex exposure, host-pathogen interactions necessary to recreate an accurate dose-response relationship were lacking," as were measures that could indicate seasonal and annual changes in the level of contamination of food products at the point of exposure. Bartholomew, G-1454 at 4.

In light of the lack of good data on dose-response, CVM determined that, rather than using predictive microbiology to estimate risk, the CVM model should use more robust information collected in surveillance systems identifying culture-confirmed cases of campylobacteriosis. Bartholomew, G-1454 at 4; *see also* Travis, G-1479 at 12-13. CVM has thoroughly and adequately explained why it chose to use actual data on human infections rather than model microbial load input and dose response to estimate the relationship between magnitude of exposure and probability of effect. Bartholomew, G-1454 at 5; Vose, G-1480 at 11-15.

In sum, I concur with the ALJ that the CVM risk assessment "does not have to follow the NRC guidelines because they are not necessary for developing a scientifically sound antimicrobial risk assessment, [and] they are not standards that must be followed." Initial Decision at 38. I further find that CVM incorporated appropriate components of the NAS risk assessment paradigm in its risk assessment.

(ii) Farm-to-fork model

Bayer and AHI also argue that the risk assessment should have followed a "farm-to-fork" model. Bayer Exceptions at 207. A farm-to-fork model mathematically approximates the effect of numerous processes involved in producing the product on the prevalence and quantity of pathogen occurring on or in the product throughout the

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evaluated the risk of resistant *C. jejuni* infections through consumption of retail beef. In that study, we conducted a quantitative risk assessment that commenced with risk at the retail level (*i.e.*, rather than in earlier stages of production). The study used a dose-response model that predicted a mean level of infection at each dose; this model, which was developed by Medema and colleagues, *see* B-517, relies on the Black study (G-67). The Medema dose-response model did not use confidence intervals to reflect the uncertainty of the underlying Black data. As a result, the outcomes of the study by Anderson and colleagues, B-147, similarly represented only the mean estimated outcomes, and not the range of uncertainty inherent in the data. In that study, we found that the prediction of outcomes such as mild illness, hospitalization, etc., was difficult to estimate from the Black and Medema studies. *Id.* at 5-10. As we noted there, while about 22% of the participants in the Black study exhibited symptoms, the degree and severity of the symptoms did not correspond to the number of ingested organisms. *Id.* at 5. Thus, we pointed out, "It is difficult to infer a relationship between dose and illness from the Black study. However, the study implied that infection was not sufficient for illness" (in other words, in some cases a person can be infected and not become ill). *Id.* In light of the lack of availability of exhaustive *C. jejuni* dose-response research and data, which limits the ability to assess risk, we also used a methodology incorporating expert judgment and elicitation, from an advisory panel to the Georgetown study and CDC experts, to predict the mean percentage of illnesses of various degrees (mild, moderate, etc.) estimated to be associated with infection. *Id.* at 5.

production continuum ranging from the rearing of livestock on the farm; transport to the slaughter facility; slaughter and production processes; handling of product by producers, distributors, retailers, and consumers to the final preparation, cooking and consumption of product. G-953 at 8-9; Travis, G-1479 at 14, Vose, G-1480 at 8.

Bayer does not allege that CVM was required to do a farm-to-fork model as a matter of law. Furthermore, while such an approach was at least theoretically available to CVM, CVM discussed at length its decision not to use the farm-to-fork approach. G-953 at 8-10; *see also* Vose, G-1480 at 8. I find, as did the ALJ, that CVM's decision in this regard was sound. *See* Initial Decision at 34. In this context, a farm-to-fork model would have required many more assumptions than the model CVM used. It would have needlessly increased the complexity of the model and uncertainty of the final risk estimate thus diminishing the risk assessment's usefulness as a tool to assist CVM in its decisionmaking.[99]

First, CVM has responsibility for the safe use of fluoroquinolones in the production of poultry. G-953 at 5; Vose, G-1480 at 5 ("the question asked was whether the use of antimicrobials under [CVM's] authority is introducing a significant human health burden and, if so, whether any action they could take would significantly reduce that burden. By law, CVM has limited actions that it is allowed to take, namely the restriction of use or withdrawal of approval of a new animal drug." Vose, G-1480 at 5. Since CVM's authority does not extend to poultry slaughter and processing facilities, a farm-to-fork risk assessment evaluating the prevalence and level of pathogen and mitigations during production was not warranted. Moreover, as Dr. Vose testified, "... the food safety risk assessment community is beginning to recognize that farm-to-fork risk assessments have not produced what was hoped, and that more decision-question focused assessments are necessary, using more efficient alternative modeling approaches." Vose, G-1480 at 4; *see also* Travis, G-1479 at 17. The risk assessment models created and the comprehensiveness of the approach used should be defined by the risk management questions being addressed. CVM could have inserted more data and more comprehensive models into its risk assessment, but these additions would not have further refined the answers useful for this decision.

Second, because only limited data detailing the behavior of *Campylobacter* through each step are available, a risk assessment addressing each component of the production and processing of poultry would have significant uncertainties that would be reflected in the final risk estimates. Dr. Curtis Travis, a risk assessment expert, testified that it is "difficult, if not impossible, to identify all the various factors that can influence the presence and growth of bacteria from farm-to-fork." Travis, G-1479 at 17. Dr. Travis explained that, "Even if one were able to conceptually include important factors in the 'farm-to-fork' model, these factors are not currently sufficiently well characterized to know their form or parameter values." *Id.* Thus, at present the value of a farm-to-fork

[99] The Initial Decision stated that a farm-to-fork model "would have resulted in greater data gaps." Initial Decision at 34. CVM filed an Exception to this phrasing, suggesting rather that such an analysis "would have suffered far more from gaps in data." I agree with CVM that this phrasing is more consistent with the testimony, but I believe it is what the ALJ was trying to convey. *See* Vose, G-1480 at 10.

model is to help identify intervention or control points in the food production process to reduce bacterial load. Dr. Travis testified, however, that "[i]t is generally agreed that currently there does not exist sufficient data to develop a predictive 'farm-to-fork' model for any one of the common food borne pathogens." Travis, G-1479 at 17. Dr. Vose concurred. Vose, G-1480 at 3-4. Significantly, one of the "farm-to-fork" models cited by Bayer as a better approach was actually similar in some respects to the CVM model. Anderson and colleagues began their risk assessment at the retail meat stage and they modeled consumer handling and a dose-response relationship -- in other words, they did not look at farming, processing, or slaughtering practices. Vose, G-1480 at 4; B-147.

In conclusion, I find that CVM was not required by law to conduct a "farm-to-fork" risk assessment and that the model it chose was appropriate to serve the agency's needs. I agree with the ALJ that "a more intricate risk assessment model, such as a farm-to-fork model, would not have yielded additional information of use to CVM and would have increased the likelihood of error in the model's calculations." Initial Decision at 34; *see also* Vose, G-1480 at 10.

(iii) Information Quality Act and FDA's Implementing Guidelines

For the reasons set forth above in section II.D, I have already found that CVM was under no obligation to demonstrate in this formal adjudication that its risk assessment—or any of its other evidence—satisfied FDA's guidelines under the IQA. I think it is important to note that it is clear that what AHI was complaining about in its request for correction under the IQA, *see* http://www.aspe.hhs.gov/infoquality/requests.shtml (accessed on June 20, 2005), is the use of the CVM risk assessment as evidence in a formal adjudication. However, the IQA request for correction process is designed to address concerns regarding the quality, objectivity, utility, and integrity of information disseminated by the federal government, *see* IQA; OMB guidelines, 67 Fed. Reg. 8452, 8452, not the policy or legal implications of that information. The OMB and FDA guidelines were not intended to create additional rights when scientific information is used in an adjudication. It is also worth noting that several of AHI's challenges to the risk assessment under the guise of an IQA request for correction are not actually challenges to the risk assessment itself, but rather raise legal issues concerning what considerations FDA must or may take into account when determining whether to withdraw approval of a new animal drug.

Although I have found that the IQA does not afford Bayer any legal basis to challenge the reliability of any of CVM's evidence in the context of this administrative proceeding, under the unique circumstances of this proceeding, I now have pending before me AHI's IQA request for correction and request for reconsideration, accessible at the website noted in the preceding paragraph, and the formal adjudication. I am therefore taking the unusual step of also resolving, in this Final Decision, AHI's request for correction of the CVM risk assessment. This action by me, and the earlier decision to defer action until resolution of the administrative proceeding, *see* note 14 above, should not be interpreted as establishing any precedent.

Based on several factual findings set forth in this Final Decision, I find that, even assuming that the risk assessment is properly considered "influential" under FDA's

Guidelines,[100] and is otherwise subject to the IQA, the process by which the risk assessment was produced (which predated the enactment of the IQA and the issuance of OMB, HHS, and FDA guidelines), was nonetheless consistent with the FDA Guidelines, even those for influential information, and that no correction of the risk assessment is warranted.

First, CVM used the "best available science and supporting studies conducted in accordance with sound and objective scientific practices" and relied on "data collected by accepted methods." *See* FDA Guidelines. The data were robust, peer reviewed, and/or compiled by federal agencies, but not for regulatory action or the withdrawal hearing.[101]

Second, the risk assessment underwent a stringent expert and public review process. *See* section III.D.6.a, above. Third, the risk assessment process, including the methodology used, the data relied on, assumptions made, and uncertainties, was transparent, reproducible, and replicable. In the assessment CVM highlighted critical assumptions and limitations, and posted the draft and final assessment model on its website. *Id.* Anyone familiar with the commonly used Microsoft Excel software program is able to use the model, incorporating different assumptions and data. The stated purpose of the assessment was to estimate the nominal mean number of patients with fluoroquinolone-resistant *Campylobacter* infections who sought treatment, were treated with fluoroquinolones, and were affected by the resistance of their infection to fluoroquinolones, for the years 1998 and 1999, and gave appropriate confidence intervals for this estimate. In the risk assessment, CVM clearly identified the potentially affected population; analyzed uncertainties, both in the assessment and in underlying data; and identified and relied on relevant peer-reviewed studies. *Id.*

I conclude that the reliability of the risk assessment was not affected by the methodology that CVM used, which was well-explained and in accordance with established scientific principles. Furthermore, Bayer has not established that the risk assessment was inaccurate and biased. I also agree with the ALJ that CVM did not act inappropriately in declining to rely in the risk assessment on research that had not yet been published in final and that was not, in any event, inconsistent with the research that was incorporated into the risk assessment model.

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[100] Bayer argues in its Exceptions that the ALJ erred in excluding the testimony of Thomas Martin, B-1907, because the proffered evidence would have shown that the impact of the withdrawal of the NADA for enrofloxacin use in poultry would exceed $100 million and thus the withdrawal should be considered "influential." Bayer Exceptions at 69, 209-210. Under the FDA Guidelines, however, Bayer must show, however, that the disseminated risk assessment itself is "influential." In any event, as discussed in section IV.C.1, below, I reviewed Mr. Martin's testimony and found that the proffered evidence on the economic impact of the withdrawal of approval was not reliable.

[101] In particular, I find that, contrary to Bayer's unsupported assertion, *see* Bayer's Exceptions at 208, the risk assessment was not written in contemplation of the NOOH. Tollefson, G-1478 at 15-16.

Finally, AHI argued that the risk assessment violates the FDA Guidelines because it is not "comprehensive." *See* RFC at 15-16.[102] The FDA Guidelines state that, "[i]n the dissemination of public information about risks, the Agency will ensure that the presentation of information about risk effects is comprehensive, informative, and understandable." FDA Guidelines, VII.C. The use of the word "comprehensive" follows the use of the word in the Safe Drinking Water Act, 42 U.S.C. § 300g-1(b)(3)(B), which directs agencies assessing risks of human safety and the environment "to ensure that the presentation of information [on risk] effects is comprehensive, informative, and understandable." I do not believe that "comprehensive" means, in this context, that the assessment must address issues that are outside of a risk assessment's defined scope or purpose.[103] For example, FDA was not required to incorporate in the risk assessment a

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[102] AHI lists numerous ways in which the assessment was not "comprehensive" many, if not all, of which are reiterated in Bayer's Exceptions:

> [t]he Vose Risk Assessment fails to take into account and disseminate information about: (1) the benefits to human health and the environment from use of enrofloxacin in poultry; (2) significant decreases in the incidence of campylobacteriosis in the U.S. during each of the past six years, even in the face of significant increases in poultry consumption during the same period; (3) limitations in the utilization of NARMS and uses of the Smith and other data; (4) absence of established consensus standards for (a) isolation of *Campylobacter*, (b) resistance testing of *Campylobacter* to ciprofloxacin, and (c) defining clinical resistance by the correlation of clinical outcome with in vitro breakpoints; (5) significant changes in the raising, processing, marketing, handling, and preparation of poultry during the past at least half decade or more, which changes have significantly lessened the potential risk of people becoming ill with campylobacteriosis as a result of eating and handling poultry, including but not limited to (a) implementation of the Hazard Analysis Critical Control ("HACCP") program, (b) safe handling label requirements for poultry, (c) consumer education regarding safe handling and cooking of poultry, (d) changes in consumer handling and cooking practices, (e) significant reductions in the percentage of poultry sold as whole birds and a major increase of sale of poultry that is commercially processed (frozen, cooked) or sold as parts; and (6) CVM's presentation of information is *not* comprehensive or informative about the risks in question. It does not (a) distinguish between risks from home-cooked and restaurant chicken, (b) does not indicate the significant reduction in risk associated with home-cooked chicken, (c) does not mention that restaurant dining is about equally hazardous for poultry and non-poultry meats; (d) does not indicate the huge variability across FoodNet areas (which its model does not explain or describe) and (e) more importantly, the presentation of information does not address the adverse human health impacts from banning enrofloxacin, but only the hypothesized benefits.

Request for Correction (RFC) at 15-16 (emphasis omitted).

[103] The Safe Drinking Water Act provision cited in the guidelines, 42 U.S.C § 300g-1(b)(3)(B), does not support an argument that the OMB or FDA guidelines call for cost-benefit or risk-benefit analysis for the straightforward reason that neither are mentioned in that provision. Moreover, another provision in the Safe Drinking Water Act, 42 U.S.C. § 300g-1(b)(3)(C), which is not cited in the IQA or the implementing Guidelines, entitled "Health risk reduction and cost analysis," does address these types of analyses. This is a further indication that 42 U.S.C. § 300g-1(b)(3)(B), entitled "Public Information," does not address those issues and that the use of the

cost-benefit or risk-benefit analysis of the costs of taking enrofloxacin off the market. *E.g.*, RFC at 15-16, Nos. 1, 6(c). Thus, these concerns are outside the scope of the IQA and the implementing guidelines, which do not require that risk assessments include or be accompanied by cost-benefit analysis or otherwise suggest that a risk assessment must address matters outside its stated scope.

(iv) Challenges to the risk assessment model and assumptions

Bayer argues that the risk assessment model, which assumes that campylobacteriosis is proportional to chicken consumption, is "invalid on its face," Bayer Exceptions at 190, because annual campylobacteriosis incidence has decreased while annual chicken consumption has increased. Bayer supports this argument with an unreferenced figure, Bayer Exceptions at 191, that purports to plot annual campylobacteriosis incidence against annual per capita chicken consumption. *Id.* Bayer does not provide any citation to the record or identify the source in the record from which its figure is copied. Immediately following the figure, Bayer notes that Bayer witness Dr. Anthony Cox "similarly undertook an 'ecological study' as an 'initial exploratory analysis,'" citing Tr. at 1070-1072 and Cox, B-1901 at 37 (Att.1). Bayer Exceptions at 192. The figure itself is not in evidence, and therefore I do not consider it.[104] Moreover, as discussed above, even if the incidence of campylobacteriosis is decreasing (as an absolute matter or in relation to poultry consumption patterns), the proportion of human *Campylobacter* infections that do occur that is resistant to fluoroquinolone treatment is increasing.

(v) Challenges to the underlying data

In estimating the probability that a case of campylobacteriosis is attributable to chicken, CVM relied primarily on two studies, G-268 and G-162. *See* G-953 at 52-53. CVM described the two studies' methodology and limitations.[105] Bayer challenged

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word "comprehensive" does not require a risk assessment to address matters beyond its stated scope.

[104] Dr. Cox's testimony was stricken from the record, *see* section II.D.3. Even if Dr. Cox's testimony had not been stricken, or Bayer had otherwise provided support for its argument, the argument is unavailing. Dr. Cox's testimony on cross-examination describes this statistical analysis as "just exploratory," Tr. at 1072, and he indicated that he did not consider it to be a "serious data analysis," Tr. at 1073. Thus, even if Dr. Cox's testimony had not been stricken, Dr. Cox's own description of it underscores that this analysis deserves to be given little weight.

[105] For example, the risk assessment noted that the results of the Harris study, G-268, were "now 17 years old and exposures and other factors may have changed in the interim, potentially affecting the level of risk attributable to chicken. Demographic characteristics of the population, the frequency, preparation and amount of chicken consumption, the proportion of the population consuming chicken and many other factors may have changed since this study." G-953 at 52. The risk assessment noted that limitations of the Deming study, G-162, included "the lack of representativeness of the study population and the absence of some exposures, such as travel and raw milk that are frequently associated with risk in the population at large. In addition, the study was limited to enteric illnesses because more invasive infections were not eligible for inclusion in the study...." *Id.* at 53.

CVM's reliance on these two studies, arguing that they were outdated and that more recent data were available to CVM and could have been used.

As described above, *see* section III.C.3, the Harris study, G-268, estimated that 48.5% of the illness in that study population (enrollees in a health maintenance organization in Washington State) was attributable to chicken, and the Deming study, G-162, estimated that 66.7% of illness in the university student population studied was attributable to chicken. As the CVM risk assessment noted, "[t]hese estimates of the etiologic fraction represent a range of risk that is likely to reflect the level of risk in the early 1980s. More recent data do not exist for United States populations." G-953 at 54. CVM assumed that the current level of risk of contracting campylobacteriosis from consumption of chicken is contained with the range of the risks found in the two studies. *Id.* at 54. Although that assumption may result in an overestimation of risk from direct consumption of chicken, as CVM noted, the risk level "does not account for cases originating from chicken and contaminating other foods or the spread from chicken to other animal hosts and resulting in human exposure." *Id.*

Bayer argues that CVM should have relied on Friedman's then-draft analysis of FoodNet data, *see* Angulo, G-1452 at 79-107 (Att. 3), rather than on the older Harris and Deming studies. Bayer Exceptions at 192-197. Because Friedman estimated that 24% of campylobacteriosis cases could be attributed to eating chicken in restaurants, and 4% to eating turkey in restaurants, Bayer argues that this study suggest that the fraction of illness that can currently be fairly attributed to chicken is much lower than the 57% figure used in the CVM risk assessment that was derived based on the Deming and Harris studies. Bayer Exceptions at 195.

