ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

Kent D. McClure, DVM, JD
General Counsel

January 22, 2003

VIA MESSENGER

Office of the Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14B03, HF-7
Rockville, MD 20857

Re: Request for Correction of Information Under Section 515, P.L.106-55

Dear Sir/Madame:

Enclosed please find two copies of a request ("Request") to FDA to correct certain information being disseminated by the Center for Veterinary Medicine ("CVM"). This request is made by the Animal Health Institute ("AHI" or "Requestor") pursuant to §515, P.L. Law 106-55[1], and in accordance with FDA's "Guidelines for Ensuring the Quality of Information Disseminated to the Public" ("FDA Guidelines").[2] In light of CVM's repeated failure to correct the information, as further explained in the Request, this Request is being filed directly with FDA's Office of the Ombudsman.

The Request for correction concerns a *Campylobacter* risk assessment[3], including specifically the model and data used in the risk assessment. The documentation attached to the Request in support of AHI's contention that the information being disseminated is in error consists largely of written direct testimony, under oath, filed on or about December 13, 2002 to FDA Docket 00N-1571. The supporting documentation has been submitted in the form attached

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[1] Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001; P.L. 106-554, § 515 (2000).

[2] The Guideline can be found on CVM's website at: http://www.fda.gov/infoquality/fda.html.

[3] "The Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken," Food and Drug Administration, Center for Veterinary Medicine, (October 18, 2000, Revised January 5, 2001) ("Vose Risk Assessment"). The Vose Risk Assessment was finalized, beginning in about January 2001. Since that time the assessment has been widely relied upon, quoted, and otherwise referenced and disseminated many times in additional publications and presentations by CVM, the Centers for Disease Control and Prevention ("CDC"), other federal agencies, and others. The Vose Risk Assessment has been since at least October 1, 2002, and continues presently to be available on CVM's Website at: http://www.fda.gov/cvm/antimicrobial/Risk_asses

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for the convenience of the Requestor only, since it was initially developed for submission to the referenced docket. The Request is not intended to, nor should it be construed as requesting that the factual assertions, presented in the Request and referenced in the testimony, be judged by or under any standard other than that set forth in FDA Guidelines. Additionally, the Request is not intended to, nor should it be construed as requesting a decision on the merits of the proceeding identified at FDA Docket 00N-1571, *i.e.*, whether enrofloxacin is "safe" for use in poultry.

In the event the Ombudsman concludes for any reason that FDA should not or cannot review the Request, including because of the pendency of the administrative hearing covered by FDA Docket 00N-1571, Requestor requests that the Request be considered by the Office of the Secretary of the Department of Health and Human Services ("HHS") or the Office of Management and Budget ("OMB"). This would appear appropriate in light of the fact that §515, P.L.106-55 directs OMB to issues guidance to provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies.[4] OMB has issued guidelines[5] and both FDA's and HHS's Guidelines[6] were issued pursuant to the OMB guidance.

Should you have any questions or need any further information please feel free to contact me.

Sincerely,

Kent D. McClure, DVM, JD

cc: Robert Nicholas, Esq.

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[4] Section 515 directs OMB to formulate and issue guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies." P.L. 106-554, § 515 (2001).

[5] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies (the "OMB Guidelines"), 67 Fed. Reg. 8452-8460 (February 22, 2002).

[6] "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public", HHS, (October 1, 2002), http://www.hhs.gov/infoquality.

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Request For Correction of Information
Under Section 515 Of Public Law 106-554

The Animal Health Institute ("AHI") ("Requestor") files this Request for Correction of Information ("Request") with the Food and Drug Administration ("FDA") under Section 515 of Public Law 105-554[1] and pursuant to the FDA "Guidelines for Ensuring the Quality of Information Disseminated to the Public" (the "FDA Guidelines").[2] Requestor files this Request for the correction or deletion of information that is in error and has been created by or for, and is currently being disseminated by, the Center for Veterinary Medicine ("CVM").

This request is being filed directly with FDA, rather than CVM. On numerous occasions various parties have brought to CVM's attention scientific criticisms regarding the validity and usefulness of the risk assessment model identified below, the quality, integrity, comprehensiveness, and objectivity of the data used in the risk assessment, and the output of the model. Notwithstanding numerous opportunities to respond to these criticisms CVM has largely failed to modify the risk assessment or respond to the criticisms, and CVM continues to rely on and disseminate the risk assessment.

I. Requester Information

Name: Animal Health Institute

The Animal Health Institute is a trade organization representing the interest of developers and manufacturers of animal drugs and biological products.

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

2 FDA, "Guidelines for Ensuring the Quality of Information Disseminated to the Public," http://www.hhs.gov/infoquality/fda.html.

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II. Specific Material that Needs To be Corrected, Including Name of Report or Data Product, Where the Information is Located, and Date of Issuance

As further detailed below, the information that is in error and needs to be corrected is the methodology, exposition (which currently inaccurately represents what was actually done), data, and conclusions of the *Campylobacter* risk assessment conducted for CVM by David Vose, and subsequently adopted by CVM. The risk assessment purports to be a quantitative risk assessment. It states that:

> To evaluate the human health impact of antimicrobial use in animals, the FDA Center for Veterinary Medicine (CVM) developed a quantitative risk assessment model. The risk assessment was intended to estimate the risk to human health from antibiotic resistant food borne pathogens associated with the domestic use of antimicrobials in food producing animals. Specifically, a mathematical model was derived 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.[3]

Title:

> "The Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken," Food and Drug Administration, Center for Veterinary Medicine. ("Vose Risk Assessment").

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[3] "The Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken," Food and Drug Administration, Center for Veterinary Medicine. (2001), p. 1-2. As used herein "Vose Risk Assessment" includes the methodology or model used in the risk assessment, including selection of parameters; the exposition and use of the model; the data used in the model; and the conclusions; whether disseminated as part of the Vose Risk Assessment or in any other form.

Document Date:

October 18, 2000, Revised January 5, 2001.

Availability:

The Vose Risk Assessment was initially available on CVM's website in final form, beginning in about January, 2001. Since that time the Vose Risk Assessment has been widely relied upon, quoted, and otherwise referenced and disseminated many times in additional publications and presentations by CVM, the Centers for Disease Control and Prevention ("CDC"), other federal agencies, and others. The Vose Risk Assessment has been since at least October 1, 2002, and continues presently, to be available on CVM's Website at: http://www.fda.gov/cvm/antimicrobial/Risk_asses.

