Toward More Effective Regulatory Decision-Making for Antibiotics Used in Both Human and Veterinary Medicine

Comments on the FDA CVM's
"Notice of Opportunity for Hearing Pertaining to Fluoroquinolone Use for Poultry"

Louis Anthony Cox, Jr.
Cox Associates
503 Franklin Street
Denver, Colorado, 80218

These comments are submitted to Docket # 00N-1571: Notice of Opportunity for Hearing Pertaining to Fluoroquinolone Use for Poultry

Since 1999, I have done work for both CVM and industry to review and try to clarify the strengths and limitations of the modeling framework proposed by CVM to manage the human health risk associated with fluoroquinolone-resistant Campylobacter derived from chickens. These comments address the technical soundness and appropriateness for use in decision-making of CVM's proposed approach. They identify several areas where changes in the framework are needed to support sound, useful decision-making consistent with principles of normative decision analysis and policy analysis.

A. CVM's Proposed Framework Can Support Unjustified Decisions

CVM proposes to use the following model to help determine action thresholds for regulatory interventions to reduce risks associated with the development of antibiotic-resistant microorganisms, specifically including fluoroquinolone-resistant Campylobacter:

$$H = kQ.$$

Here,

- H = "prevalence of people impacted"

- Q = "measurable level of exposure" = "number of pounds of a particular food animal commodity containing drug-resistant bacteria."

(Quotes are from the CVM document entitled: "An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals", henceforth called the "Threshold Document." This document uses additional notation, such as $H(x)$ and k_res, abbreviated here as $H = kQ$ for simplicity. Substantially the same framework has been applied by CVM to justify its proposal to withdraw fluoroquinolones from veterinary use in chickens.)

I am concerned that this framework is not adequate to support effective decision-making. Adopting it is likely to lead to unnecessarily high error rates in deciding when to intervene. The framework does not provide crucial information needed for rational decisions – specifically, how human health impacts are likely to *change* if different regulatory actions are taken. Therefore, using it to support decisions may promote poor resource allocation and risk management decision-making.

A related concern is that this framework may be used to justify regulatory interventions even when the interventions in question would create no health benefits. For example, in a "CVM Update" on streptogramin-resistant *Enterococcus faecium* in humans dated 4-5-01, CVM asserted that "CVM has completed a quantitative risk assessment that modeled the human health impact of fluoroquinolone resistant *Campylobacter* infections associated with the consumption of chicken. It demonstrated the extent of the adverse impact of fluoroquinolone use in poultry on human health." But, the cited risk assessment model only *assumed* that FQ use in poultry (actually, chickens) would lead to adverse health consequences in humans. It did not "demonstrate the extent of the adverse impact", or even show that one exists. Rather, it made untested modeling assumptions, many of which were carefully noted and caveated in the risk assessment document, to calculate a hypothetical impact. These modeling assumptions allowed calculation of a hypothetical number of people affected (to an unspecified degree – some or all of these people may have experienced no actual adverse consequence.) CVM then used these untested modeling assumptions and unquantified (possibly zero) hypothetical health impacts to justify a proposal to withdraw fluoroquinolones from veterinary use. All of these calculations can be made, and the proposal to ban a drug can be supported equally well, whether or not withdrawing it would lead to any human health benefit (or even if doing so would harm human health).

As illustrated in this example, the framework in CVM's Threshold Document and Campylobacter risk assessment does not enforce rational, useful, or well-justified risk-management decision-making. It allows untested and incorrect modeling assumptions to be used to justify regulatory actions whose likely human health consequences have not yet been evaluated. A more traditional approach that focuses on quantifying the probable changes in exposures and risks in the human population of taking alternative risk management actions would better support regulatory decision-making.

B. Technical Changes Needed to Support Effective Decision-Making

This section outlines several areas where the proposed framework must be changed if it is to support effective risk-management decision-making, i.e., decision-making that selects risk management acts leading to improved health outcomes. These comments focus mainly on technical limitations of the current proposal in the Threshold Document and ways to overcome them.

My main concerns about the proposed approach in the Threshold Document, along with recommendations for improvements, are as follows.