I agree with the ALJ that CVM did not act inappropriately in not relying on drafts of research published well after the October 18, 2000, posting of the risk assessment on the website (G-953 at 2).[106] *See* Initial Decision at 40. Nor do I believe that, had this research been available in final form, it would have materially changed the conclusions of the risk assessment. CVM witness Dr. Mary Bartholomew explained that if the proportion of *Campylobacter* infections attributed to chicken is overstated, as Bayer argues, then the proportion of resistant *Campylobacter* cases attributable to domestically produced chicken is actually higher than the mean of 14.2% estimated for 1998 in the risk assessment. Bartholomew, G-1454 at 14-17. This is so because, while there are multiple sources of *Campylobacter* infections in humans (which impacts the precision of quantification of attributable fractions), the available evidence supports a conclusion that virtually all domestically acquired cases of resistant *Campylobacter* infection in the United States are associated with chicken (and turkey) contaminated with resistant *Campylobacter* species. Based on data from the Harris study, Dr. Bartholomew estimated that only a very small proportion (0.2%) of resistant *Campylobacter* isolates can be attributed to a patient having received a fluoroquinolone prior to submitting their

[106] G-953 is a revised version posted in January 2001. The document indicates that the revision consists of the inclusion of a Microsoft Excel version of the risk assessment model. G-953 at 1.

stool culture.[107] Bartholomew, G-1454 at 15-17. Dr. Bartholomew's testimony is consistent with other testimony that, while the risk of getting a *Campylobacter* infection overall was lower in 2001 than in 1996, the risk that any *Campylobacter* infection that does occur will be fluoroquinolone-resistant increased over that period of time. *See* Molbak, G-1468 at 8 (27% decline in incidence of *Campylobacter* infections overall, but 61-98% increase in proportion of isolates that are resistant).

In sum, I agree with the Initial Decision that the Harris study, G-268, and the Deming study, G-162, provided appropriate support for CVM's estimation of the fraction of cases of campylobacteriosis attributable to chicken. *See* Initial Decision at 40. I also agree with the ALJ that the data Bayer argues should have been relied on by CVM in the risk assessment were not yet available in final form and that in any event incorporation of those data would not have changed the conclusions of the risk assessment in any material way.

In conclusion, I find that the CVM Risk Assessment is reliable evidence and that it provides a valuable quantitative estimate of the risk to human health from fluoroquinolone-resistant *Campylobacter* infections associated with the domestic use of fluoroquinolones in poultry. I find CVM's estimate of the number of people expected to be infected with fluoroquinolone-resistant *Campylobacter* from consuming chicken in the two years evaluated (1998 and 1999) who would be expected to receive fluoroquinolone treatment and experience a longer duration of illness because of the decreased effectiveness of the antibiotic, to be valuable information in understanding the public health impacts of fluoroquinolone-resistant *Campylobacter* infections associated with chicken consumption.

7. Clinical significance of in vitro *measurements of resistance*

A final criticism Bayer makes about CVM's evidence is that the *in vitro* measurement of resistance in the studies relied on by CVM does not reflect resistance in the clinical context. It raises two issues concerning the methods used to test bacteria for resistance, challenging both the measure used by many researchers on whose work CVM (and Bayer) rely to distinguish resistant from susceptible *Campylobacter*, and challenging as well the use by several of these studies of an *in vitro* assay known as the "E-test" as unreliable. Bayer Exceptions at 132-141. I disagree with both of these arguments. Bayer also argues that "so-called 'resistant' infections" actually respond to treatment, because what looks resistant in the laboratory is actually treatable in the clinical setting. *See* Bayer Exceptions at 120-23. I disagree with this argument as well.

a. *In vitro* measurement of resistance

The National Committee for Clinical Laboratory Standards (NCCLS), which sets standards and guidelines for laboratory methods used to measure bacterial susceptibility to antimicrobials, has not adopted an official "breakpoint" to distinguish *Campylobacter* that is resistant to ciprofloxacin from *Campylobacter* that is considered either "intermediate" or "susceptible" to ciprofloxacin. Revised Joint Stipulations 11, 12, 14;

[107] Dr. Bartholomew testified that in the Harris study, only 24 of 580 of the cases (about 4%) had received a fluoroquinolone prior to submitting their stool cultures. Bartholomew, G-1454 at 16. Of the 24, only one was resistant. *Id.*

Walker, G-1481 at 6; Kassenborg, G-1460 at 4. Such a breakpoint, known as the "minimum inhibitory concentration," or MIC, is the lowest concentration of an antimicrobial agent that it takes to inhibit the growth of a bacterium. Walker, G-1481 at 5; Besser, G-1455 at 4; Tr. at 208-209. Where feasible, FDA, which is a member of the NCCLS, uses the NCCLS standards. Revised Joint Stipulation 13. It is undisputed that the NCCLS has not set an official breakpoint for *Campylobacter*. Revised Joint Stipulation 14.

In the absence of a *Campylobacter*-specific breakpoint for ciprofloxacin resistance, many of the studies on which CVM relies use the NCCLS interpretive criteria for *Enterobacteriaceae* of an MIC $\geq$ 4 micrograms/milliliter (µg/mL). Walker, G-1481 at 7; Kassenberg, G-1460 at 4; *see, e.g.,* G-1517 at 4; G-1800 at 1; G-589 at 2; G-190 at 3. Bayer witness Dr. Diane G. Newell stated that MICs of 4 µg/mL "may be considered resistant" although lower MICs should be interpreted with caution. Newell, B-1908 at 13-14. Other countries' standard-setting organizations have adopted an MIC of 4 µg/mL or lower for measuring ciprofloxacin resistance. Walker, G-1481 at 6; Tr. at 193. For example, Britain, France, and Denmark report interpretive criteria for *Campylobacter* resistance to ciprofloxacin at $\geq$ 4 µg/mL (Britain); $\geq$ 2 µg/mL (France, proposed); and $\geq$ 2 µg/mL (Denmark). Walker, G-1481 at 6-7; Tr. at 193.

Although its complaint with the use of this breakpoint is not clear, Bayer appears to be arguing that it is arbitrary and that the fact that it is commonly used in scientific research and by international regulatory authorities is insufficient to justify CVM's reliance on research using this method.[108]

To address these concerns, it is helpful to understand the purpose of identifying a breakpoint. CVM witness Dr. Robert D. Walker testified that *in vitro* antimicrobial susceptibility testing addresses the need to understand the susceptibility of a particular pathogen in order to improve treatment outcome. Dr. Walker explained that the purpose of interpretive criteria is to guide clinicians' understanding, based on whatever *in vitro* testing method is used, of whether a particular bacterium/antimicrobial agent interaction is likely to be clinically effective. Walker, G-1481 at 4.[109] When the bacteria are

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[108] *See, e.g.*, Bayer Exceptions at 134-35 ("[i]n the absence of a NCCLS clinical breakpoint, CVM has merely assumed that an *in vitro* measurement of $\geq$ 4 µg/mL would be resistant to treatment with fluoroquinolones"); Bayer Exceptions at 136 ("The Initial Decision points to the fact that 'many scientific reports' have used the NCCLS interpretive criteria established to determine a fluoroquinolone clinical resistance breakpoint for *Enterobacteriacea*, a different class of microorganisms. The 'everyone else does it' defense is hardly a scientific justification for use of criteria that are not consistent with NCCLS methods for establishment of clinical breakpoints. What is apparent is that the NCCLS interpretive criteria for ciprofloxacin resistance to another class of organisms--*Enterobacteriacea*--has been merely appropriated and used by various researchers as the breakpoint, *i.e.*, 4 µg/mL for *Campylobacter*").

[109] Bayer's lengthy argument about the importance of NCCLS-established breakpoints in evaluating clinical resistance do not mention that, as the sponsor for ciprofloxacin, Tr. at 253, Bayer is primarily responsible for the fact that there is no NCCLS-established breakpoint. In the United States there are "basically three ways" interpretive criteria for antimicrobials are established. Walker, G-1481 at 5. In veterinary medicine, it is common for a drug's manufacturer to identify the desired interpretive criteria for the product, based on laboratory data

susceptible, there is "a high likelihood of a favorable clinical outcome when the drug is administered at its label dose." *Id.*

The fact that there is no NCCLS standard does not mean that no effort to identify resistant *Campylobacter* is possible. Instead, the issue is what standard is reasonable to use in the absence of an NCCLS standard (and indeed, there was ample testimony in the record about the limited number of organism/antimicrobial combinations for which criteria are available, making it necessary to use other criteria). *See, e.g.*, Walker, G-1481 at 5-6; Besser, G-1455 at 5. As Dr. Walker explained, "if an issue arises that requires susceptibility information for a specific organism for which there are no NCCLS standards, researchers must choose a reasonable method based on available scientific information, and describe the method in any resulting scientific publication. When a standardized method becomes available, it can be used to evaluate earlier results generated using other testing methods." Walker, G-1481 at 9-10. *See also* Besser, G-1455 at 5. I find that CVM's reliance on several studies that use the NCCLS interpretive criteria for ciprofloxacin resistance in *Enterobacteriaceae* (MIC $\geq$ 4 μg/mL) is reasonable based on the available scientific information.

I also find that 4 μg/mL is a reasonable and even conservative approximation of the likely MIC for *Campylobacter* resistance to ciprofloxacin. Dr. Walker testified that in his opinion, the NCCLS interpretive criteria for *Enterobacteriaceae* "should be used with caution" to determine resistance of *Campylobacter* to ciprofloxacin, because the site of infection and incubation conditions required for the growth of the two species are not the same. Walker, G-1481 at 7. Although Bayer cites this testimony in support of its challenge to the use of 4 μg/mL as being too low, Bayer Exceptions at 137, Dr. Walker's expert opinion was that the use of $\geq$ 4 μg/mL as a ciprofloxacin resistance breakpoint for *Campylobacter* is too high. He testified that because of the way that ciprofloxacin is absorbed, distributed, metabolized, and eliminated in humans, a bacterial pathogen with an MIC greater than 1.0 μg/mL "would most likely not respond to therapy and thus be considered resistant." *Id.* at 10. Dr. Walker explained this point in greater detail in his testimony. *Id.* at 7.

Furthermore, I agree with the ALJ that, even if this MIC value is low, it does not bias the designation of *Campylobacter* isolates as fluoroquinolone-susceptible or -resistant because fluoroquinolone resistance is highly bimodal; in other words, *Campylobacter* are either highly resistant (MICs $\geq$ 32 μg/mL)[110] or highly susceptible (MICs < 2 μg/mL) to fluoroquinolones. Initial Decision at 17, 66. There is ample evidence about this bimodal distribution pattern of *Campylobacter* in the record. McDermott, G-1465 at 4-5; Besser, G-1455 at 5; B-868 at 2; G-1800 at 2; Tr. at 249-250. This resistance pattern allows greater flexibility in testing methods, Tr. at 249-250, and it

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and interpretive criteria for a competitor's product. *Id.* For human drugs, FDA may set interpretive criteria based on analysis of data submitted by the product sponsor, *id.*; Tr. at 240-241. Finally, NCCLS has published guidelines that drug sponsors can follow to establish interpretive criteria through NCCLS. Walker, G-1481 at 5.

[110] CVM witness Dr. Angulo testified that 32 μg/mL is the highest concentration tested. Tr. at 348-349.

allows greater confidence in distinguishing resistant from susceptible organisms in the absence of an accepted standard. Besser, G-1455 at 5.[111]

Bayer's arguments against the commonly used breakpoint of 4 μg/mL turns on the testimony of Dr. Peter Silley, B-1913 at 13.[112] Dr. Silley states that "[f]aecal concentrations following oral dosage of ciprofloxacin in humans suggest that *Campylobacter* spp. with MICs of 32 μg/mL should in most cases be clinically susceptible. Whilst intuitively appearing to be very high this would support a ciprofloxacin breakpoint of 64 μg/mL." Silley, B-1913 at 13. As Dr. Silley himself concludes: "[o]n the basis of the available data there is evidence to support a clinical breakpoint for ciprofloxacin of 64 μg/mL, this would of course need to be substantiated in accordance with NCCLS guidelines." Silley, B-1913 at 18.

I find Dr. Walker's analysis to be more compelling and more in accord with the weight of scientific opinion on this matter. Thus, I find that, in meeting its burden of proof in this proceeding, CVM can appropriately rely on data about resistance that was quantified using the 4 μg/mL breakpoint.

(i) The E-test

I also find that CVM can appropriately rely on research that used the "E-test" to measure *in vitro* susceptibility or resistance of *Campylobacter* to ciprofloxacin.

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[111] CVM filed an exception to a statement by the ALJ that "Many of the studies in evidence used ciprofloxacin to measure MIC values. However, the MIC value from these studies cannot be extrapolated to calculate the MIC value for enrofloxacin." Initial Decision at 16; CVM Exceptions at 6. The Initial Decision cites in support of this statement testimony by Dr. Marja Liisa Hanninen concerning the use in Denmark of an MIC of 1 μg/mL to define resistance, and whether raising the MIC to 4 μg/mL would result in reporting of lower prevalence of resistance in poultry Campylobacter isolates. Tr. at 692-694. As Bayer noted in its response to CVM's exceptions, Dr. Hanninen did not address the use of resistance for one fluoroquinolone as a measure of resistance to a second fluoroquinolone at all in her testimony, *see* Bayer Reply to CVM Exceptions at 14-15, and it does not appear to be a real issue in this case. I therefore reject this finding of the ALJ as it is not supported by the record.

[112] Dr. Silley's sworn testimony, B-1913 at 5-22, appears to be the "Executive Summary" of a literature review he prepared, which is attached to his testimony as Attachment 1. There are no references in the actual sworn testimony. Thus, it is difficult to ascertain the strength of the unsupported statements contained therein. In any event, his testimony about the appropriate breakpoint is essentially his own theory, based on a literature review, B-1913 at 13; he does not testify about any research he himself has actually done to demonstrate the appropriateness of a resistance breakpoint of 64 μg/mL. I also note that despite Bayer's arguments to the contrary, Bayer Exceptions at 138, the study by CVM witness Dr. Patrick F. McDermott, B-868, shows that when enrofloxacin was used at FDA-approved doses of 40 μg/mL in drinking water for 5 consecutive days, fluoroquinolone resistance developed rapidly and persisted in *C. jejuni* in broiler chickens. In that particular study, the MICs of ciprofloxacin-resistant isolates rose from 0.25 μg/mL to 32 μg/mL and that of enrofloxacin-resistant isolates from 0.06 μg/mL to 8 μg/mL. There is no information on the actual amount of the drug consumed by or excreted from individual chickens, and Dr. McDermott did not attempt to identify a clinical breakpoint. *See* B-868.

I disagree with Bayer's argument that the E-test is not sufficiently accurate for regulatory decisions. Bayer Exceptions at 139-41. Selection of a testing method is based on factors such as "the growth characteristics of the organism to be tested, practicality, flexibility, automation, cost, reproducibility, accuracy, and individual preference." Walker, G-1481 at 3. Standardized susceptibility testing involves one of three methods: agar dilution, broth dilution, or disk diffusion. *Id.*[113] The E-test is a diffusion testing method that can generate quantitative results. *Id.* at 4. Citing numerous references, Dr. Walker testified that the E-test, when employed in a single laboratory, is a "relatively accurate method to test antimicrobial susceptibilities of fastidious organisms," including *C. jejuni*. Walker, G-1481 at 8. The E-test is easy to use and useful for monitoring changes in the prevalence of ciprofloxacin resistance in *Campylobacter*. Tr. at 245-246. Most importantly, there is correlation between the E-test and other measures of resistance. *Id.* at 246-247. Dr. Walker's own research found that, with respect to ciprofloxacin, the agreement between the E-test and agar dilution MICs for 81 *C. jejuni* isolates and 54 *C. coli* isolates recovered from retail raw meats was 85.2%. Walker, G-1481 at 9; G-763. Using a breakpoint of either 1 or 4 μg/mL, Dr. Walker found in that study that the E-test underreported the number of ciprofloxacin resistant strains; in other words, the agar dilution found 21% of the isolates tested to be resistant, while the E-test found 18% to be resistant. *Id.*

Bayer's complaint with the E-test is, in part, that it is not NCCLS approved. *Id.* at 139-141. However, as discussed above, when much of the research before me was conducted, no NCCLS-approved test method existed. It was not until May 2002, after the research discussed in the administrative record was conducted, that NCCLS adopted agar dilution as the standardized antimicrobial test method for the *in vitro* measurement of animal-origin *Campylobacter* resistance to ciprofloxacin. Revised Joint Stipulations 29, 30. Likewise, it was not until April 2004, in a guidance to sponsors of new veterinary medicinal products for food-producing animals, that CVM recommended determination of MIC values "'[w]here possible'" with "'a validated and controlled method, such as those described in NCCLS documents.'" *See* Bayer Exceptions at 140.[114]

Bayer also argues that the E-test "overstates resistance at the higher end of the scale." Bayer Exceptions at 140. However, because of the bimodal pattern of resistance and the breakpoint being at the lower end, overstating resistance -- *e.g.*, reporting resistance at 32 μg/mL when it is really only 16 μg/mL -- is not relevant to determinations about the overall prevalence of fluoroquinolone resistance in *Campylobacter*.

In sum, I find that the microbiologic data relied on by CVM are reliable. For the reasons discussed above, I find acceptable and appropriate the use in these studies of the breakpoint criteria for *Enterobacteriaceae*, and I find that the use of the E-test was

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[113] These methods are described in detail by Dr. Walker. G-1481 at 3-4.

[114] The guidance did not become final until April 30, 2004, well after all of the studies in the administrative record were completed. 69 Fed. Reg. 23,795 (2004). Furthermore, the guidance does not mandate the use of agar dilution and is not binding on the agency; approaches other than the one set forth in the guidance may be used as long as they comply with applicable law. *See* 21 CFR § 10.115(d).

acceptable, widely used in the scientific community, and adequately validated, and that it is sufficiently reliable in the context of this proceeding.

E. Specific evidence linking fluoroquinolone-resistant Campylobacter *infections in humans to turkeys*

I also find that there is sufficient evidence in the record to support a determination that the use of enrofloxacin in turkeys poses human health risks similar to those posed by the use of the antibiotic in chickens. A number of the studies described in the preceding sections concerned turkeys as well as chickens. In addition, research specifically on turkeys demonstrates that, like chickens, they are easily colonized by *Campylobacter* species and stay colonized until slaughter. Jacobs-Reitsma, G-1459 at 4; G-686; Logue, G-1464 at 2, 7-8. Thus, I find that the record shows that, like chickens, commercially raised turkeys may become contaminated at the farm or during transportation and slaughter.

Retail turkey meat is second only to retail chicken meat in the extent to which it is contaminated with *Campylobacter*, although the data show that chicken is much more likely to be contaminated. Meng, G-1466 at 1-3; G-727; White, G-1484 at 2-9; G-746.[115] While the results of these studies may vary with regard to the percentage/occurrence of *Campylobacter* isolates from retail turkey meat, the evidence shows that the bacteria are present in retail turkey meat. For example, in their analysis of 719 samples of retail raw meats (chicken carcasses, turkey breasts, pork chops, and beef steaks), the University of Maryland researchers found that 14.5% of 172 turkey samples yielded *Campylobacter* (compared with 70.7% of the chicken samples, 1.7% of the pork samples, and 0.5% of the beef samples). G-727 at 2 (Table 2). Almost a fourth (24%) of the 92 sampling visits (to 59 stores) visited yielded *Campylobacter*-positive samples of turkey. *Id.* at 3. Preliminary data collected through NARMS showed 8% of 372 ground turkey samples were positive for *Campylobacter*, compared with 58% of 356 chicken breasts, 3% of 373 ground beef samples, and 2% of 343 pork chop samples. White, G-1484 at 4.