III. Reasons for Believing the Information Does Not Meet Applicable OMB, HHS or FDA Guidelines and is in Error

The Vose Risk Assessment (in reality, just a ratio) does not in fact quantify risks, establish a causal relation between exposures and adverse health effects, demonstrate or use any dose-response relation, or establish that any ill effects in humans are "associated with the consumption of chicken". As further detailed herein, and in the exhibits hereto, the Vose Risk Assessment and related materials are inaccurate and should be corrected. The Vose Risk Assessment is methodologically flawed. It also contains critical errors and omissions rendering its conclusions incorrect and misleading and making its use for risk management decision-making and for publicizing the alleged (but incorrectly calculated) human health hazards from use of enrofloxacin in poultry inappropriate. In particular, its flaws, errors, and omissions result in an estimate of risk to human health from the use and/or continued use of enrofloxacin in poultry that is not validated, is inaccurate, conflicts with available data, and constitutes a vast overestimation of the potential risk. Additionally, by failing to consider the risks (especially the human health risks) from withdrawing enrofloxacin for use in poultry, the Vose Risk Assessment provides an incomplete, incorrect, and misleading analysis not useful for risk assessment or risk management. For these and other reasons set out below, the Vose Risk Assessment does not meet the standards for information quality set forth in the FDA Guidelines in terms of utility, objectivity and integrity. In addition, the Vose Risk Assessment fails to meet the required higher standards set forth in the FDA Guidelines for "Influential Information" and "Risk Assessment."

A. The Vose Risk Assessment Constitutes "Influential Information" and a "Risk Assessment" under the FDA Guidelines.

i. Influential Information

Dissemination of the Vose Risk Assessment and of results said to be based on it have been key components supporting the CVM's proposed regulatory action to withdraw approval of the new animal drug application for use of the fluoroquinolone enrofloxacin in poultry. Notice of Opportunity for Hearing, 65 Fed. Reg. 64,954 (October 31, 2000), as amended 66 Fed. Reg. 6623 (January 6, 2001) ("NOOH").[4] This action is reasonably expected to have an annual effect on the economy of $100 million or more and/or will adversely affect in a material way the poultry industry, productivity in the poultry industry[5], the environment,[6] and/or public health or safety.[7] Accordingly the Vose Risk Assessment constitutes "Influential Information," as is defined by the FDA Guidelines.[8]

The FDA Guidelines require that when FDA disseminates information, but particularly in those cases involving influential information, the FDA "strive[s] to ensure that the information is accurate and unbiased, as well as substantially

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[4] In testimony offered into evidence on December 9, 2002 CVM's Deputy Director Tollefson stated:

> What the risk assessment showed me, as an epidemiologists, was that not only was there a quantifiable impact on human health from fluoroquinolone-resistant Campylobacter infections in humans acquired from chicken, but that the risk was substantial.

Written Direct Testimony of RADM Linda Tollefson, DVM, MPH (G-1478), p. 16, ln 30-34, FDA Docket 00N-1571 (December 9, 2002).

[5] The Vose Risk Assessment is being used in support of an agency action (i.e., withdrawal of enrofloxacin in poultry) that has been reasonably estimated to cause an annual loss to the poultry industry in excess of $200 million. Written Direct Testimony of G. Thomas Martin, Jr. (B-1907), p. 14 (ln. 12-14), p. 24 (ln. 21-22), FDA Docket 00N-1571 (December 13, 2002). Exhibit A, hereto.

[6] The withdrawal of enrofloxacin in poultry has been reasonably projected to cause an increase in adverse environmental impacts. Written Direct Testimony of Steven Woodruff (B-1918), FDA Docket 00N-1571 (December 13, 2002). Exhibit B, hereto.

[7] The removal of enrofloxacin has been reasonably projected to cause a significant increase in adverse public health effects. See generally, FDA Docket 00N-1571 (December 13, 2002): (1) increases in pathogen load of broilers in processing and resulting human illness (Written Direct Testimony of Scott Russell (B-1912); Written Direct Testimony of John Glisson (B-1903); Written Direct Testimony of Bruce Tompkin (A-204); Written Direct Testimony of Ronald Prucha (A-203); Written Direct Testimony of L. Anthony Cox (B-1901); Written Direct Testimony of Charles Haas (B-1904)); (2) increased adverse human health effects from environmental impacts of withdrawal (Written Direct Testimony of Robert Harris (B-1919)). Testimony of Russell, Glisson, Tompkin, Purcha, Cox, Hass, Harris are appended hereto, respectively as Exhibits C, D, E, F, G, H, and I.

[8] FDA Guidelines, § VII, "Influential Scientific, Financial, and Statistical Information."

reproducible and replicable. The goal is accomplished by using reliable data sources and sound analytical techniques ..." FDA Guidelines, § VII B. The Vose Risk Assessment does not meet these requirements, as further set out below.

ii. **Risk Assessment**

The FDA Guidelines define for purposes of the guidance, "risk" as the likelihood that injury or damage is or can be caused by a substance, technology, or activity."[9] The Vose Risk Assessment purports to be an assessment of health or safety risks relied upon by the FDA. Accordingly the Vose Risk Assessment, in addition to the ordinary standards of utility, objectivity, and integrity that apply to dissemination of information, is subject to heightened standards that apply to risk assessments that provide the basis for dissemination of influential information. For quantitative risk assessments in support of the dissemination of influential information, such as the Vose Risk Assessment,

1. The agency will use:

a. the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available;

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

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

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

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

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

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9 FDA Guidelines, § VII.C, "Risk Assessment".

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

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

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

FDA Guidelines, § VII.C.

As further detailed below and in the exhibits attached hereto, the Vose Risk Assessment does not comply with the above guidance, for the following among other reasons. CVM:

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

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

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

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

B. <u>The CVM Risk Assessment Is In Error and Should Be Corrected</u>

The CVM Risk Assessment is in error and should be corrected to address the following among other flaws, errors, and omissions.

i. The Vose Risk Assessment Does Not Use the Best Available Science. The Model Used In the Vose Risk Assessment Does Not Adhere to The National Academy of Sciences Paradigm, Or Any Other Paradigm For A Quantitative Risk Assessment That Is Widely Accepted Among Relevant Domestic And International Public Health Agencies. The Model Is Not Based On Sound Analytical Techniques And Has Not Been Published in a Peer Review <u>Publication or otherwise Subject To Peer Review.</u>

The Vose Risk Assessment does not adhere to the National Academy of Sciences ("NAS") paradigm for conducting quantitative risk assessments, as set forth in the NAS "Risk Assessment in the Federal Government: Managing the Process," National Academy Press, Washington, DC, 1983 or in more recent updates and in other authoritative sources and guidelines (e.g., Codex Alimentarius).