1. *It is not a decision framework.* Any model used to guide regulatory decisions should relate alternative acts to their probable health consequences. The proposed model (based on the H = kQ assumption) does not do that. Its explicit inputs do not include *changes* in the frequency distribution of food contamination reaching

consumers if different risk management acts are taken. Its outputs do not include resulting changes in health consequences (e.g., illness-days, severity-weighted illness-days, or QALYs.) As clarified by CVM at the January Workshop "Use of Antimicrobial Drugs in Food Animals and the Establishment of Regulatory Thresholds on Antimicrobial Resistance" (Rockville, MD, January 22-24, 2001), the $H = kQ$ is not intended to be a predictive model. Yet, good risk management decision-making and policy analysis require a predictive model that relates alternative impacts to their predicted probable health consequences. A framework that does not make this connection cannot be expected to support sound or useful decision-making.

Recommendation: Replace the current non-predictive risk attribution model ($H = kQ$) with a predictive model that (a) Represents proposed risk management options by the changes they will cause in the population frequency distribution of exposures (ingested microbial loads); and (b) Predicts human health consequences as a function of the distribution of exposures in the population. Such a model can predict the changes in human health consequences from acts that change exposures. This is essential for rational decision-making among choices that affect risk by affecting exposures.

2. ***CVM's proposed model is not a causal model.*** The $H = kQ$ model does *not* imply that changing Q by one unit will change H by k units. In fact, it can be fit to data on H and Q even if Q has no causal impact on H. (For example, as demonstrated in CVM's risk assessment for fluoroquinolone-resistant *Campylobacter*, the "attributable risk" calculations used are based only on statistical associations. Hence, the health impacts *attributed* to contamination in the Threshold Document's framework need not be *caused* by contamination.) The $H = kQ$ approach produces the same output numbers from the same statistical inputs on Q and H, regardless of whether or how changing contamination would change health impacts. It could trigger regulatory actions even in the absence of any true causal relation (or even if the causal relation is negative) between exposure and adverse health impacts. It assumes a relation where none may exist.

Recommendation: Replace the $H = kQ$ model with a causal model in which only the changes in human health that will be *caused* by proposed alternative actions (e.g., do nothing vs. ban a drug from veterinary use) are used to evaluate and choose among them. Purely statistical associations (which may reflect ecologic biases, statistical modeling choices, effects of uncontrolled confounders and omitted explanatory variables, multiple-testing and model-selection biases, and other non-causal associations) should *not* be used as a basis for decision-making. A possible approach for implementing this recommendation is to use a discrete-event simulation model to consolidate and apply available knowledge and modeling assumptions to determine how proposed actions will affect human health.

3. ***The Threshold Document makes use of undefined concepts, especially involving attributable risk.*** For example, it suggests calculating H from a formula that includes the "proportion of total cases *due to exposure* to animal-derived food commodity" (emphasis added). But the meaning of "due to exposure" is not specified. For example, if home preparation and consumption of chickens *reduces* total number of cases of *Campylobacteriosis* (at least among people old enough to have acquired some immunity to chicken-borne CP), while consumption of chicken

and other meats in restaurants with poor food safety practices *increases* cases, then how is the "proportion of total cases due to exposure to animal-derived food commodity" to be calculated? If CVM proposes to use cases "due to exposure" as an essential part of its framework, then it must define how it is to be calculated, so that others can carry out and verify risk calculations. (Note that traditional attributable-risk calculations are not adequate to identify the proportion of cases "due to" exposure when multiple variables, such as age of consumer and location of food consumption, affect the outcome.)

Similarly, the Threshold Document suggests calculating H from a formula that includes a term for "proportion of cases with resistance *attributed to* animal-derived food commodity" (emphasis added). But this crucial concept is also left undefined. (In addition, "resistance" is not a dichotomous concept, so it is not clear what constitutes a "case with resistance" for purposes of risk assessment.) For example, suppose that someone has been made ill by ingesting 2000 CFUs of a non-resistant strain in a contaminated meal, but also happens to have ingested 1 CFU of a slightly resistant strain that plays no role in either the etiology of the infection or in response to treatment. Would this be considered a "case with resistance"? Would it be considered a "case with resistance attributed to animal-derived food commodity"? Until it is clearly specified how such questions are to be answered, the practical meaning of CVM's proposed framework is not defined well enough to evaluate carefully.

Recommendation: Do not use attributable risk calculations. Instead, calculate or simulate how human health impacts will change if different risk management actions are taken. This makes attributable risk calculations unnecessary. (However, if this recommendation is rejected, then please provide definitions and calculation formulas for unambiguously and objectively determining attributable risks, taking into account the effects of multiple risk factors, confounders, and possible protective effects of exposures in some sub-populations. Note that attributable risks should not be based on non-causal statistical associations and should be constrained to sum to 100% of the total risk being attributed.)