Consumption of turkey in commercial establishments has been shown to be a statistically significant risk factor in human cases of *Campylobacter* infection. Angulo, G 1452 at 10, 88 (Att. 3). In their study of patients with culture-confirmed *Campylobacter* infections, Friedman and colleagues found that eating chicken, turkey, or non-poultry meat prepared at a commercial food establishment were each independently significantly associated with illness. *Id.* They calculated the population attributable fraction of illness associated with turkey prepared at a restaurant at 4% (95% CI 1%-6%), compared with 24% who had eaten chicken prepared at a restaurant (95% CI 17%-30%). *Id.*

Bayer argues that turkeys are fundamentally different from chicken because there are some data indicating that turkeys are more likely to be contaminated with *C. coli* than

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[115] Bayer cites an apparently unpublished draft review article by Hollinger (G-945) on the issue of *Campylobacter* contamination of turkey. Dr. Hollinger's summary of a 1996-1997 turkey carcass rinse study cannot be relied on here because, although she provides four reference cites (typed references "104, 109, 110, and 111," with handwritten notes changing the numbering to "10, 11, 12, and 13," the draft of the paper included in the record does not contain any reference information corresponding to either set of numbers. Thus, I give no weight to this evidence.

with *C. jejuni*. Bayer Exceptions at 222. For example, in the University of Maryland study, *C. coli* were more often recovered from turkey samples than *C. jejuni*. Meng, G-1466 at 3; G-727 at 3.[116] While these data are interesting, further research would be needed to make definitive conclusions about their significance,[117] particularly since there is other evidence in the record that is contradictory.[118]

Even if turkeys are more likely to be predominantly colonized with *C. coli* than *C. jejuni*, it would not undermine my finding that serious questions exist on the safety of enrofloxacin use in turkeys. It is undisputed that live turkeys and retail turkey meat are contaminated with *both C. jejuni* and *C. coli*, as are chickens and other species, and that both are human pathogens. Bayer Exceptions at 222 and 229; *see also* Logue, G-1464 at 5-8; Jacobs-Reitsma at 4-5; G-686; Section III.A above. Although *C. jejuni* is estimated to cause about 90-95% of human *Campylobacter* infections, Nachamkin, G-1470 at 2, 3, some experts believe *C. coli* causes about 5-10% of infections attributed to *C. jejuni*, because it is difficult to differentiate between the two species in the laboratory. Nachamkin, G-1470 at 3; Tauxe, G-1475 at 2-3. Fluoroquinolone resistance develops in *C. coli,* as it does in *C. jejuni.* Logue, G-1464 at 8-9; White, G-1484 at 3; Meng, G-1466

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[116] Eighteen chicken samples and one turkey and one pork sample contained more than one *Campylobacter* species, and 2 chicken samples had 3 *Campylobacter* species. Meng, G-1466 at 3.

[117] I note that the University of Maryland study included a much larger sampling of chicken meat (595 isolates from 150 chicken carcasses) than of turkey meat (112 isolates from 26 turkey breasts). G-727 at 1 (type of meat) and 3 (Table 4).

[118] In her research, Dr. Catherine Logue found *Campylobacter* species distributions more similar to those found in chickens. Logue, G-1464 at 6, 8. Logue and colleagues sampled turkey carcasses at two Midwestern poultry processing plants monthly, over the course of a year, at three sampling points (pre-immersion in chill water, post chill, and the chill water itself, a source of cross-contamination). Logue, G-1464 at 5-6. They found that of the 2,414 pre-chill and post-chill swabs and chill-water samples, 34.9% were positive for *Campylobacter* species. *Id.* at 5. *Campylobacter* species most often isolated were *C. jejuni* and *C. coli*. *Id.* at 6. There were differences in species prevalence between the two plants -- at one plant, 51.6% of isolates were identified as *C. jejuni* and 40.5% as *C. coli*, while at the second plant 76.8% of the isolates were identified as *C. jejuni* and 14.6% as *C. coli*. *Id.* at 8. Dr. Logue cited earlier research as consistent with these findings on species prevalence. *Id.*

Bayer challenges Dr. Logue's research as "superficial and unreliable." Bayer Exceptions at 231. Among Bayer's specific complaints are Dr. Logue's alleged failure to "apply statistical analysis" and a lack of detail in some of her testimony. *Id.* I do not find that the record supports a finding that Dr. Logue's testimony is unreliable. Dr. Logue provided appropriate quantitative information. Although Dr. Logue's testimony does not indicate any history of antimicrobial use on the two farms, as Bayer points out, *id.* at 232, but that limitation is relevant only with respect to Dr. Logue's data on the prevalence of fluoroquinolone-resistant *Campylobacter*, and could be part of the explanation for the fact that 8.8% of the *Campylobacter* isolates from one turkey processing plant were resistant to ciprofloxacin, while 65.3% of the isolates at the second plant were resistant. *Id.* at 6. This issue, however, has no bearing on the issue of whether the *Campylobacter* that are present are *C. jejuni* or *C. coli*.

at 3-4.[119] Thus, I find that the research in the record concerning a possible difference in the proportion of *C. jejuni* in turkeys compared to the proportion of *C. jejuni* in chicken does not refute the evidence that turkeys, like chickens, are colonized with *Campylobacter* species capable of causing illness in humans.

In addition to the evidence that shows that turkeys are colonized with *Campylobacter* and that *Campylobacter* are often present on turkey carcasses and retail turkey meat, there is evidence of fluoroquinolone-resistant *Campylobacter* in turkey carcasses and retail turkey products. *See* Logue, G-1464 at 6-9 (8.8% of *Campylobacter* isolates from carcasses at one turkey processing plant in the Midwest, and 65.3% of the isolates from a second plant, were resistant to ciprofloxacin; G-1778; Meng, G-1466 at 3 (in University of Maryland research, isolates from 25 contaminated retail raw turkey meat samples, including *C. jejuni* and *C. coli*, "showed significantly higher resistance rates ($p<0.05$) to ciprofloxacin ... than *Campylobacter* isolates from retail chickens"); G-746; G-1352; White, G-1484 at 7 (9/151 retail turkey samples tested positive for *Campylobacter*, second only to chicken, and 5 of the 38 isolates from poultry found to be resistant to ciprofloxacin were from turkey); B-36 at 1, 2 (in study by Dr. Jacobs-Reitsma, 43% of 30 isolates from turkey flock were completely cross-resistant to quinolones tested).

Furthermore, in addition to these data specific to turkeys, I find that in all relevant respects turkeys are sufficiently similar to chickens that it is appropriate to rely on the studies solely concerning chicken contamination and exposure in evaluating the risks posed by turkey. *See Rhone-Poulenc*, 636 F.2d at 753 n. 3. Turkeys are colonized by *Campylobacter*, as are chickens; the pathogens are present on retail meat products; and people can and sometimes do become ill as a result of that contamination.

The emergence, selection, and mechanism of fluoroquinolone-resistant *Campylobacter* are not different in turkeys and chickens, and are based on the antibiotic-bacteria interaction, not the host species. Levy, G-1463 at 4. Bayer, relying in part on testimony by Dr. Eric Gonder, A-201, and Dr. Dennis Wages, B-1917, that was stricken from the record, *see* Order, March 3, 2003, argues that differences in production and marketing of turkeys and chickens (*e.g.*, more turkeys sold cooked or processed) may play a role in the lower risk associated with turkeys as compared with chickens. *See* Bayer Exceptions at 224. These alleged differences, even if demonstrated, do not undermine the basic point that turkeys and retail turkey meat are contaminated with *Campylobacter*; fluoroquinolone use in turkeys results in fluoroquinolone resistant *Campylobacter* in live turkeys and on retail turkey meat; and consumption of turkey meat is associated with human illness. As described in Section III.B.1, the mechanism by which ill turkeys are treated with enrofloxacin is the same as for chickens, *i.e.*, treatment of an entire flock through drinking water. *See* McDermott, G-1465 at 6-7; A-54. Indeed, the package insert for Baytril® does not differentiate between treating chickens or turkeys. *See* A-54. The drug insert states, "based upon comparisons of intravenous versus oral gavage doses of enrofloxacin solution, data from bioassays conducted in

[119] Resistance to fluoroquinolones may be higher in *C. coli* than in *C. jejuni*. G-763 at 12; Meng, G-1466, at 3; White, G-1484 at 3; Pasternack, B-1909 at 9.

chickens and turkeys indicate that bioavailability of oral enrofloxacin exceeds 84% in both species." *Id.*

Finally, Bayer argues that CVM's risk assessment does not provide a basis for withdrawing Baytril use in turkeys since it only encompasses data about chickens. Bayer Exceptions at 228-230. This argument is specious. While it is true that the risk assessment only evaluated the public health impact of fluoroquinolone use in chickens, it is reasonable to conclude, in light of the record evidence concerning turkeys, that the risk assessment provides a reasonable basis on which to infer that there is a parallel, measurable incremental impact on human health associated with consumption of turkeys contaminated with fluoroquinolone-resistant *Campylobacter*. Indeed, evidence from the University of Maryland and other studies demonstrates that fluoroquinolone resistance is higher in *Campylobacter* isolates from retail turkey samples than from chicken samples, *see* Meng, G-1466 at 3, the CVM risk assessment may actually underestimate the full public health impact of enrofloxacin use because it only addresses chicken and not all poultry. Finally, while the risk assessment is helpful in estimating the public health impact of the use of enrofloxacin in poultry, it was not necessary for CVM to prepare a risk assessment for it to demonstrate that there are serious questions about the safety of enrofloxacin use in poultry.

In sum, for the reasons set out above, I find that CVM has met its burden of showing that there are serious questions about whether the use of enrofloxacin in turkeys is safe, similar to the questions that are posed by the use of enrofloxacin in broiler chickens.

IV. DISCUSSION OF LEGAL ISSUES

A. New evidence

1. Meaning of "new" evidence

As set out above, § 512(e)(1)(B) of the FDCA requires withdrawal of a new animal drug application if the Commissioner finds that "new evidence not contained in [a new animal drug] application or not available to the [Commissioner] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Commissioner] when the application was approved" shows that the new animal drug is no longer shown to be safe. 21 U.S.C. § 360b(e)(1)(B). The ALJ held that CVM's evidence met this standard and that the term "new evidence" encompasses not only data developed after approval, but also reevaluation of data that existed prior to approval. Initial Decision at 6.[120]

In its exceptions, Bayer contests whether there is "new evidence" on enrofloxacin use in poultry. Bayer Exceptions at 15-19. Bayer argues that evidence about a drug that is generated after approval of the drug cannot be "new evidence" under § 512(e)(1)(B) of the FDCA unless it "points to a different conclusion that was not contained in the original application ...." *Id.* at 16. In effect, Bayer argues that if FDA is aware that a human

[120] Because I find that CVM relies on new evidence, I do not need to reach the latter issue.

health risk could occur or exists when it approves a new animal drug, then post-approval evidence relating to that risk cannot be "new evidence."

Bayer's interpretation of the term "new evidence" means that, in order to determine if a piece of evidence relied on by CVM is "new," I must look at the content of the evidence to see whether what it shows in terms of safety is conceptually "new."[121] While it is clear that the content of the evidence is critical to my determination of whether CVM has met its burden to produce evidence raising serious questions about enrofloxacin's safety, I do not find support for such a content-driven definition of "new" in the statute or its legislative history. To the contrary, § 512(e)(1)(B) requires that I must make my determination about whether an animal drug "is not shown to be safe" based on "new evidence ... evaluated together with the evidence available to [me] when the application was approved." 21 U.S.C. § 360b(e)(1)(B). In other words, I must find both that there is "new" evidence, and that that the collective weight of the evidence in front of me, old and new, shows that the drug in question is no longer shown to be safe.

The word "new" is not defined in § 512. Neither is "new" defined in § 505,[122] one of the predecessors to § 512, nor elsewhere in the FDCA.[123] When used as an adjective, a contemporaneous (1960) dictionary provides numerous possible meanings for "new":

- "having existed or having been made but a short time: having originated or occurred lately: not early or long in being : RECENT, FRESH, MODERN -- opposed to old ‹a ~ coat› ‹a ~ regime› ‹~ fashions›"
- "having been seen or known but a short time although perhaps existing before; recently manifested, recognized or experienced: NOVEL ‹a ~ crop for this region›; *broadly*: STRANGE, UNFAMILIAR ‹~ doctrines› ‹~ concepts› ‹liked visiting ~ places›"

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[121] Bayer cites to *Upjohn v. Finch*, 422 F.2d 944 (6th Cir. 1970), to support its argument that evidence must point to a different conclusion to be considered "new." Bayer Exceptions at 16. However, the Sixth Circuit's discussion of "new evidence" focuses on when the evidence was available to FDA, not what it showed, 422 F.2d at 951, so I see nothing in this case that supports Bayer's argument. Bayer also relies on statements from *Hess & Clark*, 495 F.2d at 992, Bayer Exceptions at 16. The "newness" of the evidence was not in issue in that case, however, and the statements Bayer cites are simply general statements that describe § 512 of the FDCA.

[122] Section 505(e)(1)(B) was enacted in 1962 as part of the Drug Amendments of 1962, Pub. L. No. 87-781, § 102(d) (1962). As explained in greater detail in section VI.B.2, the relevant portions of § 512 were created by combining elements of § 505 of the FDCA, 21 U.S.C. § 355, which deals (now) with new drugs for human use and § 409 of the FDCA, 21 U.S.C. § 348, which addresses food additive safety. Section 512(e)(1)(B) was taken, almost word for word, from § 505(e)(1)(B), 21 U.S.C. § 355(e)(1)(B). Hence, the legislative history of § 505(e)(1)(B) is also the legislative history of § 512(e)(1)(B).

[123] The word "new" is used in the FDCA in §§ 201(p) and 201(v), which define the terms "new drug" and "new animal drug." 21 U.S.C. §§ 321(p) & (v). As their definitions make clear, these terms are both terms of art. Thus, the discussion of "new" in this Final Decision is not relevant to the meaning of "new" when used in the terms "new drug" or "new animal drug."

- "being other than former or old: having freshly come into a relation (as use, connection, or function) ‹turning a ~ leaf› ‹the ~ teacher› ‹a ~ product› ..."
- "having been in a relationship, position, or condition but a short time and usu. lacking full adaptation thereto ‹a ~ new member› ‹~ from school› ‹~ to the plow›"
- "beginning or appearing as the recurrence, resumption, or repetition of a previous act or thing ‹a ~ year› ‹a ~ start› ‹a ~ edition›"
- "RENOVATED: RECREATED, REGENERATED ‹rest had made him a ~ man›"
- "different or distinguished from a person, place, or thing of the same kind or name that has longer or previously existed ‹the ~ reservoir› ‹the ~ theology› ..."
- "of dissimilar origin and usu. of superior quality to or capable of causing improvement in what preexists ‹introducing ~ blood into an ancient but outworn line› ‹try a ~ strain of hybrid corn› ..."

Webster's Third New International Dictionary 1522 (1960).[124]

Not all of these definitions make sense when placed in the immediate textual context of § 512(e)(1)(B), *i.e.*, as an adjective that modifies "evidence." The five meanings that are not facially inapplicable are:

- "having existed or having been made but a short time: having originated or occurred lately: not early or long in being ..."
- "having been seen or known but a short time although perhaps existing before; recently manifested, recognized or experienced ..."
- "being other than former or old: having freshly come into a relation (as use, connection, or function) ..."
- "different or distinguished from a person, place, or thing of the same kind or name that has longer or previously existed ..."
- "of dissimilar origin and usu. of superior quality to or capable of causing improvement in what preexists ...."

None of these contemporaneous meanings of "new" supports Bayer's interpretation. Applying each of these definitions as an adjective to "evidence," the first three meanings of "new" relate to when the evidence was created or uncovered, not what it shows. If these meanings pertain, then any evidence created or uncovered after approval would be "new." The fourth meaning relates to similarity (or difference) between evidence that has been in existence less time than was previous evidence or was not previously in existence at all. While the idea of "different" or "distinguished from" previous evidence has some facial similarity to Bayer's argument that the content of the evidence plays a key role in determining whether it is "new," this definition does not require that the older and newer

[124] Unquoted parts of the definition dealt with usage that was plainly not applicable, *e.g.*, relating to land, family, and language. *Webster's Third* at 1522.

evidence be substantively different.[125] Finally, the fifth meaning would relate to difference as well, but to origin and quality. Under this meaning, if evidence has a different origin and adds to what the existing evidence shows, the evidence would be "new" even if it were similar in some ways.

Thus, I find that standard dictionary definitions of "new" fully support a determination that "new" evidence means evidence not previously seen or available, regardless of what the content of that evidence is and the extent to which it is consistent with previously available data.

The context in which "new" is used also informs my analysis of its meaning. First, the additional descriptions of evidence that follow "new evidence" in that provision -- "not contained in such application or not available to the Secretary until after such application is approved" -- emphasize that "new" refers to evidence that was not in front of CVM when the original application was approved. In addition, § 512(e)(1)(B) also calls for withdrawal when "tests by new methods, or tests by methods not deemed reasonably applicable when [the] application was approved" show that a drug is no longer shown to be safe. When used here, "new" clearly relates to when the method was developed or discovered -- methods that existed when an application became effective are described in the text that follows "new methods." Moreover, as noted earlier, the way § 512(e)(1)(B) is written indicates that whether the evidence is "new" is separate from what the evidence shows.

Nothing in the legislative history of this provision suggests a different result. This language was added by the Drug Amendments of 1962, Pub. L. No. 87-781, § 102(d) (1962). It was developed in response to requests from the Secretary of Health, Education, and Welfare and President Kennedy that FDA be given additional authority to remove approved drugs from the market if "substantial doubt" arose as to safety or effectiveness after approval.[126] Letter from President John F. Kennedy to Senator James O. Eastland (April 10, 1962), *reprinted in* 108 *Cong. Rec.* 10,105 (1962). Industry objected to the Administration's proposal as too broad and proposed instead that "FDA should have authority, after a hearing, to withdraw a new drug from the market if in light of new evidence it is not shown to be safe ...." *Hearings before the House Committee on Interstate and Foreign Commerce on H.R. 11581 and H.R. 11582*, 87th Cong. 177 (1962). Industry representatives testified that they were concerned that the

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[125] Consider, for example, a person who buys identical shoes from year to year; under this definition, the person can say that one pair of shoes is "new," despite their being identical to last year's pair.

[126] Prior to the 1962 Amendments, § 505(e) read:

> The effectiveness of an application with respect to any drug, after due notice and opportunity for hearing to the applicant, shall by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective or (2) that such application contains any untrue statement of a material fact. The order shall state the findings on which it is based.

21 U.S.C. § 355(e) (1961).

Administration's proposal would allow withdrawal "on the basis of any evidence -- even just the evidence in the NDA [*i.e.*, new drug application] file alone." *Id.* at 240 (testimony of Dr. Klump, M.D., President of Winthrop Labs and Pharmaceutical Manufacturers Association Board Member).

The final House and Senate versions of the 1962 Amendments both contained the provision at issue here. According to the House Report, what became § 505(e)(1)(B) allows FDA to withdraw approval of a new drug "if, on the basis of new evidence, evaluated with that originally submitted, the Secretary finds the drug is no longer shown to be safe...." H.R. Rep No. 87-2464, at 8 (1962). The Senate Report stated:

> The purpose of the proposed legislation, as amended, is to strengthen and broaden existing laws in the drug field so as to bring about better, safe medicine and to establish a more effective system of enforcement of the drug laws....
>
> The bill ... would permit the prompt removal from the market of [new] drugs when new evidence, considered with what was known originally, establishes that the drug should not have been cleared for safety in the first instance.

S. Rep. No. 87-1744 (Part 1), at 8 (1962); *see also id.* at 17.

Based on the foregoing analysis of the plain meaning, context, and legislative history, I believe that Congress unambiguously intended "new" to relate simply to when the evidence was developed or discovered and whether it is evidence other than that relied on for approval.