The FDA Guidelines implicitly recognize that the Vose Risk Assessment should have followed key aspects of the NAS paradigm.[10] However, the approach used by the Vose Risk Assessment is at variance with the NAS steps that are generally regarded as the best available science and the accepted method in quantitative microbial risk assessment: (1) hazard identification that indicates some reason to believe that exposure *causes* adverse effects (rather than just dividing effects by exposure without regard for causation); (2) exposure assessment that considers the *extent* of exposures, not just whether exposures are present or absent; (3) at least approximate qualitative or quantitative dose-response assessment that reflect at least the most important aspects of the relation (e.g., non-linearity at low doses), rather than use of a direct proportionality relation that conflicts with all available data (including human feeding studies as well as epidemiological data); and (4) risk (or hazard) characterization that integrates the estimated human health harm from a proposed action as well as the estimated benefits. The Vose Risk Assessment is also at variance with other established paradigm's for quantitative risk assessment and as a novel model should have been subject to peer review.[11]

A more specific and extensive analyses of these deficiencies in the Vose Risk Assessment are set out in the following documents, which are attached hereto and incorporated herein, as if fully set forth.

A. Written Direct Testimony of Charles H. Hass, Ph.D. (B-1904), submitted under oath to FDA Docket 00N-1571, on December 13, 2002; Exhibit H, hereto.

B. Written Direct Testimony of Louis Anthony Cox, Jr., Ph.D. (B-1904), submitted under oath to FDA Docket 00N-1571, on December 13, 2002 ; Exhibit G, hereto.

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

FDA Guidance § VII C.

[11] To the best of Requestor's knowledge, information, and belief the Vose Risk Assessment was submitted to and rejected by at least one scientific peer review journal.

CVM has been aware of the substantial criticism and deficiencies in the Vose Risk Assessment at least since December 1999, when it held a workshop on a draft of the Vose Risk Assessment.[12] CVM did not respond, or not fully respond to the many comments and criticisms from the workshop and the final Vose Risk Assessment remains largely unchanged from the draft risk assessment. Between October 31, 2000 and February 21, 2001 many additional comments were submitted to FDA Docket 00N-1571 in reply to the NOOH, including extensive comments on why the final Vose Risk Assessment does not comport with the NAS paradigm[13] and comments raising questions about the validity, objectivity, data integrity, and usefulness of the Vose Risk Assessment.[14] These comments also remain largely unresponded to date, including

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12 CVM held a workshop on the risk assessment draft at which time various experts and other persons provided comments on the draft of the Vose Risk Assessment. Documents, including the transcript of the workshop can be found at http://www.fda.gov/cvm/antimicrobial/oldmeet.html

13 For example, comments on missed critical steps, including quantification of microbial loads received by individuals and dose-response modeling. *See* Affidavit of Mary Alice Smith, Ph.D., (B-1113), FDA Docket 00N-1571 (February 21, 2001) (hereinafter "Smith Affidavit") ("Exhibit J-1", hereto); Animal Health Institute Comment to FDA, (B-1120), FDA Docket 00N-1571 (February 21, 2001), pp. 15-16 (hereinafter "AHI Comment") ("Exhibit J-2," hereto).

14 The following are illustrative of the errors, flaws and omissions in the CVM Risk Assessment, provided to CVM in response to the NOOH, set forth against the four-part framework of the NAS paradigm: (1) hazard identification, (2) exposure assessment, (3) dose-response or toxicity assessment, and (4) risk (or hazard) characterization. All citations are to exhibit numbers for documents filed to FDA Docket 00N-1571, between October 31, 2000 and February 21, 2002.

Exposure Assessment

1. **Overestimates Risk From Chicken.** The CVM Risk Assessment overestimates the attributable risk from chicken. First, the CVM Risk Assessment does not correct for the fact that the pattern of chicken consumption has altered dramatically over the past 20 years since the epidemiological studies that underlie the assessment were conducted. Second, the CVM Risk Assessment does not consider or account for the quantifiable historical decrease in risk associated with better food safety practices. Third, the CVM Risk Assessment includes as an input a study of students at the University of Georgia. This study contains extreme discrepancy in results between males and females, and students living on and off campus, that were not accounted for in the CVM Risk Assessment. *See* Affidavit of Charles N. Haas, Ph.D., February 15, 2001 (C-156), (hereinafter "Haas Affidavit"),("Exhibit J-3," hereto) ; Affidavit of Louis Anthony Cox, Jr., Ph.D., February 19, 2001 (C-160) (hereinafter "Cox Affidavit"), ("Exhibit J-4," hereto).

The modeling of the proportion of Campylobacter infections relating to domestically consumed chicken does not reflect the full plausible range of uncertainties about this variable. In addition, CVM's estimate of this proportion is unrealistically high. *See* Cox Associates "Comments on FDA CVM Risk Model for Campylobacter," (G-136) (hereinafter "Cox Comment"), (Exhibit J-5, hereto).

2. **Nominal Mean Too High**. CVM's nominal mean chicken-acquired Campylobacter cases is too high because the CVM estimate fails to remove infants and young children from the population considered as candidates for ineffective fluoroquinolone treatment. A plausible upper bound on population risk is less than 1 case per 100,000 person-years, and the CVM Risk Assessment falls outside this bound. See Cox Affidavit.

3. **Omits Necessary Explanation for Inconsistency**. The CVM Risk Assessment model shows an inconsistency between "K" values for "total" and "fluoroquinolone resistant" Campylobacter and omits a necessary potential explanation: that the estimated number of Campylobacter cases that are fluoroquinolone resistant is too large. See Haas Affidavit.

4. **Dismisses Distributional Importance**. The CVM Risk Assessment dismisses the distributional importance by treating the process of estimating risk as a purely linear process. This is incorrect because microorganisms are unlikely to be exponentially distributed. See Haas Affidavit.