4. ***The proposed framework should be revised to model the distribution of individual exposures in the population (under different risk management scenarios.)*** The $H = kQ$ framework is limited by the fact that different population distributions of exposures corresponding to the exact same Q value may create very different public health risks. For example, if the most-contaminated servings of meat are allocated to the most vulnerable (e.g., youngest) members of a population, the health impact may be greater than if they are allocated to the least vulnerable members of the population. Yet, the proposed framework does not include the allocation of contamination amounts to individuals with different susceptibilities (e.g., of different ages or with different covariates in their multivariate dose-response functions) as part of its description of what affects risk and need for intervention. In the *Campylobacter* example, Q should exclude chicken meat that is processed to kill all CFUs, chicken meat consumed by age groups not prescribed fluoroquinolones, etc. Different sub-populations therefore have different H and Q values, and hence different values of k. Using a single aggregate equation, $H = kQ$, instead of multiple equations for different at-risk populations, does not reflect the frequency distribution of exposures and risks in the population.

A related problem is that the same aggregate Q value can result from two situations, one involving a large number of people exposed to enough CFUs to cause illness with high probability (e.g., 2000 CFUs or more per portion) and the other involving no such high exposure concentrations. Because the Threshold Document framework only uses "the number of pounds of a particular food animal commodity containing drug-resistant bacteria" and not the *amount* of drug-resistant (or total) bacteria per portion, the same Q value can correspond to very different risks. Hence, the aggregate value of k estimated from a particular pair of H and Q values may not represent risks from the same pair of H and Q values having a different underlying frequency distribution of ingested CFUs in the population. In other words, the information that determines risk is not captured in the H = kQ framework.

Recommendation: Same as for issue 1: Replace the H = kQ framework with one that (a) Represents proposed risk management options by the changes they will cause in the population frequency distribution of exposures (ingested microbial loads); and (b) Predicts human health consequences as a function of the distribution of exposures in the population.

5. **The proposed framework should be modified to include information about dose-response relations.** For example, if it were known that there is a minimum infective dose of *d* CFUs per meal necessary to cause illness, then only the right tail of the exposure distribution above *d* should be modeled for purposes of risk assessment. The rest of the distribution should not be considered and should not be used in the calculation of Q, as it is irrelevant to health effects. Q values calculated without regard for dose-response information may be based primarily on irrelevant information (e.g., average amount of CFUs consumed) while neglecting relevant information (e.g., the amount of CFUs consumed in quantities that could cause illness, weighted by the probabilities that they will cause illness.) Calculations based on causally irrelevant information are unlikely to be useful in guiding effective risk management and resource allocation decisions. To be sure that causally relevant information is included, the shape of the dose-response relation for different at-risk populations (e.g., different age groups) must be considered.

6. **The proposed framework should be modified to include key uncertainties currently omitted. Specifically, it should address model uncertainties due to model form selection, variable selection and coding, errors and omissions in explanatory variables, and effects of confounders.** Taking the risk assessment of fluoroquinolone-resistant *Campylobacter* as an example, the current framework supports a variety of uncertainty and sensitivity analyses for parameter estimates, while leaving unaddressed much larger and more important uncertainties about whether the basic form of the model is correct and about whether exposures cause adverse health effects. (Quantifying in great detail the uncertainty about the quantities H, k, and Q in the model H = kQ is not useful if the true relation is H = b − kQ, where b = background and Q has a net protective effect. Uncertainty about the correct model should therefore typically be addressed before uncertainty about model parameters. But, the proposed framework does not address such model uncertainty.)

To be causally relevant, the proposed framework should also be modified to control for the effects of confounders (e.g., age, children in day care, eating out at restaurants, pet ownership, etc.) that are associated both with exposure to certain food products and with health risks (e.g., campylobacteriosis rates) of interest. It should use explicit, well-documented multivariate risk models to show how different factors (including those associated with, but not caused by, exposure) affect risk.