Although I have concluded that Congress has spoken to the precise question at issue here, *Chevron, U.S.A., Inc. v. NRDC, Inc.*, 467 U.S. 837, 842 (1984), were I to conclude that the statute was ambiguous, I would adopt the same interpretation of "new." If the FDCA is silent or ambiguous as to the meaning of "new," I may define "new evidence" in a reasonable fashion. *Chevron*, 467 U.S. at 842-843; *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000). For the reasons set out below, I conclude that the definition of "new" I have just articulated is reasonable.

First, I believe that the interpretation I set out above is consistent with the plain meaning of the statutory language, the statutory purpose, as evidenced by the meaning of "new," the context, and the legislative history. Second, I believe sound policy reasons support my choice. Bayer's stated position is that evidence relating to a risk or potential risk that FDA was aware of during the approval process is not "new evidence." Bayer Exceptions at 15-17. Were I to adopt this interpretation of "new evidence," I would be limiting the agency's ability to rely on additional evidence about the risk to support withdrawals, even when that evidence shows that, contrary to what was anticipated based on information available at the time of approval, the risk is much more common or cannot be appropriately controlled. The 1962 Amendments were not intended to produce this result. It would mean that products about which serious safety questions are raised could not be taken off the market until we could demonstrate that the products are in fact unsafe -- the very result the1962 Amendments were intended to change. Furthermore, if I adopted Bayer's interpretation, I would be precluding FDA from acting even when the evidence confirms a suspected risk, shows that a risk is more common or serious than previously believed, or calls into question whether a risk is being adequately

controlled.[127] The result could well be slower or fewer approvals if FDA concludes it is not willing to let products on the market without the possibility of withdrawal of approval if later experience does not bear out FDA's assessment of the risks.

Thus, to determine whether the proffered evidence is "new," I conclude that I must ask: When was the evidence developed or when was it made available to FDA? Is it the same evidence as the evidence relied on for approval? If the proffered evidence was developed or discovered after approval and is not the evidence relied on for approval, then it is "new."

2. CVM's evidence

The evidence shows that much of the information available to CVM is new because it was developed after enrofloxacin was approved and is different from information available to the agency when it approved enrofloxacin.

It is clear from the record that a large part of the epidemiologic studies and most of the microbiologic and molecular studies relied on by CVM were published after approval of the NADA. The newer epidemiologic studies are typically larger than earlier studies, were conducted in the United States, and some focus on fluoroquinolone-resistant infections. *See, e.g.*, Angulo, G-1452 and attachments (describing FoodNet studies). Moreover, since approval of the use of enrofloxacin in poultry, the NARMS program was established; this program has provided critical data not previously available to CVM on trends in fluoroquinolone-resistant *Campylobacter* in humans, animals, and retail meats in the United States. Tollefson, G-1478 at 4-5, 14.

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[127] Bayer's concept of newness could have significant detrimental implications for the drug approval process. As part of the assessment of new drug safety, product sponsors submit data from various test or trials and, on the basis of that data and other information and knowledge, FDA seeks to identify if the intended use of the product could present health risks. The data upon which FDA approves products is very extensive. However, studies are done under controlled conditions and with smaller numbers of subjects than are likely to be exposed to the drug after approval. The data thus are not a perfect predictor of how the safety of the product will play out when the product is in use in the general population. Furthermore, the existence of, or potential for, a health risk may not render a product unapprovable, as some health risks can be managed or controlled. *Cf. Stauber v. Shalala*, 895 F. Supp. 1178, 1184, 1191-92 (W.D. Wisc. 1995) (FDA approach to evaluating target animal safety for new animal drugs is a "manageable risk" approach). Thus, when a risk or potential risk is identified during the approval process, FDA can have a choice: ask for additional pre-approval testing, which could slow down the drug development process and make drugs more expensive, or impose risk management controls that address the identified risks and conduct post market surveillance to ensure that the controls are working using, among other tools, the adverse event reporting required under §§ 505(k) and 512(1) of the FDCA, 21 U.S.C. §§ 355(k) & 360b(l). Both sections state that one of the purposes of requiring records and reports is to "enable [FDA] to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e)...." 21 U.S.C. §§ 355(k)(1) & 360b(l)(1). Some of the FDA regulations implementing these provisions can be found at 21 CFR § 314.80 and 21 CFR § 514.80.

Most of the microbiologic and molecular studies were also published after approval of the NADA, and they use new analytical methods, including, in particular, new genotyping techniques; some of this research also focuses specifically on fluoroquinolone-resistant infections. *See, e.g.*, McDermott, G-1465 at 4 (describing investigation in 2001 of ciprofloxacin resistance in *Campylobacter* isolates from chickens treated with enrofloxacin and sarafloxacin at the FDA-approved doses; the research used the agar dilution method, which was not available at the time enrofloxacin was approved). McDermott, G-1465 at 4. Other similar studies include work by Bayer expert Dr. Diane Newell, *see* McDermott, G-1465 at 4, 25, and work by Zhang and colleagues, who in 2002 published findings that fluoroquinolone-resistant *Campylobacter* emerge in chickens within 24-48 hours after treatment with enrofloxacin, McDermott, G-1465 at 4; G-1800 at 2-3.

Even if I adopted Bayer's interpretation of "new," I would find that the evidence that CVM relies on is "new." There is no dispute that CVM was aware at the time it approved the NADA for enrofloxacin that allowing the use of fluoroquinolones in food-producing animals posed some risk of transfer to humans of *Campylobacter* resistant to fluoroquinolones. *See* Revised Joint Stipulations 2-3, 5. In particular, CVM was aware of limited epidemiologic research by Endtz and others positing a temporal association between the use of fluoroquinolones in chickens in Europe and an increase in fluoroquinolone-resistant *Campylobacter* isolates from humans in Europe. Revised Joint Stipulation 4. However, as discussed below, the record demonstrates: 1) that CVM did not know whether the resistance trends seen in the limited data available were a result of poultry production practices not typical of the United States; and 2) that CVM believed that it could mitigate or even eliminate any risk of human infection with fluoroquinolone-resistant *Campylobacter* through use restrictions.

At FDA's joint Veterinary Medicine and Anti-Infective Drugs Advisory Committee meeting in May 1994, held to address the specific issue of approval of fluoroquinolones for use in poultry," Tollefson, G-1478 at 4; *see also* Tr. at 73, representatives of the U.S. poultry industry and pharmaceutical sponsors of the poultry fluoroquinolones "assured CVM that the broiler and turkey production practices in the foreign countries were markedly different from the U.S. situation, to the extent that fluoroquinolone use in chickens or turkeys was unlikely to result in the emergence and dissemination of fluoroquinolone-resistant enteric bacteria in the United States." Tollefson, G-1478 at 13. Dr. Tollefson testified that, at that meeting, the committee was mixed on whether to approve the fluoroquinolones at all, but unanimous in recommending use restrictions and surveillance. *Id.* FDA adopted these recommended restrictions, which included: approval of fluoroquinolones only for therapeutic use by veterinary prescription; prohibition of extra-label use;[128] and working with federal and state entities to establish a nationally representative surveillance system to monitor resistance trends among human and animal enteric bacteria (the NARMS program).[129]

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[128] Uses of therapeutics not approved by FDA are considered to be "extra-label." Tollefson, G-1478 at 4.

[129] Bayer's Exceptions, and the testimony of Bayer witness Dr. Anthony E. van den Bogaard, B-1916, are misleading in their representation of the Advisory Committee proceedings. For just two examples, statements attributed by Bayer to the Joint Advisory Committee, Bayer Exceptions at

Tollefson, G-1478 at 4, 14; *see also* G-219 and B-1819.[130] While presentations by meeting participants and the discussion of the committee members indicate that committee members were in general fairly certain that some resistance would occur and that there would be some transmission between animal and human populations, there was broad uncertainty about the mechanisms and scope of such resistance. Tollefson, G-1478 at 4, 14. While CVM was aware of the limited foreign studies on selection of fluoroquinolone-resistant Campylobacter in poultry, at the meeting there was information presented by representatives of the U.S. poultry industry and by the sponsors of the poultry fluoroquinolones that the resistance described in that country might not be realized in the United States due to differences in broiler and turkey production practices.[131] Tollefson, G-1478 at 13. Thus, based in part on these assurances, CVM believed that the development of fluoroquinolone resistance among *Campylobacter* in poultry and the associated public health risks could be prevented or substantially

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214-15, are, in fact, statements made not by a member of the Joint Committee (or by a CVM representative) but rather by two witnesses before the Committee, Dr. Thomas R. Beam Jr. of the Buffalo Veterans Administration Hospital, B-1819 at 70, 95, and Dr. Tom Murphy of Abbott Laboratories, G-219 at 133, 135. In addition, it bears noting that other witnesses before the joint committees challenged the reliability of the Endtz data from the Netherlands; for example, Dr. Dan Upson called those data "circumstantial at best," Exhibit B-1819 at 59-60, and argued that there is "no evidence to support the allegations that the use of antibacterials in veterinary medicine increases the number of resistant antibiotic strains in humans." *Id.* at 60. In any event, because a transcript of the proceedings is in evidence, the transcript is better evidence of what occurred than Dr. van den Bogaard's testimony.

[130] B-1819 is the transcript of the meeting on Wednesday, May 11, 1994, and G-219 contains the transcript of Thursday, May 12, 1994.

[131] Bayer is inconsistent in the value it gives the European data. On the one hand, it argues that the limited European data available before CVM approved enrofloxacin are useful in this proceeding and show that the outcome of the approval of enrofloxacin and sarafloxacin in the United States was "predictable and expected" and that therefore the subsequent investigations of resistance patterns in U.S. poultry, retail chicken products, and human infections, and of the health impacts of such resistance, are not "new." Bayer Exceptions at 218-219. Elsewhere, however, Bayer argues that "[s]tudies involving non-U.S. populations are entitled to little weight. ...The risk factors for campylobacteriosis may be different in foreign countries, the human and veterinary treatment practices may differ as well, affecting the course and duration of illness. Without controlling for these factors, it is not at all clear the relevance to this proceeding...." *Id.* at 5-6. Bayer is incorrect that non-U.S. data *per se* lacks relevance to the United States; rather, like all data, European and other studies must be evaluated for relevance to the U.S. situation. No industrialized country's experience with fluoroquinolone resistance in *Campylobacter* is irrelevant, but neither will any other nation's experience completely parallel that of the United States.

There is no evidence in the record that use conditions in the Netherlands at the time Endtz conducted the early research discussed at the Joint Advisory Committee meeting were "virtually the same" as the U.S. labeling conditions placed on enrofloxacin at the time of approval, as Bayer asserts, *see* Bayer Exceptions at 216; to the contrary, there is evidence, *see* G-190 at 4, 7, that use in the Netherlands was more extensive from the time the product was introduced in 1987 than Bayer claims has been customary (and than the use restrictions authorize) in the United States, Bayer Exceptions at 218.

mitigated by the use restrictions and monitoring procedures that CVM put into place as part of the approval. *Id.* at 14. The evidence gathered after enrofloxacin's approval does show something different and new about the safety of enrofloxacin: it shows that the restrictions on use, which CVM imposed when it approved the use of enrofloxacin in chickens and turkeys, have not been effective in preventing the emergence of fluoroquinolone-resistant *Campylobacter* in poultry or in mitigating the human health impacts of such emergence. *Id.* at 14-20. Evidence that control mechanisms adopted as part of the approval are not effective in preventing or mitigating harm and the risk of harm clearly "points to a different conclusion" regarding safety, and is thus "new," even under Bayer's interpretation of the word.

In sum, the retail meat studies and human epidemiologic investigations described more fully in section II, collected as part of the NARMS and otherwise, both provide new evidence not available to CVM at the time of its approval decision, and provide new evidence that the efforts by CVM to prevent or mitigate the potential harm through use restrictions were not successful.

B. The meaning of "safe"

1. Introduction

A central issue in the proceeding is whether, under § 512(e)(1)(B) of the FDCA, enrofloxacin "is not shown to be safe for use under the conditions of use upon the basis of which the application was approved...." 21 U.S.C. § 360b(e)(1)(B). The ALJ determined that "safe" in the context of assessing the human food safety of a new animal drug means that there is a "reasonable certainty of no harm." Initial Decision at 8. The ALJ also held that "the safety concern in this matter is limited to human food safety and human health impact, and the proper risk-benefit analysis considers only whether the benefits to human health from the use of enrofloxacin in poultry are proven to outweigh the risk to human health from such use." *Id.* at 9. The ALJ noted that there are effective alternatives to enrofloxacin[132] and that FDA is not required to put humans at risk to benefit animals. *Id.* The ALJ thus declined to weigh animal health and welfare benefits against risks to humans. *Id.* Finally, citing two Supreme Court rulings, *American Textile Manufacturers Institute, Inc. v. Donovan*, 452 U.S. 490 (1981), and *Whitman v. American Trucking Ass'ns*, 531 U.S. 457 (2001), for the proposition that costs cannot be considered as part of a safety or health assessment without explicit authorization, the ALJ rejected consideration of economic costs of the decision to withdraw approval of the use of enrofloxacin in poultry. Initial Decision at 9-10.

Bayer objected to the use of the "reasonable certainty of no harm" standard to the extent it was inconsistent with the use of cost-benefit or risk-benefit analysis. *E.g.*, Bayer Exceptions at 23. For the reasons discussed in this section, I agree with the ALJ that when assessing whether food from animals treated with a new animal drug is safe for human consumption, it is correct to frame the meaning of "safe" as presenting a "reasonable certainty of no harm." I conclude, as FDA has before, that an assessment of the human health impacts of the use of a particular drug in food-producing animals under the "reasonable certainty of no harm" standard involves a straightforward evaluation of

[132] This issue is discussed in more detail at section IV.B.2, below.

the human safety of the animal drug; it does not encompass any weighing of costs and benefits, including any weighing of human safety concerns (in other words, health risks) against human health benefits.[133] *Nitrofurans,* 56 Fed. Reg. 41,902, 41,903; *DES*, 44 Fed. Reg. 54,852, 54,881-83; *see also Olestra,* 61 Fed. Reg. 3118, 3120. I find that the FDCA as a whole, as well as its legislative history, makes clear that Congress did not intend to allow FDA to weigh costs or benefits associated with the use of a new animal drug in deciding whether its use has been shown to be safe for humans when used in food-producing animals.

2. FDA's two-part approach to assessing safety of new animal drugs used in food-producing animals

When FDA reviews an application for approval of a use of a new animal drug in a food-producing animal, the agency must find: 1) that the drug is safe and effective in the target animal, and 2) that food from the animal is safe for human consumption. *Stauber v. Shalala*, 895 F. Supp. 1178, 1190 (W.D. Wisc. 1995). This two-part approach has its origins in two sections of the FDCA that, until 1968, applied to approval of drugs used in food-producing animals: the new drug approval provisions in § 505, 21 U.S.C. § 355, which applied to new drugs for both animals and humans, and the food additive approval provisions of § 409, 21 U.S.C. § 348. Before 1968, under these two distinct provisions of the FDCA, a drug for use in a food-producing animal had to be approved as safe and effective in the target animal under the new drug provisions of § 505 and any substance formed in or on food as a result of its use as an animal drug had to be approved as safe under the food additive provisions of § 409. *See* H.R. Rep. No. 90-2168, at 2 (1968); *Hearing before the Subcomm. on Health of the Comm. on Labor and Public Welfare on S.1600 and H.R. 3639*, 90th Cong. 92-96 (1968) (AHI testimony and charts describing pre-1968 approval process for animal drugs). Thus, applicants had to submit two different applications to FDA, and each application was reviewed by a different part of the agency.

In the Animal Drug Amendments of 1968 (1968 Amendments), Congress streamlined the process by combining parts of § 505 and § 409 into a new section, § 512. Pub. L. No. 90-399, § 101(b) (1968). Congress created a category of drugs called "new animal drugs" (defined in § 201(w) of the FDCA, 21 U.S.C. § 321(w)) and excluded them from the definition of "new drug" at § 201(p) and from the definition of "food additive" at § 201(s). Because § 512 contained the necessary language from both § 409 and § 505, after 1968, FDA continued to apply the same two approval standards (safe and

[133] Different terms have been used throughout this proceeding to describe the weighing of costs and benefits. The ALJ, as well as Bayer and CVM, generally use the term "risk-benefit analysis" to refer broadly to consideration of animal and human health effects, economic effects, and environmental effects, but "cost-benefit analysis" when referring to economic effects. Initial Decision at 8-9; Bayer Exceptions at 21-23; CVM Reply to Bayer Exceptions at 5-6. I use the term "cost-benefit" analysis to refer to a broad assessment of health, economic, and environmental costs and benefits. I use "risk-benefit analysis" or "risk-risk analysis" to refer to a subset of cost-benefit analysis -- the assessment of the human health effects.

effective as a drug, and safe as a food additive) to new animal drugs as it had before 1968.[134]

Because an explanation of the origins of each of these predecessor provisions (§§ 505 and 409) and FDA's subsequent interpretation of them is critical to understanding how FDA applies § 512 to new animal drugs for use in food-producing animals, I provide it below.

a. FDA's interpretation of "safe" in § 505

Section 505 was enacted in 1938, as part of the FDCA. Pub. L. No. 75-717, § 505 (1938). It required the submission of an application for approval of a use of a new human drug (and, until 1968, a use of a new animal drug). Section 505 also provided that a NDA became effective unless FDA determined, among other things, that the NDA did not include adequate safety data or that the data "show that such drug is unsafe" under its conditions of use. *Id.* The 1938 FDCA did not define "safe." The legislative history likewise contains no definition of "safe." The legislative history states only that the purpose of the addition was to require that manufacturers adequately test new drugs for safety for their prescribed use before the new drugs are marketed. H.R. Rep. No. 75-2139, at 9 (1938).[135]

Since § 505's enactment in 1938, FDA has interpreted the new drug safety standard to include a balancing of health benefits (*i.e.*, effectiveness) and health risks (*i.e.*, safety) to the patient. *See, e.g., Terfenadine; Notice of Opportunity for a Hearing*, 62 Fed. Reg. 1889, 1891 (Jan. 14, 1997). In other words, the risk-benefit analysis that FDA performs when reviewing a new drug is limited to health impacts. Then-FDA Commissioner George Larrick explained, during hearings in the mid-1960s, that FDA, from 1938 on, has interpreted "safe" in § 505 not to mean free from risk, but to mean that the health benefits to a patient of taking a new drug outweighed the health risks to the patient of taking the drug:

> Basically drugs have certain degrees of toxicity. If we had used the term "safety" in the dictionary definition, we would have taken nitroglycerin off the market, sulfanilamide off the market, and drugs the value of insulin off the market [sic]. It was obvious to us as administrators that was not what Congress intended. So taking what we thought was the legislative history of this section into account, we then announced to the world and repeatedly announced in hearings before the Interstate and Foreign Commerce Committee and before the appropriation committees of Congress ... and we repeatedly in our public pronouncements said that in dealing with lifesaving drugs we would have to consider whether a drug was effective in considering safety.

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[134] The legislative history indicates that this continued use of the two standards is what Congress expected: "The enactment of this legislation would merely consolidate provisions under existing law and would in no way weaken the authorities of the Food and Drug Administration with respect to the regulation of animal drugs." H.R. Rep. No. 90-2168, at 1, 3.

[135] Section 505 was adopted late in the legislative process to avoid a repeat of a tragedy that occurred in 1937 in which "nearly 100" people died due to ingestion of elixir sulfanilamide, an untested product that was highly toxic. H.R. Rep. No. 75-2139, at 9.

Drug Safety (Part 1): Hearings Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations 185 (1964).