5. **Not a Dynamic Model**. Fluoroquinolone resistance and fluoroquinolone development are dynamic processes. Realistic modeling of the risks of fluoroquinolone resistant microorganisms requires a dynamic model. The CVM Risk Assessment is not a dynamic model, for example, it ignores the dynamics of fluoroquinolone use and the survival or extinction of resistant strains in assessing the incremental risk from fluoroquinolone use in chickens. The CVM Risk Assessment should consider: (a) physician prescription practices, (b) availability of new fluoroquinolones, (c) the current prevalence of resistant strains in the human and poultry populations, (d) the intensity of fluoroquinolone exposures from various sources in the human population, and (e) whether fluoroquinolones are prescribed in conjunction with other agents. See Cox Comment.

6. **Biases Not Quantified**. The biases from estimating quantities by taking products and ratios from random variables (a non-standard alternative to both Bayesian inference and conventional statistical methods) should be quantified. See Cox Comment.

7. **Inappropriate Use of Assumptions**. The CVM model relies on assumptions, without explaining or addressing them, that directly affect the conclusion of the human health impact:

   a. The entire modeling process is based on the assumption that the presence of resistant *Campylobacter* on the animal carcass was due to antimicrobial use. This assumption should be thoroughly discussed and the supporting data clearly explained.

   b. The model assumes that all *Campylobacter* resistant illness results from consumption of boneless poultry. The model should examine what ratio of the population eats boneless chicken and whether there is a difference in the ratio of resistant *Campylobacter* between bone-in and boneless chicken. *See* Smith Affidavit.

Dose-Response Modeling

8 **Fails to Recognize That Infection Is Not Illness**. The CVM Risk Assessment fails to recognize that infection is not illness, and does not recognize the necessity of dose-response modeling. The model makes a primary assumption that risk of response is proportional to exposure. This assumption is highly uncertain, and should be expanded to include appropriate dose-response models for individuals, an estimate of the population frequency distribution of individual parameters (e.g., tolerance thresholds, scale parameters) for dose-response function, an estimate of the population frequency distribution of exposures in past data, and a new sensitivity analysis showing how total annual risk of illnesses varies with np when an appropriate dose-response model is used to interpret past data. See Cox Comment.

9. **Lacks Information for Human Health Outcomes**. The CVM model lacks information on how much resistant Campylobacter is needed to result in adverse human health outcomes. See Smith Affidavit.

10. **Inappropriate Use of Assumptions**. The CVM model relies on assumptions, without explaining or addressing them, that directly affect the conclusion of the human health impact. The model assumes that exposure to a *Campylobacter* contaminated carcass carries the same risk no matter what amount of *Campylobacter* is on the carcass. This assumption is not true if a threshold exists below which illness does not occur. The model should address this issue. *See* Smith Affidavit.

Risk Characterization

11. **Ignores Important Variables**. The current model does not explicitly identify decision, state, and outcome variables. The scope of the model used in the CVM Risk Assessment should be broadened to: (a) attribute risks of illness from fluoroquinolone-resistant Campylobacter infection to multiple causes and decisions; and (b) recognize that the socially optimal use of fluoroquinolones requires coordinating multiple decisions and policies. Also, the model's inputs should be modified to include more decision variables and fewer random variables. Due to this error, the model does not provide an adequate basis for policy-making, as the CVM has used it. See Cox Comment.

12. **Underlying Policy Judgments Not Explicit**. The risks attributed to fluoroquinolone resistant Campylobacter reflect implicit policy judgments. These judgements and their policy consequences should be made explicit. The CVM Risk Assessment contains the policy decision that the risks to be quantified will be attributed solely and specifically to consumption of contaminated broiler meat. Attributing all of the health risks, resulting from the several likely interactions, solely to the producer's level of care is a policy decision not dictated by science. The assumptions and biases behind this decision should be enumerated. See Cox Comment.

13. **Does Not Support Predictive Modeling**. The current comparative statistics model used in the CVM Risk Assessment does not support the predictive modeling of the health impacts of changes in some of the inputs to the model. The model is intended for use in estimating past illnesses, and not for predicting future ones, as the CVM has used it. See Cox Comment.

14. **The CVM Model Does Not Fit the Data**. The CVM model does not test its fundamental assumption that the amount of contaminated meat is roughly proportional to the number of people who become ill from consuming it. This assumption should be tested in the model. See Cox Affidavit.

15. Several kinds of validation should be carried out before the model is used to guide or support risk management decision-making, including validation for internal validity and external validity. See Cox Comment.

16. **Not Compatible With Other Normative Frameworks**. The "acceptable-risk" framework in Section 5 of the CVM Risk Assessment is not compatible with many normative frameworks for public risk management decision making. To correct this, the options to be considered should include various strategies for allocating fluoroquinolone treatments and alternatives to poultry, other animals, and human patients. See Cox Comment.

17. **Population Heterogeneity Should Be Modeled More Fully**. See Cox Comment.

18. **Statistical Interdependencies Among Components of Risk Should be Modeled**. See Cox Comment.

19. **Confounding Factors**. The CVM Risk Assessment has not been adjusted for confounding factors. To correctly quantify the attributable risk of campylobacteriosis illness due to chicken consumption, the effect of confounders (such as age) must be removed. See Cox Affidavit.

comments on why the Vose Risk Assessment does not comport with the NAS paradigm.[15]

ii. The Vose Risk Assessment Fails to Use the Best Available Science and Supporting Studies Conducted in Accordance With Sound and Objective Scientific Practices, Including Peer Reviewed Science and Supporting Studies When Available.

The Vose Risk Assessment fails to employ the "best available science" and fails to "collect data through accepted methods" as required by the FDA Guidelines for "influential information" and "risk assessments."

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20. **Underestimates Probability of Seeking Care**. The CVM Risk Assessment underestimates the probability that a person with Campylobacteriosis will seek care. The CVM has combined all causes of illness that have diarrhea as a symptom, regardless of the duration in terms of days of the diarrhea. Because Campylobacteriosis is associated with a longer duration of diarrhea, this lumping together fails to take into account the increase in likelihood that people with Campylobacteriosis, and an attendant longer duration of diarrhea, are more likely to seek medical care. See Haas Affidavit.

21. **Inappropriate Use of Assumptions**. The CVM model relies on assumptions, without explaining or addressing them, that directly affect the conclusion of the human health impact: Information on people seeking medical care and for stool samples was based on diarrheal illness and not on Campylobacter exposure specifically. These diarrheal diseases could have resulted from exposure to other food born pathogens. The model should include discussion of the probability that diarrheal disease is a result of infection from Campylobacter. See Smith Affidavit.