7. ***To support effective risk management decision-making, the scope of the CVM model should be expanded to include all health impacts of interest – including those from other bacteria that would be affected by the proposed control measures.*** A useful framework for regulatory decision-making should quantify the increases or decreases in human health risks from all of the microorganisms affected by the proposed risk management alternatives being considered. For example, if a proposed restriction on veterinary use of a drug would increase microbial load reaching the consumer and increase resulting human illnesses for some types of bacteria, while reducing it for others, then the *total* health impact of the change should be considered in evaluating the proposed change. Focusing on one bacterium (e.g., Campylobacter) at a time may over-estimate or under-estimate the total human health benefits (or losses) from proposed actions, thus leading to decisions that do not best protect total human health.

Recommendation: Quantify the total human health impacts (considering effects on multiple microorganisms) of proposed decisions before deciding which decisions to take.

In summary, I believe that the framework proposed in CVM's Threshold Document requires fundamental changes in order to capture and express information about the probable health consequences of different proposed risk management actions. Without these changes, the results of the framework will not reflect important risk-relevant information (e.g., the shapes of dose-response relations and the quantities of exposures received, as well as how exposure distributions and resulting risks will change if proposed actions are taken). They will probably reflect causally irrelevant information (e.g., aggregate Q values representing unknown exposure distributions and/or parts of the distribution that do not affect risk.) And they may lead to decisions based on examining only some of the health impacts of proposed changes, rather than all of the impacts.

To overcome these difficulties, I strongly recommend adopting key ideas from a more traditional risk analysis approach. This approach should quantify the predicted effects of proposed changes, i.e., risk management actions, on (a) Exposure (represented by the population frequency distribution of CFUs ingested); and (b) Adverse health consequences of exposures (e.g., changes in QALYs or in severity-weighted illness-days). Such an approach can be implemented (e.g., using discrete-event simulation modeling) at a small fraction of the cost and effort put into CVM's *Campylobacter* risk assessment. It is more consonant with what professional risk analysts have advocated and is likely to produce more relevant and informative results for guiding health-protective policy decisions.

FedEx Express ® USA Airbill

FedEx Tracking Number **8284 3075 6721**

Form 0200

1 From

Date 3/31/01

Sender's Name Tanya Cox

Company

Address 583 Franklin St.

City Denver   State CO   ZIP 80218

Phone 303-399-1778

2 Your Internal Billing Reference

3 To

Recipient's Name Dockets Management Branch Phone

Company Food and Drug Administration (FDA)

Address 5630 Fishers Lane (Room 1061)

City Rockville   State MD   ZIP 20852

Dept/Floor/Suite/Room

To "HOLD" at FedEx location, print FedEx address.
We cannot deliver to P.O. boxes or P.O. ZIP codes.

HEA-305

mail code 17 U2

Barcode: **8284 3075 6721**

L
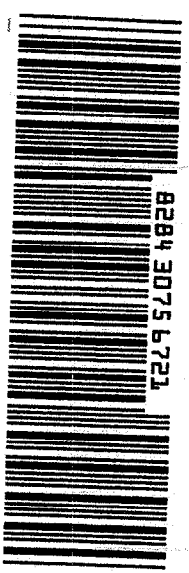
4a Express Package Service   Packages up to 150 lbs.

☒ FedEx Priority Overnight
Next business morning

☐ FedEx Standard Overnight
Next business afternoon

☐ FedEx First Overnight
Earliest next business morning delivery to select locations

☐ NEW FedEx Extra Hours
Later drop-off will meet next business afternoon delivery to select locations

4b Express Freight Service   Packages over 150 lbs.

☐ FedEx 1Day Freight*
Next business day

☐ FedEx 2Day Freight
Second business day

☐ FedEx 3Day Freight
Third business day

☐ FedEx 2Day
Second business day

☐ FedEx Express Saver
Third business day

5 Packaging

☒ FedEx Envelope*

☐ FedEx Pak*

☐ FedEx Box

☐ FedEx Tube

☐ Other Pkg.

6 Special Handling

☐ SATURDAY Delivery

☐ SUNDAY Delivery

☐ HOLD Weekday at FedEx Location

☐ HOLD Saturday at FedEx Location

Does this shipment contain dangerous goods?

☐ No   ☐ Yes As per attached Shipper's Declaration   ☐ Dry Ice

7 Payment *Bill to:*

☒ Sender   ☐ Recipient   ☐ Third Party   ☐ Credit Card   ☐ Cash/Check

Total Packages   Total Weight   Total Declared Value $ .00

Total Charges 11.95

404

8 Release Signature *Sign to authorize delivery without obtaining signature.*

Recipient's Copy