Thus, although efficacy was not expressly made part of § 505 when the FDCA was enacted in 1938, the agency nonetheless included an evaluation of the efficacy of critical new human (and animal) drugs in treating or preventing human (and animal) illness in its review of the product's safety. In 1962, with the enactment of the Drug Amendments of 1962, the approval standard for new drugs was amended to include a requirement that new drugs be shown not only to be safe, but also to be effective. Pub. L. No. 87-781, § 102 (1962). Thus, Congress signaled its agreement with FDA's risk-benefit approach to safety in the context of new drug safety evaluations under § 505.[136] In the legislative history of the 1962 amendments, Congress recognized and approved of FDA's practice of considering effectiveness (or therapeutic benefit) as part of safety in some situations:

> [FDA] now [in 1962] requires, in determining whether a 'new drug' is safe, a showing as to the drug's effectiveness where the drug is offered for use on the treatment of a life-threatening disease, or where it appears that the 'new drug' will occasionally produce serious toxic or even lethal effects so that only its usefulness would justify the risks involved in its use. In such cases, the determination of safety is, in light of the purposes of the new drug provisions, considered by [FDA] to be inseparable from consideration of the drug's effectiveness.

S. Rep. No. 87-1744, at 15 (1962); *see also* H.R. Rep. No. 87-2464, at 3 (1962).[137]

The target animal safety standard of § 512 originated from the new drug safety standard used in § 505 which, until 1968, applied to both human and animal drugs. Thus, FDA, when implementing the 1968 Animal Drug Amendments, continued to use, and still uses, this same standard when it is reviewing whether a new animal drug is safe for use in or on the target animal. Thus, FDA may, in evaluating a NADA, look at both the risks and benefits a new animal drug will have with respect to the target animal. *DES*, 44 Fed. Reg. 54,852, 54,881. Section 505 however, provides no direct insight into the process by which FDA evaluates the human food safety of animal drugs. Rather, it concerns only the first part of the two-part test enunciated in *Stauber,* 895 F. Supp. at 1190; in other words, a risk-benefit analysis is appropriate in determining whether the new animal drug is safe and effective for its intended use in the target animal.

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[136] One event precipitating the passage of the 1962 Amendments was another drug tragedy – this time involving thalidomide, which FDA struggled to keep off the market due to reports from Europe of severe birth defects in children born to women who had taken the drug. 108 Cong. Rec. 14,678 (1962) (statement of Sen. Kefauver).

[137] As this and other evidence from the enactment of the 1962 Amendments makes clear, Congress has long acquiesced in and indeed ratified FDA's interpretation that "safe" in the context of § 505 incorporates risk-benefit considerations, despite the plain meaning of the word "safe." *See, e.g., Barnhart v. Walton*, 535 U.S. 212, 220 (2002); *Public Citizen v. HHS*, 332 F.3d 654, 668-69 (D.C. Cir. 2003) (congressional ratification cannon applies where there is evidence that Congress was aware of agency interpretation and amended the relevant provisions).

b. FDA's interpretation of "safe" in § 409

Section 409 of the FDCA was enacted in 1958. Pub. L. No. 85-929, § 4 (1958). Section 409(a), 21 U.S.C. 348(a), requires that uses of "food additives" be approved by FDA as safe prior to their use in food. A "food additive" was originally defined in 1958 as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of or otherwise affecting the characteristics of any food" that was not "generally recognized as safe," a pesticide chemical, or "prior sanctioned." Pub. L. No. 85-929, § 2. This broad definition of food additive included drugs used in animal feed and food-producing animals. Therefore, these animal drugs were subject to § 409's safety standard.

Congress defined "safe" for purposes of § 409. Section 201(t) (now § 201(u)) provided: "The term 'safe' as used in paragraph (s) of this section [the definition of food additive] and in section 409, has reference to the health of man or animal." Pub. L. No. 85-929, § 2. Section 409 also tells FDA what factors to consider when assessing safety:

> In determining ... whether a proposed use of a food additive is safe, the Secretary shall consider, among other relevant factors -- (A) the probable consumption of the additive and of any substance formed in or on food because of the use of such additive; (B) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substances in such diet; and (C) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.

21 U.S.C. § 348(c)(5).

The meaning of "safe" is also addressed extensively in both the Senate and House reports that accompanied the bills that became the 1958 Food Additives Amendment:

> The concept of safety used in this bill involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstances....
>
> In determining the 'safety' of an additive, scientists must take into consideration the cumulative effect of such additive in the diet of man or animals over their respective life spans together with any chemically or pharmacologically related substances in such diet. Thus, the safety of a given additive involves informed judgments based on educated estimates by scientists and experts of the anticipated ingestion of an additive by man and animals under likely patterns of use.
>
> Reasonable certainty determined in this fashion that an additive will be safe, will protect the public health from harm and will permit sound progress in food technology.
>
> The legislation adopts this concept of safety by requiring the Secretary to consider in addition to information with regard to the specific additive in question, among others, the following relevant factors: (1) the probable consumption of the additive and of any substance formed in or on food because of the use of such

additive; (2) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substances in such diet; and (3) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.

S. Rep. No. 85-2422, at 6-7 (1958) (emphasis added); *see also* H.R. Rep. No. 85-2284, at 6-7 (1958).

By framing the safety standard as "reasonable certainty of no harm," this legislative history makes it clear that weighing costs and benefits, including any weighing of health risks and benefits, was not envisioned by Congress as part of the assessment of the safety of food additives.[138]

Furthermore, Congress explicitly rejected consideration of benefits as part of the food additive approval process.[139] FDA actively sought to include consideration of the benefits or functional value of food additives as part of the approval process. *E.g., Hearings Before the Subcomm. on Health and Science of the House Interstate and Foreign Commerce Comm. on H.R. 4475, etc.*, 84th Cong. 194-95 (1956) (testimony of FDA Commissioner Larrick); *Hearings Before the Subcomm. on Health and Science of the House Interstate and Foreign Commerce Comm. on Bills to Amend Federal Food, Drug, and Cosmetic Act with Respect to Chemical Additives in Food*, 85th Cong. 21-22 (1958) (letter from M.B. Folsom, Secretary of the Department of Health, Education, and Welfare (HEW), to Oren Harris, Chairman, House Interstate and Foreign Commerce Comm. (July 12, 1957)).[140] Food industry representatives were strongly opposed, arguing that safety and benefits were separate issues, and that once safety was determined, the decision to use an additive was an economic one for industry and consumers:

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[138] The ALJ states that it is acceptable to look at health risks and benefits when determining safety because "'reasonable certainty of no harm' does not mean zero risk." Initial Decision at 8. I agree that the standard of "reasonable certainly of no harm" does not mean that there must be evidence demonstrating that a product is absolutely harmless. However, as the 1958 Senate and House Reports make clear, this issue is not related to weighing benefits against risks; it is related only to the amount of safety evidence that I must have before I can determine the safety of the use of an additive or the use of a new animal drug in a food-producing animal. *See also Olestra*, 61 Fed. Reg. 3118, 3119.

[139] Congress was well aware of the benefits of additives, but was focused on ensuring that those benefits flowed only from safe additives. For example, in describing the need for the legislation, the Senate Committee Report states, in response to receiving the House bill for consideration, "Your committee agrees with [FDA] that existing law should be changed to permit the use of such additives as our technological scientists may produce and which may benefit our people and our economy when the proposed usages of such additives are in amounts accepted by [FDA] as safe." S. Rep. No. 85-2422, at 2.

[140] FDA was part of the Department of Health, Education, and Welfare from 1953 to 1980. FDA moved to the Department of Health and Human Services when that department was created in 1980.

> If the Secretary, upon examination of a proposed new food additive, finds that it is without hazard to the health of man or other animal, the question of what its function is should be of no concern to him. This is an economic determination which is the prerogative of the potential user. ...[T]he question of functional value should not be injected into a bill concerned solely with the safety of an additive.

Hearings Before the Subcomm. on Health and Science of the House Interstate and Foreign Commerce Comm. on Bills to Amend Federal Food, Drug, and Cosmetic Act with Respect to Chemical Additives in Food, 85th Cong. 250 (1958) (statement of G. Faunce, Jr., American Bakers Ass'n); *see also id.* at 69 (statement of C.W. Dunn, Grocery Mfrs. of Am.); *id.* at 213 (statement of H.T. Austern, Nat'l Canners Ass'n); *id.* at 472 (statement of C.M. Fistere, Dairy Indus. Comm.); *id.* at 117 (statement of L.A. Coleman, Mfg. Chemists Ass'n); *id.* at 408-09 (statement of Nat'l Ass'n of Frozen Food Packers); *id.* at 411 (letter from G.P. Lamb, Waxed Paper Inst.); *id.* at 417 (letter from J.D. Hayden, Drug, Chemical, and Allied Trades Sec., New York Bd. of Trade).[141] A compromise was reached: as set out in § 409(c)(4)(B), when determining a tolerance, FDA looks at whether the use of the additive will "accomplish the intended physical or other technical effect." 21 U.S.C. § 348(c)(4)(B).[142] The House and Senate Reports are clear that this assessment does not encompass benefits:

> The phrase "physical or other technical effect" refers to the objective effect which the additive may have on the appearance, flavor, texture, or other aspect of a food. The questions of whether an additive produces such effect (or how much of an additive is required for such effect) is a factual one, and does not involve any judgment on the part of the Secretary of whether such effect results in any added "value" to the consumer of such food or enhances the marketability from a merchandising point of view.

S. Rep. No. 85-2422, at 7; *see also* H.R. Rep. No. 85-2284, at 6.

By spelling out that "safe" means "reasonable certainty of no harm," and by also refusing to allow consideration of benefits in that context, Congress made clear that it was not adopting the interpretation of "safe" that FDA had developed for § 505.[143] Based

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[141] C.W. Dunn stated: "[W]here a food additive is actually safe under the conditions of its use, the question of its functional value, that is its industrial functional value, is clearly one of a food manufacturer to decide...." *Id.* at 69. H.T. Austern testified: "[T]he determination of functional value is hardly scientific. It is probably esthetic and inescapably economic. It ought to be answered on the grocery store shelf or by the consumer in the kitchen and not by either a Federal bureau or a learned society." *Id.* at 213.

[142] This assessment of whether the additive actually does what it is claimed to do is separate from whether the additive is safe. *Compare* 21 U.S.C. §§ 348(c)(1) & (3) *with* § 348(c)(4).

[143] Nothing in the language or legislative history of the 1962 amendments suggests that Congress intended to alter the manner in which FDA was interpreting and applying "safe" in § 409. Indeed, the 1996 changes to the FDCA's pesticide tolerances provisions in § 408, 21 U.S.C. § 346a, made by the Food Quality Protection Act, Pub. L. No. 104-170, § 405 (1996), make it clear that Congress continues to believe that § 409's safety standard does not incorporate any consideration of benefits. H.R. Rep. No. 104-669 (II), at 30 (1996) (explaining that benefits

on the legislative history of the 1958 Food Additives Amendment, FDA has consistently interpreted "safe" in § 409 to mean "reasonable certainty of no harm," *see* 21 CFR § 170.3(i) (definition of safe in FDA's food additive regulations); *Olestra,* 61 Fed. Reg. 3118, 3119. In addition, FDA has interpreted the reasonable certainty of no harm standard as permitting, in the context of approval of food additives, no weighing of benefits against health risks. *Olestra,* Fed. Reg. 3118, 3120.

Because the human food safety standard of § 512 originated from the "reasonable certainty of no harm" standard used in § 409, FDA, when implementing the 1968 Animal Drug Amendments, continued to use, and still uses, this same standard when it is reviewing whether food from an animal treated with a new animal drug is safe for human consumption. Thus, in making a determination concerning the second part of the *Stauber* analysis, 895 F. Supp. at 1190, *i.e.*, whether food from animals treated with a new animal drug is safe for human consumption, FDA looks only at whether there are human health risks from the use of the drug and does not consider whether there are any benefits to humans from the use of the drug.

3. Authority for consideration of benefits

Bayer argues that § 512's safety standard requires FDA to consider a very broad array of benefits—specifically, direct and indirect human health, economic, and animal health and welfare, environmental benefits—in determining whether enrofloxacin is "safe." Bayer Exceptions at 12, 20-22; 64-74. However, as the discussion above makes clear, consideration of such a broad array of benefits is not appropriate in the context of either a human food safety review of a new animal drug under § 512 or risk-benefit assessment under § 505. Under § 505, the agency's risk-benefit analysis weighs the risks of a patient taking the drug against the risks to that patient of not taking the drug. Were I to agree with Bayer, I would not only have to weigh the alleged human health benefits of leaving Baytril on the market (prevention of human foodborne illness) against the human health risks to consumers (more severe foodborne illness), but also the economic costs of taking the drug off the market to poultry producers (*e.g.*, increased production due to greater loss of birds) against the human health risks to consumers.[144]

Bayer relies on two D.C. Circuit cases, *Hess & Clark, Inc. v. FDA*, 495 F.2d 975 (D.C. Cir. 1974), and *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750 (D.C. Cir. 1980), in

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could be considered when setting tolerances for pesticide residues on food under § 408, but could not be considered when approving food additives under § 409).

[144] Bayer identifies direct human health costs as an increase in foodborne illness. *E.g.,* Bayer Exceptions at 72-74. Its alleged economic costs encompass the costs of increased production due to loss of birds, *e.g.*, Bayer Exceptions at 68-69, and its alleged environmental costs encompass increases in wastewater production and landfilling, *e.g.*, Bayer Exceptions at 71. In addition, Bayer argues that I should consider indirect health effects caused by the poultry industry's need to increase production to offset losses and the resulting increase in environmental contamination; these changes, Bayer alleges, would result in increases in cancer associated with contaminated drinking water and in gastrointestinal illnesses associated with recreational swimming in contaminated water, as well as increased workplace injuries and fatalities associated with increased production and with changes in production. Bayer Exceptions at 65-66. The evidence supporting these arguments is discussed more fully below.

support of its argument that, in assessing human food safety, I must weigh all of these alleged benefits of enrofloxacin's use in poultry against the human health risks such use poses. The ALJ found that these D.C. Circuit cases implicitly have been overruled by two Supreme Court rulings, *Donovan*, 452 U.S. 490 (1981), and *American Trucking*, 531 U.S. 457 (2001). Initial Decision at 9-10. Bayer argues that *Donovan* and *American Trucking* do not overrule *Hess & Clark* and *Rhone-Poulenc* because the Supreme Court cases did not involve the FDCA. Bayer Exceptions at 22 n. 6.[145]

I have considered Bayer's argument that *Hess & Clark* and *Rhone-Poulenc* remain good law and require FDA to consider benefits in determining whether a new animal drug has been shown to be safe for human food use under § 512. However, while D.C. Circuit panels are bound by prior Circuit decisions, "[they] obviously cannot blindly follow prior rulings in the face of clearly contradictory doctrine later enunciated by the Supreme Court." *Rapho v. Bell*, 569 F.2d 607, 629 (1977) (privilege/right distinction relied on in previous, almost identical due process case overruled by intervening Supreme Court cases on entitlements). I have also examined closely the holdings and the statutory analyses set out in *Donovan* and *American Trucking,* and reviewed *Hess & Clark* and *Rhone-Poulenc* in light of these two Supreme Court cases. Based on my review, I conclude that the Supreme Court has effectively overruled those parts of *Hess & Clark* and *Rhone-Poulenc* that address consideration of costs and benefits as part of a withdrawal of approval of a new animal drug based on human food safety risks.

Hess & Clark, 495 F.2d 975, involved a challenge to FDA's decision to withdraw, without a hearing, the approval of the new animal drug diethylstilbestrol (DES) for use in cattle and sheep. After ruling that FDA had not given the sponsors adequate notice of the grounds for withdrawal, the D.C. Circuit stated:

> Outside of the *per se* rule of the Delaney Clause, the typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use. In the present case, DES is asserted to be of substantial benefit in enhancing meat production, and this is not gainsaid by FDA. The FDA must consider, after hearing, whether DES pellets would be safe in terms of the amounts of residue consumed. Or the FDA might restrict such consumption by a ban on sale of liver, the only food material in which any residues have even been detected.

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[145] Bayer also cites *United States v. Rutherford*, 442 U.S. 544, 556 (1979), and *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000), for the proposition that assessing safety of drugs requires a risk-benefit analysis. Bayer Exceptions at 22 n.6. However, the statements in these cases that Bayer cites to pertain to the safety of human drugs; neither case addresses the human food safety of new animal drugs. 442 U.S. at 556; 529 U.S. at 140. As explained in this section, I do not agree that Congress intended for FDA to use the same "safety" standard when assessing the safety of human drugs and the human safety of new animal drugs. Thus, I do not agree with Bayer that these cases are helpful in analyzing the scope of § 512's human food safety standard.

Id. at 993-94 (footnotes omitted).[146]

In *Rhone-Poulenc,* the D.C. Circuit upheld FDA's withdrawal of DES after additional notice and a hearing, but rebuffed FDA's efforts to revisit the meaning of "safe"; the court noted that it was "bound by the holding of the *Hess & Clark* court until we are instructed otherwise by the Supreme Court or an *en banc* decision of this court." 636 F.2d at 754 (emphasis added).

A year after *Rhone-Poulenc* was decided, the Supreme Court decided *Donovan.* At issue was whether the Occupational Safety and Health Administration (OSHA) was required to compare costs and benefits when setting a standard for harmful agents under § 6(b)(5) of the Occupational Safety and Health Act (OSH Act), 29 U.S.C. § 655(b)(5). 452 U.S. at 495. This provision states that OSHA is to set a standard "which most adequately assures that, to the extent feasible, ... no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by the standard for the period of his working life." 29 U.S.C. § 655(b)(5). The Supreme Court concluded that this provision did not permit comparison of costs and benefits. First, based on the plain meaning of "feasible," the Court reasoned that Congress had directed an analysis of ability to achieve the level of protection, not a balancing of benefits and costs. 452 U.S. at 509. By contrast, the Court said, "[w]hen Congress has intended that an agency engage in cost-benefit analysis, it has clearly indicated such intent on the face of the statute." *Id.* at 510. After citing numerous examples, some as far back as 1936, the Court concluded that these examples "demonstrate that Congress uses specific language when intending that an agency engage in cost benefit analysis." *Id.* at 510-11. The Court also determined that other provisions of the OSH Act did not suggest a different result, finding that to interpret the other parts of the statute as calling for a cost-benefit analysis essentially would render § 6(b)(5) largely meaningless. *Id.* at 511-13.[147] In the *Nitrofurans* Final Decision, FDA Commissioner David Kessler concluded that *Donovan* is "ample authority for the proposition that clauses like the [FDCA's] general safety clause do not permit, much less invite, cost/benefit analysis." *Nitrofurans,* 56 Fed. Reg. 41,902, 41,903. I agree.

At issue in *American Trucking* was whether the Environmental Protection Agency (EPA) could consider costs of implementation under a provision of the Clean Air Act (CAA), 42 U.S.C. § 7409(b)(1), that states that EPA is to set standards "'the attainment and maintenance of which ... are requisite to protect the public heath' with 'an adequate margin of safety'." 531 U.S. at 464, *quoting* 42 U.S.C. § 7409(b)(1). The Court held that costs of implementation should not be considered, rejecting arguments that the statutory language was ambiguous enough to permit EPA to weigh such cost (including indirect health costs) against the health benefits to be achieved by the air quality standard. First, the Court noted that the statute did not make costs an explicit consideration in the

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[146] To the extent that the last two sentences of this quotation suggest that FDA must consider whether to restrict sale of a portion of the treated animal, that consideration does not apply here. No participant has suggested that the human health issues before me might be addressed by simply restricting the sale of portions of the birds treated with enrofloxacin.