Quality of Mathematical Calculations

22. **Contains Mathematical Errors**. The example for the calculation of the total number of Campylobacter infections in the U.S. in 1999 (pages O-3 and 1-2) is incorrectly described and contains several mathematical errors. See Smith Affidavit.

23. **Not Consistent With Data.** The CVM Risk Assessment is not consistent with data from the Centers for Disease Control and Prevention's ("CDC") FoodNet, even though the human illness data in the risk assessment is based on this data. CDC reported a 19% decrease in cases of *Campylobacter* infections between 1998 and 1999 in the original five FoodNet sites. However, the risk assessment only shows a 5% decline. The risk assessment model therefore greatly understates substantial improvements in food safety. *See* American Veterinary Medical Association Comment to FDA, December 15, 2000, (C-21) (hereinafter "AVMA Comment"), (Exhibit J-6, hereto).

15 Recently, in testimony submitted to FDA Docket 00N-1571, CVM has attempted to explain away some of the deficiencies in the Vose Risk Assessment. *See*, Written Direct Testimony of David J. Vose (G-1480), FDA Docket 00N-1571 (December 9, 2002); Written Direct Testimony of Dr. Mary J. Bartholomew (G-1454), FDA Docket 00N-1571 (December 9, 2002). Written Direct Testimony of Curtis Travis, Ph.D. (G-1479), FDA Docket 00N-1571 (December 9, 2002). These efforts are also largely unresponsive and unsuccessful.

For example, but not limited to, instead of using "the best available science and supporting studies" such as the 1998 and 1999 CDC case-study data,[16] the 2001peer-reviewed study of Effler et al.,[17] the peer-reviewed 2001 study of Rodrigues et al., etc.,[18] CVM has relied entirely on two small, outdated, non-representative studies (Harris et al.[19] and Deming et al.,[20] both from the early eighties) for the critical calculation of what fraction of total campylobacteriosis cases to attribute to chicken.[21] Instead of an analysis "conducted in accordance with sound and objective scientific practices", CVM has used unjustified, highly subjective estimates of key parameters (such as the fraction of human campylobacteriosis cases assumed to be resistant, for which CVM uses a subjective uniform prior with a mean of 50%) even though these subjectively estimated values directly conflict with multiple years of data. Additionally, but not limited thereto, the Vose Risk Assessment fails to take into considerations numerous legitimate scientific criticisms and limitations on use of data generated by the National Antimicrobial Resistance Monitoring Program ("NARMS"),[22] critiques of deficits of the Smith study,[23]

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16 Friedman, C., S. Reddy, et al. Risk factors for sporadic Campylobacter infections in the United States: a case-control study of FoodNet sites. 2nd International Conference on Emerging Infectious Diseases, Atlanta, Georgia, 2000. http://www.cdc.gov/foodnet/pub/iceid/2000/friedmsn_c.html (Hereinafter "CDC Data Set").

17 Effler P, Leong MC, Kimura A, et al. Psoriatic Campylobacter jejuni infections in Hawaii: associations with prior antibiotic use and commercially prepared chicken. J. Infect Dis 2001; 183(7): 1152-1155. (Hereinafter "Effler").

18 Rodrigues LC, Cowden JM, Wheeler JG, et al. The study of infectious intestinal disease in England: risk factors for cases of infectious intestinal infectious disease with Campylobacter jejuni infection. Epidemiol Infect. 2001 Oct;127(2) 185-93. (Hereinafter "Rodrigues").

19 Harris, N. V., N. S. Weiss, et al. "The role of poultry and meats in the etiology of Campylobacter jejuni/coli enteritis." American Journal of Public Health 1986; 76(4): 407-11. (Hereinafter "Harris").

20 Deming, M. S., R. V. Tauxe, et al. "Campylobacter enteritis at a university: transmission from eating chicken and from cats." American Journal of Epidemiology 1987;126(3): 526-34. (Hereinafter "Deming").

21 AHI recognizes that both Effler and Rodrigues published after the Vose Risk Assessment was final. However, CVM has continued to disseminate the Vose Risk Assessment and make uncorrected statements of risk based on the Vose Risk Assessment long after CVM was aware of the studies by Effler and by Rodrigues, and long after CVM was aware that more recent data made its initial assessment inaccurate.

22 The National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as a collaborative effort among the Food and Drug Administrations' Center for Veterinary Medicine, U S. Department of Agriculture (USDA), and the Centers for Disease Control and Prevention (CDC). The NARMS program monitors changes in susceptibilities of human and animal enteric bacteria to 17 antimicrobial drugs, including *Campylobacter* resistance to ciprofloxacin. Bacterial isolates are collected from human and animal clinical specimens, from healthy farm animals, and raw product from food animals. The objectives of the system include: to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in Salmonella and other enteric organisms from human and animal populations; to facilitate the identification of resistance in humans and animals as it arises; and to provide timely information to veterinarians and physicians. The ultimate goal of these activities is to prolong the lifespan of approved drugs by promoting

and of the CDC Data set, and limitations and lack of a consensus on selection, identification, resistance testing, and correlation of *in vitro* resistance of *Campylobacter* with clinical outcome.

A more specific and extensive analyses of these and other deficiencies in the Vose Risk Assessment are set out in the following documents, which are attached and incorporated herein as if fully set forth.

A. A "Request for Correction of Information Under Section 515 of Public Law 106-554" was made by Requestor to the Centers for Disease Control and Prevention ("CDC") seeking correction of inaccurate data generated and disseminated by CDC ("CDC Request"). The CDC Request sets forth in detail reasons why the data disseminated by CDC are in error. Data requested to be corrected in the CDC Request were utilized by CVM in the Vose Risk Assessment and continue to be circulated by CVM as part of the Vose Risk Assessment and otherwise. A copy of the CDC Request (as amended) is attached hereto as Exhibit K.

B. Written Direct Testimony of Charles H. Hass, Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1904) (Exhibit H);

C. Written Direct Testimony of Louis Anthony Cox, Jr., Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1901) (Exhibit G);

D. Written Direct Testimony of Gregory A. Burkhart, MD, MS, submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1900) (Exhibit L);

E. Written Direct Testimony of Bradley D. deGroot, DVM, Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (A-200) (Exhibit M);

F. Written Direct Testimony of Diane G. Newell, Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1908) (Exhibit N);

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prudent and judicious use of antimicrobial drugs and to identify areas for more detailed investigation. See generally, http://www.fda.gov/cvm/index/narms_pg.html. (Hereinafter "NARMS").

[23] Smith, K. E., J. M. Besser, et al. (1999). "Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998." New England Journal of Medicine 340(20). 1525-32. (Hereinafter "Smith").

G. Written Direct Testimony of Roger A. Feldman, MD, submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1902) (Exhibit O).

H. Written Direct Testimony of Peter Silley, Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1913) (Exhibit P).

I. Written Direct Testimony of Richard A. Carnevale, DVM, submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (A-199) Exhibit R).

To the best of Requestor's knowledge, information, and belief CVM has merely relied on the authors' conclusions and failed to independently review the raw data from, or otherwise test the conclusions of, the studies it has relied on in the Vose Risk Assessment, including but not limited to NARMS and Smith. As previously noted CVM has been aware of the substantial criticism and deficiencies in the Vose Risk Assessment at least since 2000 and has done little or nothing to correct them.

iii. The Vose Risk Assessment Does Not Use Data Collected By Accepted Methods (where reliability of the method and the nature of the decision justifies use of the data).

The Vose Risk Assessment does not use data collected by accepted methods (where reliability of the method and the nature of the decision justifies use of the data), as required by the FDA Guidelines for "influential information" and "risk assessments."

For example, but not limited to, CVM has not used *any* recent data, specifically the data collected by the CDC, for its key calculation of what fraction of total campylobacteriosis cases to attribute to chicken. Instead, it has used someone else's interpretation of data collected from university students in Georgia (Deming) and from King County (Harris) in the early eighties. CVM extrapolates these numbers to the general current U.S. population without making any corrections or adjustments for what is now known about relevant confounders and risk factors, changes in the industry, changes in US demographics, etc. The reliability of the data collected and extrapolated in this way and the nature of the decision (a nation-wide ban) do not justify this use of the data.

Additionally, and as detailed in the Exhibits appended hereto, including specifically Exhibit K (CDC Request), Exhibit M (WDT de Groot), Exhibit L (WDT Burkhart), Exhibit O (WDT Feldman), Exhibit N (WDT Newell), and Exhibit P (WDT Silley), the data utilized by CVM in the Vose Risk Assessment was collected without regard to accepted scientific methods, or otherwise does not meet widely accepted scientific standards, including specifically that the data utilized cannot support the

conclusions adopted by CVM in the Vose Risk Assessment. These data at a minimum include the NARMS, Smith, and Marano.[24]

iv. The Vose Risk Assessment Does Not Ensure, in Dissemination of Public Information About Health Risks, That the Presentation of Information is Comprehensive.

The Vose Risk Assessment does not ensure, in dissemination of public information about health risks, that the presentation of information is comprehensive, as required by the FDA Guidelines for "influential information" and "risk assessments."

For example, and as detailed in the Exhibits appended hereto, including specifically Exhibit C (WDT Russell), Exhibit D (WDT Glisson), Exhibit E (WDT Tompkin), Exhibit F (WDT Prucha), Exhibit I (WDT Harris), Exhibit G (WDT Cox), Exhibit M (WDT de Groot), Exhibit L (WDT Burkhart), Exhibit O (WDT Feldman), Exhibit N (WDT Newell), Exhibit P (WDT Silley) the Vose Risk Assessment does not ensure, in dissemination of public information about health risks, that the presentation of information is comprehensive. Specifically, but not limited thereto, the 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 ("HAACP") 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

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[24] Centers for Disease Control and Prevention, FoodNet *Campylobacter* Case Control Study 1998-99, preliminary data. Atlanta, GA. 1999 personal communication Dr. Nina Marano. Identified in the Vose Risk Assessment at Fn. 28.

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 both chicken 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.

v. The Vose Risk Assessment Does Not Identify, Use Or Explain Why Additional Studies Not Used To Produce The Risk Estimate That Support Or Fail To Support The Findings of the Assessment, Were Not Used.

The Vose Risk Assessment does not identify, use or explain why additional studies not used to produce the risk estimate that support or fail to support the findings of the assessment, were not used, as required by the FDA Guidelines for "influential information" and "risk assessments."

For example, and as detailed in the Exhibits appended hereto, including specifically but not limited to Exhibit O (WDT Feldman), Exhibit N (WDT Newell), Exhibit P (WDT Silley), and the Written Direct Testimony of James W. Patterson, Ph.D., submitted under oath to FDA Docket 00N-1571, on December 13, 2002 (B-1910) (Exhibit Q) the Vose Risk Assessment does not utilize or explain why it did not use the CDC Data Set, Effler et al., Rodrigues et al., CDC data on the declining incidence of campylobacteriosis in the U.S., various studies examining the relationship between sources other than poultry as a potential risk for campylobacteriosis, and studies examining the genetic relationship between *Campylobacter* isolated from poultry and non-poultry sources, including human sources.

Moreover, it does not specify each population addressed by any estimate of applicable effects (namely, university students (Deming) and residents of King's County, WA (Harris) in the early eighties) or offer any methodology used to reconcile the inconsistencies in the scientific data (such as the large differences in illness rates and resistance rates among FoodNet area, or the changing isolation and operational definition procedures for *Campylobacter* jejuni, which tended to create the appearance of increasing resistance even in the absence of any real change.)

vi. The Vose Risk Assessment and Underlying Data Do Not Meet the Requirements of the FDA Guidelines

In summary, the Vose Risk Assessment and underlying data do not meet the FDA Guidelines, for at least the following reasons:

- The Vose Risk Assessment uses an *inaccurate value* of about 57% for the fraction of domestically acquired campylobacteriosis cases that it attributes to chickens.

This is more than twice the value estimated in written testimony by the CDC[25] and more than ten times the correct value when calculated from the most recent, largest, and representative data set made available by the CDC.[26] Unlike CDC's estimate, CVM's incorrect value does not take into account the facts that (a) It is only chicken eaten in restaurants or outside the home that is associated with increased campylobacteriosis risk; and (b) Non-poultry meats eaten in this setting are also about equally strongly associated with campylobacteriosis risk; and (c) Home-cooked chicken is associated with a statistically significant *reduction* in risk of campylobacteriosis. Thus, CVM attributes to chicken a risk that is actually associated with restaurant dining (of chicken or of other foods). Moreover, it is based on small, old, non-representative studies that do not correct for known confounders and that attribute zero risk to known risk factors, such as drinking contaminated water. Thus, the information presented and used in the Vose model is both inaccurate (the 57% number is greatly inflated by failure to attribute risk to other known risk factors and confounders) and biased (Vose chooses results from small, out-dated studies when much more recent and representative data are available that give much smaller, but more accurate, numbers.)