[147] The Court also reviewed the legislative history and found that it supported the plain meaning. *Id.* at 514-22.

standard setting process. *Id.* Second, the Court concluded that "public health," in context, must be given its ordinary and primary meaning ("'the health of the community'") as opposed to its secondary meaning ("'the ways and means of conserving the health of the community...'"). *Id.* at 465-66. Third, the Court determined that Congress was aware of potential economic costs that might result from implementation of the CAA, as well as the health consequences of those costs, and had explicitly taken them into account in other provisions of the statute. *Id.* at 466-67.

Based on all these factors, the Court in *American Trucking* concluded that the three textual bases cited by petitioners in support of their argument that the statute was ambiguous were simply not clear enough to create any ambiguity: "Congress, we have held, does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions...." *Id.* at 909-10 (citations omitted). Thus, the Court found that the use of the terms "adequate margin" and "requisite" in § 109(b)(1) of the CAA did not create ambiguity, stating that it did not believe that Congress would have used such "modest words" to deal with an issue as significant as whether costs can be considered under § 109(b)(1). *Id.* at 468-69. The Court also found that the fact that the section that governs the development of the documents on which the CAA standards at issue are based does not expressly exclude cost considerations did not create ambiguity:

> [Cost] is both so indirectly related to public health and so full of potential for canceling the conclusions drawn from direct health effects that it surely would have been expressly mentioned ... had Congress meant it to be considered. Yet while those provisions describe in detail how the health effects ... are to be calculated and given effect ... they say not a word about costs.

Id. at 469 (emphasis in original.)

Finally, the Court simply disagreed that ambiguity arose because cost considerations were mentioned in various implementation provisions of the CAA, rejecting petitioners arguments that these provisions make no sense unless costs are considered when setting standards. *Id.* at 469-70.

In light of the decisions and reasoning of *Donovan* and *American Trucking*, I conclude that *Hess & Clark* and *Rhone-Poulenc* are no longer controlling precedent. *See Rhone-Poulenc*, 636 F.2d at 754 (D.C. Circuit must follow *Hess & Clark* until "instructed otherwise"). Both Supreme Court cases hold that congressional silence is not sufficient to support a conclusion that cost-benefit analysis is implicit in the plain meaning of words like "public health," "safety," and "health." Neither the human food safety standard of § 512 nor its direct precursor, the food additive safety standard in § 409 contains the words "costs," "benefits," or anything analogous. Nor is there evidence in other provisions of the FDCA or its legislative history that Congress intended the word "safe" in either § 512 or § 409 to include any kind of cost-benefit balancing. To the contrary, the relevant legislative evidence makes it clear that Congress intended FDA not to use cost-benefit risk-benefit balancing when determining the human food safety of new animal drugs.

4. The language of § 512

Although I have already described how § 512 was created and how its origins in § 505 and § 409 have driven FDA's interpretation of § 512, under the analytical framework set out in *Donovan* and *American Trucking*, the starting point is the language of the statute, 452 U.S. at 508; 531 U.S. at 465, as it usually is when the meaning of a statute is in question, *e.g.*, *Consumer Product Safety Comm'n v. GTE Sylvania, Inc.*, 447 U.S. 102, 108 (1980). Section 512(e)(1)(B) provides for withdrawal of approval of a new animal drug if FDA finds that:

> new evidence not contained in such application or not available to the Secretary until after such application was approved, ... evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved ....

21 U.S.C. § 360b(e)(1)(B).

Two other provisions also bear directly on the meaning of "safe" in § 512(e). First, § 201(u) of the FDCA states that, "[t]he term 'safe' as used in paragraph (s) of this section and in sections 409, 512, and 721 of this title, has reference to the health of man or animal."[148] 21 U.S.C. § 321(u). Second, § 512(d)(2) provides FDA with further guidance in assessing safety. It provides:

> In determining whether such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, the Secretary shall consider, among other relevant factors, (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data, and (D) whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice.

21 U.S.C. § 360b)(2).

Neither costs nor benefits are mentioned in § 201(u), § 512(e)(1)(B), or § 512(d)(2).[149]

5. The larger legislative context of § 512

Other food safety provisions in the FDCA, enacted prior to § 409 (and § 512), provide explicitly for cost-benefit balancing, making it clear that Congress uses different words when it intends the result that Bayer wants. *Cf. American Trucking*, 531 U.S. at 467 ("We have therefore refused to find implicit in ambiguous sections of the CAA an authorization to consider costs that has elsewhere, and so often, been expressly

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[148] The use of the word "health" in § 201(u)'s definition of "safe" is also evidence that Congress intended to limit safety assessments to health issues.

[149] Likewise, none of the approval provisions of § 512 explicitly refer to costs or benefits. *See* 21 U.S.C. §§ 360b(b)(1); 360b(c)(1); 360b(d)(1).

granted."); *Donovan*, 452 U.S. at 510 ("When Congress has intended that an agency engage in cost-benefit analysis, it has clearly indicated such intent on the face of the statute.") First, § 408(b) of the FDCA, 21 U.S.C. § 348a(b) (as enacted in 1954), permitted consideration of benefits when setting tolerances for pesticide residues on most food. Until revised in 1996 (to preclude consideration of benefits in most situations),[150] § 408(b) read:

> The Secretary shall promulgate regulations establishing tolerances with respect to the use ... of pesticide chemicals ... to the extent necessary to protect the public health. In establishing any such regulation, the Secretary shall give appropriate consideration, among other relevant factors, to (1) the necessity for the production of an adequate, wholesome, and economical food supply; (2) to other ways in which the consumer may be affected by the same pesticide chemical or by other related substances that are poisonous or deleterious; and (3) to the opinion of the Secretary of Agriculture as submitted with a certification of usefulness under subsection (1) of this section.

21 U.S.C. § 346a (1995).

In addition, § 406 of the FDCA, 21 U.S.C. § 346, authorizes consideration of non-health factors in setting tolerances for added poisonous or deleterious substances. While directing FDA to set tolerances "to the extent as [FDA] finds necessary to protect the public health," § 406 also directs FDA to consider "the extent to which the use of such substance is required or cannot be avoided in the production of" food. 21 U.S.C. § 346.

The only possible support that exists for an argument that § 512 authorizes any consideration of benefits is the way FDA has interpreted "safe" in § 505 to call for a risk-benefit assessment, and, by extension, the way FDA uses risk-benefit assessment to evaluate the safety of a new animal drug for use in the target animal. Of course, while there is a "natural presumption" that words should be given the same meaning when they appear in different sections of the same statute, the presumption "is not rigid." *Atlantic Cleaners & Dyers, Inc. v. United States*, 286 U.S. 427, 433 (1932); *see also, e.g., General Dynamics Land Systems, Inc v. Cline*, 540 U.S. 581, 595 (2004); *United States v. Cleveland Indians Baseball Co.*, 532 U.S. 200, 213 (2001); *Martini v. Federal Nat'l Mortgage Ass'n*, 178 F.2d 1139, 1343-44 (D.C. Cir. 1999). The presumption gives way, according to the Supreme Court, "[w]here the subject matter to which the words refer is not the same ... or the conditions are different ...." In such a case, "the meaning may well vary to meet the purposes of the law...." *Atlantic Cleaners,* 286 U.S. at 433.[151]

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[150] This section was revised in 1996 by the Food Quality Protection Act, Pub. L. No. 104-170, § 405, in part to limit consideration of benefits and to require, except in very limited circumstances, the use of a safety standard ("reasonable certainty of no harm"). H.R. Rep. No. 104-669 (II), at 30 (1996).

[151] The FDCA contains other key words that have more than one meaning, depending on context. For example, the word "food," which is defined in § 201(f), 21 U.S.C. § 321(f), has been held to have two meanings: its broad, defined meaning and its narrower, common sense meaning, which prevails when the word is used in part of its definition, § 201(f)(1) ("food" includes "articles used as food"), as well as in the definition of "drug" at § 201(g)(1)(C) ("drug" includes "articles (other than food) intended to affect the structure or function of the body"). *Nutrilab, Inc. v. Schweiker*,

That is the case here. Even though the word "safe" appears in both § 409 and § 505, the sections apply to different kinds of products (food additives and drugs, respectively). As demonstrated above, Congress and FDA have long agreed that the word "safe" has a different meaning when used in each of those provisions. Congress carried over those two different meanings when it enacted the 1968 Animal Drug Amendments: Congress stated that it was consolidating, not changing, the provisions in the FDCA that applied to animals drugs. H.R. Rep. No. 90-2168 at 1 ("The enactment of this legislation would merely consolidate provisions under existing law and would in no way weaken the authorities of the Food and Drug Administration with respect to the regulation of animal drugs."); *see also id.* at 3.[152] Accordingly, I conclude that the legislative record does not support the extension of FDA's interpretation of "safe" in § 505 to the human food safety assessments performed under § 512.

6. The reasonableness of cost-benefit analysis

Although I have concluded that Congress has spoken to the precise question at issue here, *Chevron,* 467 U.S. at 842, were I to conclude that the statute was ambiguous, I would adopt the interpretation of "safe" described above. If the FDCA is silent or ambiguous as to the meaning of "safe" in the context of human food safety assessment under section § 512, I may define it in a reasonable fashion. *Chevron*, 467 U.S. at 842-843; *Brown & Williamson*, 529 U.S. at 132. I do not believe it would be reasonable to adopt the interpretation of "safe" urged by Bayer and consider the various benefits of enrofloxacin use in poultry cited by Bayer in determining whether the use of the product is safe.

First, based on the legislative context set forth above, I believe defining safe to mean "reasonable certainty of no harm" when assessing the human food safety of a new animal drug under § 512 is consistent with Congress' expectations at the time it was enacted, as well as FDA's and the industry's expectations. Moreover, it would be very difficult to implement the type of broad assessment Bayer advocates. To do so would require me to evaluate and give objectively determined weights to a wide range of disparate costs and benefits without any guidance from Congress on what weighting approach to use. *See DES*, 44 Fed. Reg. 54,852, 54,883. With no statutory guidance on very difficult questions, including how to weigh a benefit of one kind (*e.g.*, economic) against a different kind of cost or risk (*e.g.*, health) to that same person, or, even more difficult, how to weigh benefits to one group against different costs or risks to another group, I do not believe it would be reasonable to interpret "safe" to encompass cost-benefit analysis. How, for example, should I judge whether any alleged economic benefits to poultry producers and consumers of using enrofloxacin outweigh the health

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713 F.2d 335, 337-38 (7th Cir. 1983). Likewise, courts have ruled that the word "drug" means different things in different places of the FDCA. *Pharmanex v. Shalala*, 221 F.3d 1151, 1157-59 (10th Cir. 2000); *Baker Norton Pharms, Inc. v. FDA*, 132 F. Supp.2d 30, 35-36 (D.D.C. 2001).

[152] Indeed, the animal drug industry, represented by AHI, testified that the bill that was enacted into law, H.R. 3639, "retains all of the standards of safety and effectiveness now in the law." *Hearing before the Subcomm. on Health of the Comm. on Labor and Public Welfare on S.1600 and H.R. 3639*, 90th Cong. 97 (1968) (James Holt, on behalf of AHI); *see also id.* at 68 (Luther S. Roehm, on behalf of AHI).

risks of fluoroquinolone-resistant campylobacteriosis? Given that taking costs into account would have the "potential for canceling out the conclusions drawn from direct health effects ... [cost] would surely have been expressly mentioned ... had Congress meant it to be considered." *American Trucking*, 531 U.S. at 469.

Even if I were authorized under § 512 to adopt the interpretation of "safe" that FDA uses under § 505 to evaluate the safety of human drugs, the evaluation would encompass only a balancing of direct human health risks and health benefits. In this risk-benefit analysis, FDA asks if a risk to the human of using the drug is greater than the risk to that particular human of not using the drug. For human therapies, the risks and benefits run to the patient and are made in the context of a doctor-patient relationship, with a medical professional making an individualized risk-benefit assessment before prescribing the drug. The approved health benefits from using enrofloxacin run to the treated animals, however, not to consumers. It therefore would not be possible to perform the kind of individualized risk-benefit analysis for humans under § 512 that is contemplated by the meaning of safe under § 505.[153] The nature of the human health benefits that Bayer is claiming for enrofloxacin (primarily, that by reducing variability in the size of broiler carcasses, the mechanical processing results in lower rates of fecal contamination of retail chicken meats, thus reducing the risk of human foodborne illness associated with exposure to fecal bacteria) is too remote, as discussed in section IV.C.4 below. Thus, I conclude that I do not need to address whether, if § 512's meaning of "safe" is ambiguous when it comes to consideration of benefits as part of the assessment of the human food safety of a new animal drug, I should consider the kinds of human health benefits Bayer relies on. *Accord DES*, 44 Fed. Reg. 54,852, 54,883

7. Conclusion

For the reasons set out above, I conclude that § 512 of the FDCA is clear that FDA may not consider benefits in the determination of the safety to humans of a new animal drug. Even if the law were found to be ambiguous, I also conclude that it would not be reasonable to interpret the meaning of "safe" in § 512 as it applies to the human food safety of new animal drugs to permit the agency to offset risks with benefits. In order to provide a complete record in the event of judicial review, however, I will discuss the evidence submitted by Bayer with respect to alleged benefits.

[153] Unlike the risk and benefits associated with human drugs, the benefits and risks of a new animal drug used in a food-producing animal are not likely to run consistently to the same people. Indeed, those who get a case of fluoroquinolone-resistant campylobacteriosis caused by contaminated chicken will have suffered significant adverse health effects, but not, at least in that instance, the alleged health benefit.

C. Bayer's evidence on costs and benefits

Because I conclude that CVM has met its initial burden of coming forward with evidence to show that there are serious questions about enrofloxacin's safety, the burden then shifts to Bayer to show that the use of enrofloxacin in chickens and turkeys is safe and that FDA should continue to approve such use. I conclude, as described more fully below, that Bayer has not met its burden.

1. Economic impact

Bayer sought to introduce the testimony of G. Thomas Martin, Jr. as an expert in the economics of poultry processing. Martin, B-1907. In his testimony Mr. Martin presented a projection of the potential economic impacts of the withdrawal of enrofloxacin from the U.S. market. The ALJ excluded Mr. Martin's testimony, holding broadly that "[e]conomic and environmental evidence is not relevant to the issues in this proceeding," and specifically striking the testimony of Mr. Martin and a number of other witnesses. Order on Motions to Strike, March 3, 2003. The ALJ noted that Mr. Martin's testimony was stricken "because it was found to be altogether unreliable, and not just on the issue of economic effects of Baytril's withdrawal." Initial Decision at 41.

Although, as discussed at length above, I find the issue of economic benefit has no relevance to this proceeding, I have nonetheless reviewed Mr. Martin's proffered written direct testimony, and I agree with the ALJ that, even if it were relevant, this testimony is not sufficiently reliable to be given any weight.[154]

2. Environmental impact

I also find that Bayer's evidence concerning alleged adverse environmental impacts associated with the withdrawal of enrofloxacin is irrelevant to this proceeding.

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[154] In particular, I find that Mr. Martin did not provide sufficient evidence that his analysis adequately recognized and addressed uncertainties in the underlying data and assumptions. For example, although a range of different mortality rates (from 200 to 500 birds per house per day) are discussed as a possible threshold trigger for treatment with enrofloxacin, Martin, B-1907 at 5, he uses the highest mortality rate in developing his analysis, which assumes a constant rate of 500 mortalities per day for two scenarios: 1) 3 days, with an unidentified alternative antibiotic plus enrofloxacin; and 2) 18 days, with the other antibiotic alone. Mr. Martin's testimony also fails to identify the basis for other key assumptions in his testimony, such as the duration of drug therapy and mortality rates over the course of treatment. *Id.* at 5-9. The absence of a stated scientific basis for selection of the mortality rate, duration of treatment, and effectiveness of the various therapies used in this calculation, creates a possible source of uncertainty in the testimony. Consider, for example, that, using the 500 birds per day assumed mortality rate, the incremental increase in mortality when enrofloxacin is not used equals 7,500 birds per house (15 days x 500 birds/day). If instead the lower mortality rate of 200 birds/day is used, the incremental increase in mortality without enrofloxacin is 3,000 birds per house (15 days x 200 birds/day), an estimate 60% lower than Mr. Martin's. In addition, there are errors in the presentation that undermine the credibility of Mr. Martin's analysis (*e.g.*, using Mr. Martin's figures, the combined average for the bottom one-third of flocks should be 11.6, not 16.2, an error that is carried throughout to the derivation of excess mortality in the absence of enrofloxacin treatment). *Id.* at 18, 21. Finally, there is no market analysis in support of his conclusion that the industry will increase production to maintain current slaughter rates. *Id.* at 24.

Bayer argues that this evidence is relevant and must be considered because CVM, like all federal agencies, is subject to the requirements of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321-4347. Bayer Exceptions at 23-26. With the exception of complying with NEPA, however, Bayer cites no statutory authority for consideration of environmental impacts in the context of a NADA withdrawal proceeding.[155]

NEPA requires federal agencies to consider the environmental consequences of "major Federal actions significantly affecting the quality of the human environment." 42 U.S.C. § 4332 (2)(C). Regulations passed by the Council on Environmental Quality (CEQ) to implement NEPA provide that if an action may have a significant impact on the environment, federal agencies are to prepare an environmental assessment (EA). The EA may lead to a finding of no significant impact, or, if there is a determination that an action may have a significant impact on the environment, to preparation of an environmental impact statement (EIS). 40 CFR Part §§ 1508.9, 1508.13. The CEQ regulations, however, also allow agencies to identify categories of actions that "do not individually or cumulatively have a significant effect on the human environment . . . and for which, therefore, neither an environmental assessment nor an environmental impact statement is required." 40 CFR § 1508.4. FDA has by regulation categorically excluded "[w]ithdrawal of approval of an NADA or an abbreviated NADA" from the requirement that an EA be prepared.[156] 21 CFR § 25.33(g).[157] In the NOOH, FDA invoked this

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[155] In the Initial Decision, the ALJ found that "[o]n a NADA withdrawal proceeding ... [e]ffects on the environment are only considered under exceptional circumstances, which this case does not present." Initial Decision at 67. To the extent this finding can be read to suggest that something other than NEPA might trigger an assessment of the environmental effects of withdrawing approval of a new animal drug, I overrule it for the reasons discussed in the text.

[156] The categorical exclusions for withdrawal of human and animal drugs have been in effect since 1985. Because such withdrawals involve terminating the introduction of FDA-regulated products into the environment, the critical issue is whether a substitute product might pose environmental risks. *See* 50 Fed. Reg. 16,636, 16,640 (1985). In proposing the current version of the categorical exclusions for human and animal drug withdrawals, FDA stated (with respect to human drugs) that "[t]he agency is proposing that all types of withdrawals of approval, whether requested by industry or initiated by the agency, be categorically excluded because, based on CDER's [the Center for Drug Evaluation and Research] experience, these types of actions will not result in the production or distribution of any substances and, therefore, will not result in the introduction of any substance into the environment." 61 Fed. Reg. 19,476, 19,480 (1996). The agency came to a similar conclusion with respect to a proposed categorical exclusion for actions to prohibit or restrict the use of a substance in food, food packaging, or cosmetics. *Id.* at 19,483. With respect to veterinary drugs, FDA stated that "FDA has determined that withdrawal of an NADA or ANADA approval does not significantly affect the environment because any change in introduction of the drug will generally be a decrease.... In those cases where the withdrawal of the NADA [or] ANADA ... has resulted in the use of a substitute product, the agency has found in all instances that the increased use of the substitutes will not significantly affect the environment." *Id.* at 19,487.