- It uses an *inaccurate value* of nearly 20% for the fraction of domestically acquired campylobacteriosis cases that are resistant to fluoroquinolones. This is more than three times the actual historical value (ranging from about 5% in 1978 to about 6.4% in 1998 and 1999). CVM supported this inaccurate parameter value with a psuedo-Bayesian argument in which they repeatedly combine a uniform prior (having a mean of 50%) with the empirical value (about 6%). But the uniform prior is inappropriate given national and international data showing that the true rate is far lower. And the use of the same uniform prior multiple times to prevent learning from accumulating data is an incorrect application of Bayesian methodology. It conflicts with correct Bayesian updating procedures for sequentially acquired data, e.g., as set forth in Morris H. DeGroot's text *Probability and Statistics* (Addison Wesley, 1975, p. 265),

- The Vose Risk Assessment uses *unreliable and non-representative data* sources for its estimation of chicken-attributable risk. This is recognized in Vose's own written testimony, which correctly identifies the desirability of using more comprehensive and recent data.[27] Although CDC has made such data available, CVM has repeatedly failed to use it. Instead, CVM continues to disseminate and publicize the incorrect numbers from attributable risks calculated from two relatively small studies (one in a student population where meals were routinely

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25 The Vose Risk Assessment also conflicts with written testimony from the CDC, submitted under oath, by CVM to FDA Docket 00N-1571. See, Written Direct Testimony of Fredrick J. Angulo, pp. 10-11 (G-1452), FDA Docket 00N-1571 (December 9, 2002).

26 Cox LA, Popken DA, Quantifying Human health Impacts of Antimicrobial Risk Management Alternatives for Enrofloxacin, J. Risk Analysis (in press). (Exhibit S, hereto).

27 Written Direct Testimony of David J. Vose (G-1480), FDA Docket 00N-1571 (December 9, 2002).

prepared outside the home) performed approximately twenty years ago. Multiple recent studies in the US and other countries have documented that the population attributable risks from these early studies cannot be reproduced using modern data that correctly accounts for other risk factors and confounders. To the contrary, multiple studies published since 2000 have documented the reduced risk of campylobacteriosis associated with chicken consumption and have implicated other sources, such as restaurant dining (not necessarily associated with chicken) and drinking water, as important risk factors. The Vose Risk Assessment thus uses and promulgates obsolete data and fails to take into account or warn of the recognized risk factors identified in modern literature.

- The Vose Risk Assessment uses unsound analytic techniques, including: (a) A psuedo-Bayesian approach that uses the same uniform prior (with a mean of 50%) multiple times to exaggerate the fraction of campylobacteriosis cases that are claimed to be resistant to fluoroquinolones (which should be about 6.4%' see above); (b) Incorrect interpretation of population attributable risk estimates as cases caused by chicken; (c) Incorrect interpretation of the ratio of two aggregate quantities (cases of campylobacteriosis and chicken consumption) as a causal parameter. It is completely unsound scientifically to present such aggregate ratios as causal relations, which the Vose model has done and which CVM has disseminated; (d) Inappropriate use of a Poisson model even though the FoodNet data clearly indicate huge extra-Poisson variance; (e) Failure to include the significant negative relation between home-cooked chicken and campylobacteriosis risks (found in multiple independent recent studies) in its model or in its disseminated results; (f) Misspecification of the statistical model relating chicken consumption and risk of campylobacteriosis as a direct proportional relation without allowing for an intercept term; (g) Omission of other known risk factors (including restaurant dining, contact with pets or other animals, drinking in or swimming in raw water, consumption of produce, etc.) from the model, even though these have been identified in other studies as being more important than chicken; (h) Deliberate attribution to chicken of all fluoroquinolone-resistance in domestically acquired, non-treatment related cases of campylobacteriosis, even though a significant proportion of such resistance was documented before the introduction of fluoroquinolones in poultry. (This is related to the model misspecification issue, and failure to include an intercept term.) (i) Use of an incorrect formula for calculating the fraction of fluoroquinolone-resistant *Campylobacter* cases attributed to chicken. This formula in fact estimates the fraction of chicken-associated cases that are resistant, not the fraction of resistant cases that are chicken-associated. (j) Use of exposure metrics that ignore the extent of exposure (microbial load) and consider only whether exposure is present.

- CVM has also disseminated inaccurate information that fluoroquinolone-resistance is associated with additional days of illness. This claimed association is completely explained away by the confounding effects of foreign travel; thus, CVM is attributing to fluoroquinolone resistance effects that are in fact caused by

foreign travel and that do not apply to the domestically acquired cases that they purport to be describing.

IV. Specific Recommendation for Correcting the Information

Requestor recommends that the following steps be taken to ensure that the information listed above complies with the standards for information quality outlined in the FDA Guidelines.

1. A qualified and independent risk assessment expert should be appointed to make an initial and timely determination of,

a. whether the Vose Risk Assessment model complies with the NAS criteria, or any other paradigm for a quantitative risk assessment that is widely accepted among relevant domestic and international public health agencies, and whether the Vose Risk Assessment has been peer reviewed;

b. whether the Vose Risk Assessment is valid, using available data to confirm or dispute the validity of the existing model;

c. whether the Vose Risk Assessment utilizes the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available;

d. whether the Vose Risk Assessment utilizes only data collected by accepted methods (where reliability of the method and the nature of the decision justifies use of the data);

e. whether the Vose Risk Assessment ensures, in dissemination of public information about health risks, that the presentation of information is comprehensive;

f. whether the Vose Risk Assessment identifies and explains why additional studies that failed to support the findings of the assessment, were not used;

2. In the event the initial expert review confirms that the Vose Risk Assessment does not meet the NAS or other criteria set forth in 1, above, or any other requirements of the FDA Guidelines, including specifically standards for quantitative risk assessments, CVM should not disseminate or otherwise use for any purpose the Vose Risk Assessment until such time as the Vose or any other *Campylobacter* risk assessment complies with all requirements of the FDA Guidelines, including those set out in 1. above.