[157] Even when a categorical exclusion applies, however, "FDA will require at least an EA for a specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment...." 21

provision: "The agency has determined under 21 CFR 25.33(g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required." 65 Fed. Reg. 64,954, 64,963.

I find that the FDA's statement in the NOOH was sufficient to discharge the agency's duty under NEPA. As the Eleventh Circuit Court of Appeals recently explained, "[d]ocumentation of reliance on a categorical exclusion need not be detailed or lengthy. It need only be long enough to indicate to a reviewing court that the agency indeed considered whether or not a categorical exclusion applied and concluded that it did." *Wilderness Watch and Public Employees for Envtl. Responsibility v. Mainella,* 375 F.3d 1085, 1095 (11th Cir. 2004). "In most instances, a short statement that a categorical exclusion has been invoked will suffice to assure a reviewing court that environmental effects have been considered." *Id. Wilderness Watch* confirms the legal standard previously articulated by other courts, *e.g., California v. Norton*, 311 F.3d 1162, 1176 (9th Cir. 2002) ("In many instances, a brief statement that a categorical exclusion is being invoked will suffice."). As the District Court for the District of Columbia noted, "a requirement that any agency prepare a full-blown statement of reasons for invoking a categorical exclusion" would "detract from the legitimate governmental interest in avoiding unnecessary paperwork for actions that legitimately fall under a categorical exclusion and do not require an EA or EIS." *Edmonds Inst. v. Babbitt*, 42 F. Supp.2d 1, 18 n.11 (D.D.C. 1999).

Contrary to Bayer's implied position, the duty to document the reliance on the categorical exclusion and to make the appropriate determination about whether extraordinary circumstances existed was with the agency as it proposed to withdraw the NADA, not with the ALJ. The ALJ's duty was simply to review whether that action by the agency had taken place, and the ALJ appropriately cited CVM's claim of a categorical exclusion. Initial Decision at 10. The ALJ went beyond this duty and reviewed the evidence Bayer sought to introduce concerning adverse environmental impacts, finding that "[e]ven if the allegations set forth by Bayer were substantiated, they fall far short of the quality and quantity of evidence necessary to require the preparation of an EA or EIS." Initial Decision at 11.

CFR § 25.21. Examples of such extraordinary circumstances include: "(a) Actions for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment; and (b) Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora or Fauna to be endangered or threatened wild flora or fauna that are entitled to special protection under some other Federal law." 21 CFR § 25.21. As FDA explained in promulgating its current NEPA regulations, "application of the extraordinary circumstances provision should be limited." 62 Fed. Reg. 40,570, 40,573 (1997).

I also find that Bayer's stricken evidence[158] does not, even if I were to consider it, support a finding under 21 CFR § 25.21 that "extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment" such that an EA is warranted despite the categorical exclusion for NADA withdrawals.[159] *See* Bayer Exceptions at 72. Bayer's calculations about the adverse impact of the withdrawal of enrofloxacin on the environment rests to a large degree on a series of broad and poorly supported calculations about the potential consequences of withdrawal of enrofloxacin, including an estimation of the number of birds that would be needed to replace those that die or are condemned at slaughter, Woodruff, B-1918 at 7, based on the analysis by G. Thomas Martin, B-1907; how much additional fresh water would be needed to raise and process those additional birds, Woodruff, B-1918 at 8-13; and the resulting increase in wastewater, air emissions, and on-land waste disposal, *id.* at 13-45. In addition to being based on Mr. Martin's flawed testimony about consumer demand for poultry meat, described above, Mr. Woodruff's testimony includes an unstated assumption that federal and state resource protection and pollution control laws and programs, evolving technologies, and the market would play no role in preventing the potential adverse impacts of such additional poultry production, were it to actually occur. Woodruff, B-1918. Bayer's analysis would require me to make a series of unsupported assumptions concerning the industry's ability or responsibility to revise its husbandry and slaughterhouse practices to adapt to variability in the size of individual chickens it processes or to the total amount of chickens it must produce to meet consumer demand. It is not even clear that the production changes projected by Bayer's witnesses, even if realized, would result in more than an incremental increase in an already substantial environmental burden. Such hypothetical information is not sufficiently reliable to trigger the "extraordinary circumstances" provision of FDA's NEPA regulations.

3. Availability of alternatives to enrofloxacin

Bayer argues that the ALJ erred in finding that there are alternatives to enrofloxacin. Bayer Exceptions at 59-64; *see* Initial Decision at 9, 61. The legal relevance of the availability of alternative drug therapies is limited, as Bayer apparently concedes. Bayer Reply to CVM Exceptions at 26 ("Bayer has conceded the Initial Decision's finding that 'the issue of the availability of alternative animal drug therapies is at best, marginal,' but only because the benefits and potential risks only arise if

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[158] The stricken evidence includes the entire written direct testimony of Mr. Steven R. Woodruff, an environmental consultant. Woodruff, B-1918. Mr. Woodruff's testimony is based in part on other testimony by Dr. Scott Russell, B-1912, a poultry scientist whose testimony was stricken in part, and Mr. G. Thomas Martin, Jr., B-1907, the economist whose testimony is discussed immediately above in section IV.C.1.

[159] Although I agree with the ALJ's ultimate conclusion that FDA did not need to prepare an EA under NEPA, I do not adopt his analysis. It was not incumbent upon the ALJ to analyze whether CVM's proposed action was a "major Federal action" under NEPA or whether, under the reasoning of *Rhone-Poulenc,* 636 F.2d at 754-755, there are alternatives to enrofloxacin that would mitigate any environmental harm. *Rhone-Poulenc* predates FDA's promulgation in 1985 of the first version of its categorical exclusion for withdrawal of NADAs. *See* 50 Fed. Reg. 16,636 (1985). As a result, the analysis in that case is inapplicable to the present situation.

enrofloxacin is used."). Because, as explained in section IV.B, the FDCA does not permit me to weigh health risks to humans against health benefits to animals or economic benefits to the poultry industry, the only possible relevance of the availability of alternatives could be with respect to the applicability of NEPA. In *Rhone-Poulenc, Inc.*, 636 F.2d at 754-55, the D.C. Circuit, in reviewing an Environmental Impact Analysis prepared by FDA before the categorical exclusion for NADA withdrawals was promulgated), quoted from an FDA staff report that found that "'continued use of DES would provide some environmental benefits, namely, a decrease in animal wastes and a reduced need for food to be grown for the animal.' [The report] notes that other growth promotants are available to replace DES, however, and concludes that their use will mitigate any environmental harm caused by the unavailability of DES." *Id.* However, because, as described above, FDA satisfied the requirements of NEPA by issuing a categorical exclusion for withdrawal of NADAs, *Rhone-Poulenc* is not controlling on this point and there is no need for the analysis from that case relied on by Bayer. I also find that the evidence in the record does not support a determination that the alleged lack of available alternatives is itself an "extraordinary circumstance" triggering the requirement that a broader environmental assessment should be undertaken despite the categorical exclusion. Bayer Exceptions at 70. Although the record shows that some alternative treatments that currently exist may be ineffective or impractical for a variety of reasons, Glisson, B-1903 at 9; Wages, B-1917 at 9; Hofacre, A-202 at 24-27, there are nonetheless some other treatments available, Glisson, B-1903 at 7-9; Wages, B-1917 at 14, 16, 19; Hofacre, A-202 at 24-27. Finally, as set out in section IV.C.2, I do not agree that the testimony of Dr. Woodruff would otherwise be a sufficient basis for a finding of extraordinary circumstances. Bayer Exceptions at 71. As discussed above, his testimony, and the testimony of Mr. Martin on which it is based, are not deserving of much weight.

4. Health benefits

To rebut CVM's showing that there is a reasonable basis from which serious questions about the safety of enrofloxacin may be inferred, Bayer argues that enrofloxacin is safe for use in poultry because the benefits to human health from such use outweigh any potential risks. Bayer Exceptions at 72-74. Bayer argues that the withdrawal of approval of enrofloxacin use in chickens and turkeys will result in an increase in human health risk because birds processed for human consumption are more likely to be ill, underweight, and contaminated with fecal bacteria. These health impacts, they argue, will result in an increase in annual days of diarrhea in the U.S. population that exceeds the excess diarrhea that CVM estimates will result from failed fluoroquinolone treatment of fluoroquinolone-resistant *Campylobacter* infections.[160] Bayer Exceptions at 74.

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[160] Bayer also alleges and attempts to quantify more indirect health benefits of enrofloxacin, namely: decreased incidence of waterborne gastrointestinal illness, decreased cancer risk associated with chlorination byproduct reductions, and decreased incidence of workplace injuries. Bayer Exceptions at 64-66; Harris, B-1919 at 5. This evidence, and the testimony on economic and environmental modeling on which it is based, Martin, B-1907; Woodruff, B-1918, were properly stricken from the record by the ALJ. OR31. Not only is this evidence not relevant, but I

Bayer argues that: 1) in the absence of enrofloxacin, more poultry will be untreated or ineffectively treated for air sacculitis;[161] 2) these birds will be "smaller/underweight" and/or more variable in size; 3) because they are undersized and/or more variable in size, when these birds are mechanically processed there is a higher incidence of intestinal cuts and tears; 4) this higher rate of tearing and cutting results in the introduction of a higher than normal level of fecal contamination to the bird carcass; 5) higher fecal contamination on the bird carcass results in a higher *Campylobacter* load on the bird carcass immediately after evisceration; 6) the higher microbial load persists through processing; and 7) an increase in foodborne illness associated with chicken consumption, measured as annual days of diarrhea, results. *See* Bayer Exceptions at 38. The evidence, however, does not adequately support each of the steps necessary for Bayer to make out its claim of health benefits.[162]

Bayer's argument is built on the strength of one study, by Dr. Scott Russell, *see* Russell, B-1912.[163] I have reviewed Dr. Russell's testimony and the report of the study, *id.* at 35 (Att. 1), very closely. I find that there are problems with the methodology of the study that undermine its reliability. Moreover, even if the methodology of the study were reliable, the results do not support Bayer's broad conclusions about the import of the study.[164]

Dr. Russell looked at carcass weights and uniformity, fecal contamination, processing errors, and microbiologic contamination in flocks of chickens that he had classified as "air sacculitis-positive," as compared to flocks that he had classified as "air sacculitis-negative." Russell, B-1912 at 20-22. "Positive" and "negative" are qualitative,

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also find that the remote and hypothetical harms described in Dr. Harris's testimony are not sufficiently concrete or proximate that they can or should be considered by me in this proceeding.

[161] *E. coli* air sacculitis is a bacterial infection of the air sacs. Hofacre, A-202 at 8.

[162] Bayer argued that the ALJ improperly struck "corroborating proof of the Russell study and enrofloxacin's safety" in striking portions of the testimony of three other Bayer and AHI witnesses. Bayer Exceptions at 42. However, the testimony of Ronald Joseph Prucha, A-203, Michael Robach, B-1911, and Robert Bruce Tompkin, A-204, focused on food safety measures generally and does not provide any specific corroboration of the Russell study. As noted in section II.D.1, I generally agree with the ALJ's order on the participants' cross-motions to strike, and I find that the portions of the testimony of these witnesses that were stricken by the ALJ are not relevant.

[163] In its exceptions, Bayer cites Dr. Charles N. Haas as support with respect to the issue of increased exposure to pathogens in the absence of enrofloxacin as a treatment for air sacculitis. *See* Bayer Exceptions at 39. However, Dr. Haas's testimony on this point, Haas, B-1904 at 23-24, is based entirely on Dr. Russell's research. As a result, I find that it is duplicative and not independently probative.

[164] Bayer argues in its exceptions that Dr. Russell's study, B-1912 at 35 (Att. 1) is "unrebutted" and that "no CVM witness testified regarding the purported limitations in Dr. Russell's study...." Bayer Exceptions at 53. This argument fails to recognize the role of the Commissioner as both an expert and a fact-finder in this Final Decision. Dr. Russell's testimony and written research report are subject to scrutiny, like all scientific evidence, to identify strengths and limitations of the study and its conclusions.

undefined terms that reflect that some proportion of carcasses in a particular flock have been rejected by the USDA inspector. *Id.* at 20.

According to Dr. Russell, positive flocks were "evidenced by a high number of air sacculitis scores or USDA inspector hangback sheets, and a high number of carcasses placed onto the salvage lines," *id.* at 20, while negative flocks were those with "very few" scores, *id.* Dr. Russell, in describing his research, stated that he had "examined the impact on processed broilers if Baytril is not available," *id.* at 16, and Bayer makes this assumption in its exceptions, *see* Bayer Exceptions at 72-73. However, Dr. Russell's testimony provides no analysis demonstrating that, with respect to *Campylobacter* load on the chicken carcasses, air sacculitis-positive flocks are a reasonable proxy for flocks that have not been treated with enrofloxacin. Although Dr. Russell reported that flocks from both groups were treated with tetracycline and sulfa drugs, but not fluoroquinolones, no details were provided about the prior treatment of the flocks, making it difficult to evaluate any potential bias introduced by prior antibiotic history. *See* Russell, B-1912 at 20. While Dr. Russell adjusted for an age difference in most of the replicates, Russell, B-1912 at 42 (Att. 1), there is no information about whether other possible sources of bias existed with respect to the flocks, such as source, feeding, or handling differences. Finally, Dr. Russell's outcome measurements include weight, fecal contamination, processing errors, and microbiologic contamination. *Id.* at 21-22. Although some of these measures were subjective, there is no information in either Dr. Russell's testimony or the study report draft about how these measurements were carried out or validated.

The microbiologic contamination analysis is the component of Dr. Russell's study on which much of Bayer's benefits argument turns. In that analysis, a subgroup of carcasses from each flock was evaluated for *Campylobacter* and *E. coli* contamination before they were placed into an "inside/outside bird washer." Russell, B-1912 at 22.[165] For 3 out of 5 of the replicates, pre-washer *Campylobacter* contamination of the carcasses from the flock classified as air sacculitis-positive[166] was statistically significantly higher than *Campylobacter* contamination of the carcasses from the air sacculitis-negative flocks; for one replication, however, the pre-washer fecal contamination of the carcasses from the air sacculitis-negative flock was statistically significantly higher than for the air sacculitis-positive flock, and for the 5th day there was no significant difference between the two groups, but again the air sacculitis-negative carcasses had a higher microbial load than the air sacculitis-positive carcasses. Russell, B-1912 at 25, 50-51 (Att. 1, Table

[165] As Dr. Russell testified, carcasses that have been eviscerated and successfully inspected by a USDA inspector go through an "inside/outside bird washer" and are washed with high-pressure chlorinated sprayers to removal visible fecal material and begin the process of disinfection. Russell, B-1912 at 5-6. They are then placed for about an hour into chill tanks or chillers, which are large tanks full of water that is generally chlorinated and is below 40°F. *Id.* at 6.

[166] It bears noting that the flocks were classified, rather than individual carcasses introducing another source of potential misclassification. Because entire flocks are treated when air sacculitis is diagnosed in some of the birds, this system was likely the only appropriate or practical one. However, deciding what prevalence of air sacculitis is necessary to classify a flock as positive will strongly influence the results, and the use of other antimicrobial agents to treat affected flocks before classification complicates analysis.

5).[167] These data suggest that there was some misclassification or other unexamined variable that could have influenced the results (in either direction).

Furthermore, even if there is a reproducible and valid difference in microbial load on groups of chicken carcasses that can be associated with the presence of air sacculitis in the carcasses, there is no evidence concerning what the actual significance of this difference would be after the birds are further decontaminated. First, carcasses in both groups had fairly comparable microbial loads, and all carcasses would be subject to substantial further processing. Robach, B-1911 at 14. Second, the contamination levels measured by Russell in all carcasses were quite low: the microbial load in both groups was almost entirely under 2.70 $\log_{10}$ (about 500) CFUs.[168] Indeed, the only sample with a higher exception is the replication in which there was no statistically significant difference between the two groups CFU/ml, in which the air sacculitis-positive group was at 2.89 $\log_{10}$ CFU/mL and the air sacculitis-negative group was at 3.10 $\log_{10}$ CFU/mL. Russell, B-1912 at 51 (Att. 1, Table 5).

I also find (as did the ALJ, Initial Decision at 61) that Dr. Russell's study does not provide any information about the relative *Campylobacter* load on, or size of, chickens that have been treated with enrofloxacin as compared to chickens that have not been so treated, since no chickens in this study had been treated with fluoroquinolones. There is no evidence that supports an assumption that in evaluating *Campylobacter* pathogen load on chicken carcasses, it is reasonable to assume that air sacculitis-negative flocks are reasonable proxies for flocks that have been treated with enrofloxacin. *See* Bayer Exceptions at 72-73.[169] The Russell study provides minimal support for the proposition that flocks with a qualitatively measured high proportion of carcasses identified by USDA inspectors as being air sacculitis-positive are smaller and/or more variable in size

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[167] The data for *E. coli* appear to be even less compelling. Russell, B-1912 at 51 (Att. 1, Table 6). For 2 out of the 5 days, there is no significant difference in bacterial count between the air sacculitis groups. *Id.* On the other 3 days, the difference between the air sacculitis-positive and air sacculitis-negative groups is statistically significant (p=0.05); however, in one replicate, the level of *E. coli* is significantly *higher* in the air sacculitis-negative group. Thus, the *E. coli* count was significantly higher in the air sacculitis-positive group only on 2 out of 5 days studied.

[168] It bears mentioning that Bayer's position is that humans do not become ill unless they are exposed to much higher microbial loads of *Campylobacter* than those reflected in this table. For example, in discussing the testimony of Dr. Cox, Bayer stated that "low doses like doses below 500 CFU produce risk that that [sic] is so low it can be modeled as zero and still be an accurate model." Bayer Exceptions at 52. As CVM notes in its reply, the $\log_{10}$ value for 500 is about 2.70. Only 2 of the ten counts reported in Figure 5 are at or above 2.70: one is for an air sacculitis-positive replicate, and one is for an air sacculitis-negative replicate. Russell, B-1914 at 51 Table 5; CVM Reply to Exceptions at 96.

[169] The ALJ struck testimony by Dr. Russell describing another study he had done on the correlation between air sacculitis and carcass weight, fecal contamination, and the prevalence of *Salmonella*. Order March 6, 2003 (OR31); Russell, B-1912 at 27-30. Although Bayer argues that the testimony was stricken on relevance grounds, Bayer Exceptions at 55, the ALJ did not specify the reasons for striking this study. Having looked at this testimony, I find it is irrelevant, since no connection has been made between this study, focused as it is on *Salmonella*, and the issues before me.

than chickens from air sacculitis-negative flocks; that they may be more likely, before chilling and further processing, to have visible fecal contamination and to have cuts and tears after evisceration that facilitates such fecal contamination; and that they may, at this early point in processing have a higher *Campylobacter* count than carcasses from air sacculitis-negative flocks.[170] This research is not sufficient, however, to bear the weight of the health benefits calculation Bayer puts upon it.