3. In the event the initial expert review finds that the Vose Risk Assessment complies with the FDA Guidelines, the Vose Risk Assessment should be subject to a full review by a qualified and independent expert group.

4. In the event, and to the extent the expert reviewer determines that, data as collected or as used by CVM in the Vose Risk Assessment, including specifically NARMS and Smith, do not meet the standards set out in the FDA Guidelines, CVM should not disseminate or otherwise use the data, unless use of the data is in compliance with the FDA Guidelines.

5. CVM should issue a corrective statement, clearly indicating the specific information that has been found to be in error pursuant to this Request, and should prominently display the corrective statement on its website and in other appropriate venues of dissemination. The corrective statement should also be attached to every archival document that references the information that has been corrected.

V. Description of How Requester Is Affected By the Information Errors

1. Erroneous information harms human and animal health by producing data incorrectly attributing human health effects to animal drugs.

   A. To the extent that this erroneous information results in unnecessary reductions in the use of beneficial animal drugs, the overall health of both humans and animals will be negatively affected. A fluoroquinolone product is approved for, effective in, and essential to treat life threatening bacterial infections in poultry. It is the only practical alternative for reducing bacterial infections in poultry. Reductions in poultry bacterial infections result in reductions in human bacterial infections.

   B. Use of erroneous information about animal drugs results in disincentives to developers, manufacturers and other to develop and bring to market new animal drugs, which may result in unnecessary impacts on the companies, animal suffering, and loss of producer productivity.

2. The use of flawed information and unsupported reports sets a bad precedent, generally adversely effecting scientific debate, setting of public policy, and regulatory priorities.

3. Information errors undermine the credibility of the FDA and CVM.

4. The use of flawed information and unsupported reports sets bad precedent, generally adversely effecting any drug manufacturer or association involved in efforts to improve animal health.

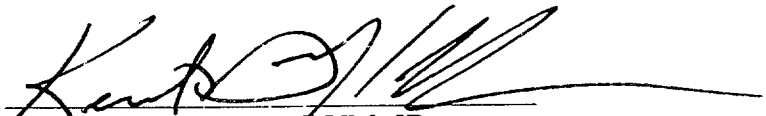
5. By failing to address the adverse human health impacts from a ban on enrofloxacin (specifically, from increases in microbial loads of Campylobacter

and Salmonella on chicken carcasses leaving the processing plant), CVM fails to correctly characterize the human health benefits of continued use and presents a misleading view of the expected health benefits of a ban. This may lead to a poor regulatory decisions.

6. Reports in the media based on inaccurate information harm the poultry industry through the creation of an erroneous conclusion that poultry may be unsafe.

Respectfully Submitted,

ANIMAL HEALTH INSTITUTE



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The following documents are attached here to and incorporated herein, as noted.

Exhibit A	Written Direct Testimony of G. Thomas Martin, Jr. (B-1907), FDA Docket 00N-1571, (December 13, 2002)
Exhibit B	Written Direct Testimony of Steven R. Woodruff, P.E. (B-1918), FDA Docket 00N-1571, (December 13, 2002)
Exhibit C	Written Direct Testimony of Scott Russell, Ph.D. (B-1912), FDA Docket 00N-1571, (December 13, 2002)
Exhibit D	Written Direct Testimony of John R. Glisson, DVM, Ph.D. (B-1903), FDA Docket 00N-1571, (December 13, 2002)
Exhibit E	Written Direct Testimony of Robert Bruce Thompkin, Ph.D. (A-204), FDA Docket 00N-1571, on December 13, 2002
Exhibit F	Written Direct Testimony of Ronald Joseph Prucha, DVM (A-203), FDA Docket 00N-1571, (December 13, 2002)
Exhibit G	Written Direct Testimony of Louis Anthony Cox, Jr., Ph.D. (B-1901), FDA Docket 00N-1571, (December 13, 2002)
Exhibit H	Written Direct Testimony of Charles H. Hass, Ph.D. (B-1904), FDA Docket 00N-1571, (December 13, 2002)
Exhibit I	Written Direct Testimony of Robert H. Harris, Ph.D. (B-1919), FDA Docket 00N-1571, (December 13, 2002)
Exhibit J-1	Affidavit of Mary Alice Smith, Ph.D. (B-1113), FDA Docket 00N-1571 (February 21, 2001)
Exhibit J-2	Animal Health Institute Comment to FDA (B-1120), FDA Docket 00N-1571 (February 21, 2001)
Exhibit J-3	Affidavit of Charles N. Haas, Ph.D. (C-156), FDA Docket 00N-1571 (February 15, 2001)
Exhibit J-4	Affidavit of Louis Anthony Cox, Jr., Ph.D. (C-160) FDA Docket 00N-1571 (February 19, 2001)
Exhibit J-5	Cox Associates "Comments on FDA CVM Risk Model for Campylobacter," (G-136), FDA Docket 00N-1571 (February 21, 2002)

Exhibit K	"Request for Correction of Information Under Section 515 of Public Law 106-554," (December 6, 2002), as amended January 8, 2003
Exhibit L	Written Direct Testimony of Gregory A. Burkhart, MD, MS, (B-1900); FDA Docket 00N-1571, (December 13, 2002)
Exhibit M	Written Direct Testimony of Bradley D. deGroot, DVM, Ph.D. (A-200), FDA Docket 00N-1571, (December 13, 2002)
Exhibit N	Written Direct Testimony of Diane G. Newell, Ph.D. (B-1908), FDA Docket 00N-1571, (December 13, 2002)
Exhibit O	Written Direct Testimony of Roger A. Feldman, MD (B-1902), FDA Docket 00N-1571, (December 13, 2002)
Exhibit P	Written Direct Testimony of Peter Silley, Ph.D. (B-1913), FDA Docket 00N-1571, (December 13, 2002)
Exhibit Q	Written Direct Testimony of James W. Patterson, Ph.D. (B-1910), FDA Docket 00N-1571, (December 13, 2002)
Exhibit R	Written Direct Testimony of Richard A. Carnevale, DVM (A-199), FDA Docket 00N-1571, (December 13, 2002)
Exhibit S	Cox LA, Popken DA, Quantifying Human Health Impacts of Antimicrobial Risk Management Alternatives for Enrofloxacin, J. Risk Analysis (in press).