First, based on Table 5 in Dr. Russell's analysis, Bayer calculates the average increase in *Campylobacter* counts for air sacculitis-positive flocks, finding a 1 $\log_{10}$ CFU/mL difference. Russell, B-1912 at 51 (Att. 1, Table 5). The data are too unstable to be reliably used for this calculation, however. First, there is no confidence interval or other information about uncertainty provided; this information is critical to evaluating the possible significance of the variability among the CFUs. Even assuming that the average figures provided can be appropriately compared, the variability of the data within the groups that are air sacculitis-positive is different from the variability of the data within the groups that are air sacculitis-negative, suggesting misclassification bias, reasons other than air sacculitis for the level of contamination, or some problem in sampling. In two of the five replicates, the air sacculitis-negative samples have a higher bacterial count than the air sacculitis-positive samples. *Id.* As a result, the data cannot support a simple averaging to develop an inference that on the whole the air sacculitis-positive group has an average count difference that is higher than the negative group. The range in microbial contamination in both groups -- which, in the air sacculitis-negative group, varies from no *Campylobacter* to more *Campylobacter* than is seen in the air sacculitis-positive group) may be due to misclassification (in other words, for example, the flocks classified as air sacculitis-negative may well have individual carcasses in which the infection is present, and vice versa). There may also have been contamination of the assay process, or some other bias-creating factor. But the bottom line is that, while this is interesting research that provides some information about microbial load in chickens, it does not provide data that can appropriately be used for a quantitative risk estimation.

Even assuming that the 1 $\log_{10}$ CFU/mL difference between the two sample groups is robust, Bayer's risk calculation is invalid for other reasons. Using that difference and assuming, without reference, that half of all broilers that are currently

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[170] The study found a statistically significant difference in weight and uniformity in only 2 of the 5 replications. Russell, B-1912 at 49 (Att. 1, Table 2). This is very weak support for the paper's major assertion.

Bayer argues in its exceptions that other research, including efficacy trials done by Dr. John Glisson comparing enrofloxacin and other antibiotic treatment of chickens, supports Bayer's contention that infected birds treated with enrofloxacin weigh more than infected birds not treated with any antibiotic. Bayer Exceptions at 54-55. Yet the cited pages of Dr. Glisson's testimony do not provide details about the weight gain component of his research. Rather, he simply reports that "[t]his study also confirms the results of a previous study (*See* results graph--Bayer Poultry 454 attached to my testimony). In that study, using a similar design and protocol, enrofloxacin treatment provided a significant difference in feed conversion and air sac [sacculitis] lesion scores when compared to oxytetracycline treatment." Glisson, B-1903 at 10-11. However, there is not enough information provided about either study (with respect to differences in weight gain among the treatment and non-treated groups) to be able to evaluate them. *Id.* at 9-11, 43 (Att. 3).

treated with enrofloxacin, or 1% of all chicken production, will be (in the absence of enrofloxacin treatment) air sacculitis-positive, Bayer then asserts that "[a] 1 $\log_{10}$ increase in microbial load conservatively can be said to result in a 10 fold increased average risk of chicken-borne campylobacteriosis." Bayer Exceptions at 72. Bayer continues: "For example, as suggested by [Rosenquist] G-1788 Figure 7C, a relative change in load of 100 times correlates with a 30 times change in campylobacteriosis and a relative change in load of 10 times correlates with a 10 times change in campylobacteriosis." *Id.* at 72-73.[171] Combining the Russell data and the information suggested in the Rosenquist figure, Bayer argues that "the risk of campylobacteriosis is conservatively about 10 times greater for carcasses from air sacculitis positive flocks compared to air sacculitis negative flocks." *Id.* at 73.

Using this risk increase figure, Bayer then calculates what it calls the "health benefits" of enrofloxacin use in poultry:

> 1% of chickens would be about 10 times riskier than at present. Mathematically, then, the percentage increase in human campylobacteriosis risk from eating chicken due to enrofloxacin's withdrawal can be shown as follows: [(99%)(1) current risk + [(1%)(10)increased risk] = 109%. This corresponds to a 9% increase in chicken-borne campylobacteriosis cases if enrofloxacin is withdrawn.

Id. at 73.

Bayer uses this figure, along with CDC data on reported incidence of *Campylobacter* in the U.S. population and estimation of unreported cases, B-1924, and FDA's population attributable fraction calculation (0.57), (Bayer cites to but does not properly reference CVM's risk assessment, G-953), to estimate that 76,276 cases of campylobacteriosis annually would be attributable to the withdrawal of approval of enrofloxacin use in poultry. Bayer Exceptions at 73. Multiplying this number of cases by 6 days of diarrhea, Bayer ends up with 457,657 days of *Campylobacter*-related diarrhea. *Id.* at 74.[172] This calculation of extra days of diarrhea is neither "conservative"

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[171] The analysis by Rosenquist and colleagues, G-1788 does not support Bayer's argument here. In their quantitative "farm-to-fork" assessment of the risk (in Denmark) of human campylobacteriosis associated with *Campylobacter* species in chickens, Rosenquist and colleagues developed a mathematical model that allowed them to estimate the impact on human illness of mitigation measures. Figure 7C, cited by Bayer, estimates the incidence of campylobacteriosis related to the consumption of a chicken meal and indicates that a relative change in the mean number of *Campylobacter* (on a log scale) reduced incidence of illness. G-1788 at 11. In that analysis, a 2 log unit decrease in the mean number of *Campylobacter* organisms (*i.e.*, the bacterial load on the whole retail chicken product) resulted in a reduction in the number of human cases from 300 to 10 cases per 100,000 population (a 30-fold decrease). Rosenquist's model indicated that to achieve such a reduction at the point of purchase, flock prevalence of *Campylobacter* should be reduced about 30 times (*e.g.*, from 60% to 2%) or kitchen hygiene improved approximately 30 times. G-1788 at 14.

[172] Bayer alleges (without citation) that "CVM has argued that the harm [associated with fluoroquinolone-resistant *Campylobacter* infections] is manifested as about two extra days of diarrhea." Bayer Exceptions at 73. Thus, Bayer argues, "one can quantify CVM's alleged harm for the purposes of argument to be 9,261 people with two extra days of diarrhea, or 18,522 extra days of illness due to the use of Baytril in chickens," Bayer Exceptions at 73. This figure, Bayer

nor "common sense" as Bayer claims. *Id.* It is, rather, a rough risk assessment thrown into the exceptions without reference to testimony, and without any effort to satisfy any of the criteria for scientific validation of such quantitative estimate of risk on which Bayer places such value at other points in this proceeding.[173] There are a number of assumptions in this calculation that are not supported or justified by the evidence, not least of which is the fundamental notion that, even if the data from the Russell study are confirmed by other researchers, a modest increase in the proportion of bacteria on carcasses before they have been processed will result in an increase in risk all the way through to human exposure/consumption.[174] There is no evidence in the record supporting the implication of Bayer's assumption that the an average 1 $\log_{10}$ CFU/mL[175] increase in bacterial contamination immediately post-evisceration and before any

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argues, is "far outweigh[ed]" by the 457,657 days of diarrhea Bayer claims are associated with withdrawal of approval of the animal drug. Bayer Exceptions at 74.

[173] Although Bayer does not cite to evidence in the record to support this calculation, it seems to derive from Bayer witness Dr. Anthony Cox's testimony that he used a risk assessment model he had developed "[t]o quantify the increase in human health risks that would be caused by a ban on enrofloxacin." Cox, B-1901 at 83 (Att. 1); *see* A-17. Dr. Cox testified that he used a farm-to-fork approach and Dr. Russell's data "to estimate the change in the probability distribution of microbial loads due to an enrofloxacin ban." *Id.* Even if Dr. Cox's testimony had not been stricken, *see* section II.D.3, I find this evidence unreliable due to uncertainties in the approach and underlying data, including Dr. Cox's assumptions about the existence of a threshold of exposure and a dose-response relationship between exposure and illness (*see* discussion at section III.C.2 above), his reliance on Dr. Russell's data, and, most significantly, the fact that the model inputs other data that are not relevant to this proceeding, and that it was designed to answer a risk management question that is not before me. *See, e.g.*, A-17 at 2 ("This paper introduces a dynamic discrete-event simulation (DES) model for quantifying the relationship between multiple risk factors (e.g., FQ [fluoroquinolone] usage in chicken flocks, animal husbandry practices, food refrigeration, transportation, storage, processing, and preparation practices, and CP [*Campylobacter*] diagnosis and FQ prescription practices) and probable excess days of illness in human populations. The DES approach is intended to support both better quantitative risk assessment and better risk management policy-making.").

[174] Compare, by way of contrast, an analysis of morbidity of infections caused by antimicrobial resistant bacteria (*Campylobacter* and non-typhoidal *Salmonella*) published in the journal *Clinical Infectious Diseases*, G-1350 at 63-66. In that article, Travers and Barza estimated, based on identified data and assumptions, that more than 410,000 excess days of diarrhea can be attributed annually to fluoroquinolone resistance in *Campylobacter* strains in domestic farm animals (not limited to poultry). G-1350 at 65-66. In that analysis, the authors excluded the proportion of infections estimated to be acquired through foreign travel. *Id.* at 66. (In the same study, the authors estimated that 8,677 extra days of hospitalization due to fluoroquinolone-resistant strains of non-typhoidal *Salmonella*, also associated with use of fluoroquinolones in farm animals. *Id.*

[175] As noted above, it is not helpful in this context to simply average the data on microbial load, especially where the direction of difference is not consistent across replicates and where some of these differences are not statistically significant. At a minimum, Bayer should have been clear about the upper and lower bounds of the confidence intervals surrounding its estimate.

processing, "conservatively can be said to result in a 10 fold increased average risk of chicken-borne campylobacteriosis." *Id.* at 72.[176]

In sum, I find that this evidence of human health benefits in terms of avoided days of diarrhea associated with chicken consumption in the absence of enrofloxacin to be unreliable as a matter of science and not probative as a matter of law.

V. CONCLUSIONS AND ORDER

My findings with respect to the factual issues raised by the exceptions, together with the citations to the record in support of my findings, have been stated as part of my discussion of those issues. Likewise, my conclusions with respect to the legal issues raised by the exceptions have been stated as part of my discussion of those issues. The following is a summary of those significant findings and conclusions:

1. *Campylobacter* is a significant cause of foodborne gastroenteritis in the United States, despite a decrease in the incidence of *Campylobacter* infections acquired domestically in recent years.

2. Campylobacteriosis and other forms of gastroenteritis are often self-limiting. However, empiric treatment with an antimicrobial is recommended for vulnerable subpopulations (*e.g.*, the young, elderly, and immune-compromised), and when illness is severe. Complications of campylobacteriosis include reactive arthritis, GBS, and, more rarely, blood stream infections.

3. When treatment is indicated, most practicing physicians will begin empiric antibiotic treatment before awaiting stool culture results or without ordering such results, in order to mitigate symptoms promptly, reduce the rate of recurrence, and decrease the risk of associated complications. Fluoroquinolones are recommended for the empiric treatment of gastroenteritis.

4. *Campylobacter* bacteria are commonly found in the intestinal tracts of chickens and turkeys. These bacteria do not generally cause disease in these birds. A minute proportion of the *Campylobacter* that are commensal in colonized birds are naturally resistant to fluoroquinolones. Chickens and turkeys can also become contaminated with *Campylobacter* through transport, slaughter, and processing.

5. The use of enrofloxacin under its approved conditions of use in poultry colonized with *Campylobacter* does not eliminate *Campylobacter* from the birds' intestinal tracts, but instead rapidly results in selection for fluoroquinolone-resistant *Campylobacter* in treated flocks. Fluoroquinolone-resistant *Campylobacter* persist and spread through transport, slaughter, and processing in the same manner as fluoroquinolone-susceptible *Campylobacter*.

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[176] Indeed, the within-group variability in Russell's data suggests that control points later in the processing of poultry meat must be able to handle a broad range of microbial loads: of the 3 carcasses with the highest *Campylobacter* counts recorded by Russell, two are in the air sacculitis-negative group; *Campylobacter* counts in that negative group range from 0 to 1,259 CFUs/mL (*i.e.*, 3.10 $\log_{10}$ CFUs/mL). Russell, B-1912 at 51 (Att. 1, Table 5).

6. *Campylobacter*, both fluoroquinolone-susceptible and fluoroquinolone-resistant, may be present on poultry sold in retail outlets. Epidemiologic, microbiologic, and molecular data indicate that poultry is a significant source of sporadic cases of campylobacteriosis, including infections that are resistant to fluoroquinolones.

7. The proportion of *Campylobacter* infections that is resistant to fluoroquinolones has increased significantly since the use of enrofloxacin in poultry was approved in the United States. The experience of the United States has been consistent with that of a number of other countries in this respect.

8. The failure of fluoroquinolone treatment of human *Campylobacter* infections that are resistant to fluoroquinolones significantly prolongs the duration of *Campylobacter* infections, and, in addition, may increase the risk of complications. Furthermore, an increase in the prevalence of fluoroquinolone-resistant *Campylobacter* infections may lead practitioners to abandon the use of fluoroquinolones for the empiric treatment of enteric bacterial infections, despite the fact that no other empiric treatment is currently available; the resulting failure to treat at all or at least until the causal agent has been identified may prolong the duration of disease and increase the risk of complications.

9. CVM has produced new evidence that, together with the evidence previously available, shows that there is a reasonable basis from which serious scientific questions may be inferred about the safety of enrofloxacin for use in poultry under the conditions of use upon the basis of which enrofloxacin was approved.

10. FDA is not authorized, under the FDCA, to weigh economic, health or other benefits that the drug provides against a health risk to the ultimate human consumers of food from or contaminated by treated animals. Even if I were to attempt to weight the benefits of enrofloxacin against its risks, the record before me is not sufficient to show that the alleged benefits outweigh the risks.

11. Enrofloxacin has not been shown to be safe for use in poultry under the conditions of use upon the basis of which the application was approved within the meaning of § 512(e)(1)(B) of the FDCA.

The foregoing opinion in its entirety constitutes my findings of fact and conclusions of law. Based on the foregoing discussion, findings, and conclusions, I affirm the ALJ's Initial Decision as corrected and supplemented by this Final Decision.

Therefore, I ORDER that the approval of the NADA for enrofloxacin listed in this document, NADA 140-828, be hereby withdrawn pursuant to § 512(e)(1)(B) of the FDCA. This order is effective on September 12, 2005.

In addition, pursuant to § 512(i), I order the removal from 21 CFR § 520.813. I also order deletions of all references to enrofloxacin for use in poultry contained in 21 CFR § 556.228.

A notice will be published promptly in the Federal Register revoking these rules.

Signed this 29 th day of July, 2005.

Lester M. Crawford, D.V.M., Ph.D.
Commissioner of Food and Drugs

Appendix - Final Decision of the Commissioner

Docket No. 2000N-1571

Guide to Finding Cited Record Evidence in Docket No. 2000N-1571

Documents cited in this decision are available for inspection by means of writing to, or visiting, the Division of Dockets Management, Food and Drug Administration located at: 5630 Fishers Lane, Room 1061 (HFA-305) Rockville, MD, 20852. All other documents related to this docket also are available for inspection, unless considered confidential.

Please refer to the tables below in requesting information on the cited record evidence. When requesting a document make sure to provide both the Document Reference number as well as the Docket Identification number.

Transcript references:

Document Reference #	Docket Identification (Doc ID#)
Tr. (transcript of cross-examination): corrected transcript located in 8 documents, TR9-TR16. Citations are to page numbers.	TR 9 : pages 1-184 TR 10: pages 185-260 TR 11: pages 261-479 TR 12: pages 480-562 TR 13 : pages 563-632 TR 14 : pages 633-723 TR 15 : pages 724-922 TR 16 : pages 923-1133

Exhibit references:

Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)
A-17	EXB1137	B-36	EXB76	G-22	EXB139
A-54	EXB1091	B-39	EXB699	G-44	DDI 1
A-190	EXB72	B-50	EXB703	G-52	EXB143
A-192	EXB1198	B-67	EXB707	G-67	EXB146
A-200	EXB862 and EXB1128	B-147	EXB736 and EXB81	G-77	EXB148
A-201	EXB683	B-205	EXB85	G-157	EXB169
A-202	EXB684	B-412	EXB99	G-160	DDI 1
A-203	EXB685 and EXB1131	B-517	EXB768	G-162;	EXB171
A-204	EXB686	B-553	EXB106	G-172	EXB172

Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)
		B-561	EXB107	G-182	EXB177
		B-678	DDI 2	G-185	EXB178
		B-686	DDI 2 and EXB 789	G-190	EXB180
		B-748	EXB798	G-219	EXB187
		B-868	DDI2, EXB123 and EXB811	G-240	EXB190
		B-1127	EXB129	G-244	EXB192
		B-1819	MO23 and EXB1011	G-261	EXB195
		B-1851	MO32 and EXB1031	G-268	EXB200
		B-1900	EXB661	G-299	EXB209
		B-1901	EXB662	G-307	EXB213
		B-1902	EXB663	G-315	EXB214
		B-1903	EXB664	G-334	EXB218
		B-1905	EXB666	G-337	EXB16 and EXB219
		B-1907	EXB668	G-354	EXB222
		B-1908	EXB670	G-407	EXB230
		B-1909	EXB671	G-410	EXB231
		B-1911	EXB672	G-440	EXB239
		B-1912	EXB673	G-444	EXB241
		B-1913	EXB674	G-455	EXB244
		B-1916	EXB677	G-459 at 10	EXB247
		B-1917	EXB678	G-491	EXB250
		B-1918	EXB679	G-524	EXB257
		B-1919	EXB680	G-529	DDI 1 and EXB259
		B-1920	MO33 and EXB1102	G-532	EXB261
		B-1924	EXB4	G-544	EXB263
		B-1935	EXB6	G-549	EXB266

Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)
				G-557	DDI 1 and EXB269
				G-561	EXB270
				G-564	EXB271
				G-586	EXB278
				G-589	EXB280
				G-593	DDI 1
				G-602	EXB283
				G-617	EXB286
				G-634	EXB293
				G-651	EXB296
				G-652	EXB297
				G-653	EXB298
				G-654	EXB299
				G-671	EXB301
				G-686	EXB304
				G-727	EXB312
				G-734	EXB314
				G-746	EXB315
				G-763	EXB320
				G-780	EXB324
				G-945	DDI 1 and EXB1078
				G-953	EXB330
				G-1350	EXB335
				G-1352	EXB336
				G-1367	EXB338
				G-1451	EXB25
				G-1452	EXB26
				G-1453	EXB27
				G-1454	EXB28
				G-1455	EXB29
				G-1456	EXB30
				G-1457	EXB31
				G-1458	EXB32

Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)
				G-1459	EXB33
				G-1460	EXB15
				G-1463	EXB37
				G-1464	EXB38
				G-1465	EXB39
				G-1466	EXB40
				G-1467	EXB41
				G-1468	EXB42
				G-1469	EXB43
				G-1470	EXB44
				G-1473	EXB47
				G-1475	EXB49
				G-1477	EXB51
				G-1478	EXB52
				G-1479	EXB53
				G-1480	EXB54
				G-1481	EXB55
				G-1482	EXB56
				G-1483	EXB57
				G-1484	EXB58
				G-1485	EXB59
				G-1488	EXB62
				G-1489	EXB63
				G-1517	EXB377
				G1609	EXB381
				G-1644	EXB388
				G-1656	EXB390
				G-1679	EXB399
				G-1681	EXB401
				G-1711	EXB411
				G-1743	EXB419
				G-1772	EXB432
				G-1775	EXB434
				G-1778	EXB436
				G-1785	EXB440
				G-1788	MO17

Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)	Document Reference #	Docket Identification (Doc ID#)
				G-1790	EXB442
				G-1791	EXB443
				G-1800	EXB1121
				G-1816	EXB659 and EXB7