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

Re: Comments to FDA Docket No. 98D-0969, "Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken"

AHI appreciates the opportunity to comment on the document, "*Risk Assessment of the Human Health Impact of Fluoroquinolone Resistant Campylobacter Associated with the Consumption of Chicken*," released in December 1999. The FDA Center for Veterinary Medicine (CVM) is to be commended for undertaking the task of attempting to quantify the potential risk of antibiotic resistant food-borne pathogens to human health. AHI has long been a proponent of quantitative risk assessment as a valuable tool to help regulators estimate public health risks in order to guide regulatory actions.

AHI is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

In unveiling this project at a December 1999 workshop, CVM asked panelists a number of questions relative to the strengths and weaknesses of the assessment. Our formal comments here attempt to follow, to some extent, that line of questioning. We have organized our comments into several parts. The first section reflects general comments on how the assessment was conducted and the assumptions and data used to perform the mathematical calculations. Second, we address in more detail our specific concerns with some of the more critical assumptions used in the assessment since these assumptions have a significant impact on the final outcome. Third, we address questions to the Agency on how the assessment may be modified, and more importantly how the assessment will be used to establish future regulatory policy.

98D-0969

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A. GENERAL COMMENTS ON THE RISK ASSESSMENT MODEL

In the Introduction to the risk assessment the document states that “... *the incremental human health impact of resistant food-borne disease can be determined without assessing all the factors influencing the cause of the food-borne illness itself.*”

AHI disagrees with this statement. In our view it is not appropriate to ascribe to “so called” resistant food-borne pathogens, some inherent quality that makes them significantly different than susceptible organisms when it comes to factors affecting illness. Factors, that affect food-borne illness, are the same regardless of whether the pathogen is classified “susceptible,” “intermediate,” or “resistant” by *in vitro* laboratory testing to all or some antibiotics. The implication is that pathogens that show resistance patterns to certain antibiotics are somehow less “safe” than pathogens which are susceptible. All food-borne pathogens are potentially dangerous to susceptible individuals. There is no compelling evidence that suggests that bacteria with certain antibiotic susceptibility patterns are either more infective or more virulent than bacteria with other susceptibility patterns. Furthermore, laboratory derived antibiotic susceptibility information is only one piece of information that helps predict if a treatment may or may not be effective. Actual resolution of an illness is the result of many factors such as immune status of the patient, other underlying illness, and actual exposure of the bacteria to effective concentrations of the antibiotic. It is interesting that for *Campylobacter*, it was recently reported that of 39 ciprofloxacin resistant isolates from human cases of enteritis, only one did not respond to ciprofloxacin therapy (1). Based on this information, one must question how reliable susceptibility data is for predicting clinical outcome for *Campylobacter* enteritis and, therefore, how useful *in vitro* data would be for regulatory purposes.

It is not valid to discount the impact of factors affecting food-borne illness, such as contamination rates of meat and poultry, infectious dose levels, and the effect of handling and cooking on the product. In this regard, we believe that the CVM assessment represents a retrospective analysis of the risk based on what has occurred rather than a prospective analysis of what the likely risk will be, given factors affecting exposure. Specifically, the CVM assessment estimated the likely number of cases of campylobacteriosis that will occur in the future based on data from the 1998 FoodNet, further estimated the number of cases of campylobacteriosis due to chicken, and finally estimated the number of cases of fluoroquinolone “resistant” campylobacteriosis, the latter two drawing from data derived in the 1980’s. In effect, what the assessment says is that what has already occurred is likely to be what is occurring or what will be occurring in the future.

The model does not factor in expected human exposure to resistant *Campylobacter jejuni* in chickens. A risk assessment should take into account what the likely exposure to the hazard may be. It is simply not enough to estimate what may be present in raw product. What is needed is some estimate of a likely infectious dose and the effect in the best and worst cases of handling and cooking. Only when these parameters are examined can a true estimate of how great the exposure could be and therefore what the true risk to the various populations may entail. We refer the Center to a recent assessment of *Campylobacter jejuni* in ground beef conducted by the

Georgetown University, which expressly factored in consumer handling of raw product and how that may affect the likely infectious dose that could be consumed (2).

We would briefly like to comment on some of the assumptions made in estimating the case incidence. More detailed discussion on these and other assumptions are covered in later sections of this document.

Priority 1 of Appendix C assumes all fluoroquinolone resistance in poultry is due to fluoroquinolone use in poultry. We believe that fluoroquinolone resistance in *Campylobacter* could, in part, be due to poultry use of fluoroquinolones, but to assume that 100% of the resistance is due to this practice is not valid in our opinion. *Campylobacter* species are present in numerous ecosystems and can be found in water, wild rodents, wild birds, and even insects. Fluoroquinolones are used extensively in human populations and have been available long before use in food animals was permitted. It is highly likely that environmental exposure of *Campylobacter* to fluoroquinolones has been occurring for years. *Campylobacter* are also well known to select for fluoroquinolone resistance in a single step mutation more rapidly than other organisms. Data is available to show that resistance was found in *Campylobacter* isolates prior to use in food-producing animals in the U.S. (3). Add to this, the fact that fluoroquinolones have been used to a very limited extent in poultry in the U.S. since their approval. (It is estimated that 1-2% of chickens are treated with fluoroquinolones in the U.S.)

Priority 2 of Appendix C assumes the same level of risk exists today from consuming poultry as was determined from the three studies conducted in the 1980's. We believe this to be a faulty assumption. There have been sweeping changes to the way meat and poultry are produced and inspected in the last decade. One only has to point to the USDA implementation of HACCP and pathogen reduction measures. Secretary of Agriculture Dan Glickman recently reported significant reductions in *Salmonella spp.* in both large and small meat and poultry plants (4). While there are no specific data on *Campylobacter jejuni*, it would not be unreasonable to assume the rate and extent of contamination of poultry with this pathogen has also been reduced. Furthermore, the FoodNet reports that between 1997 and 1998 there has been a 14% reduction in reported cases of campylobacteriosis (5). In addition, USDA a few years ago required the application of safe food handling labels to all packages of raw meat and poultry. These labels tell the consumer that raw product may contain pathogenic organisms and provides instructions on proper handling and cooking of the product (6). Most supermarkets have readily applied these labels to virtually all raw packaged products. The FDA and FSIS in conjunction with the Partnership for Food Safety Education, a coalition including numerous industry groups, have also implemented a successful FIGHT BAC campaign as part of a consumer food safety educational program (7). Even without further quantitative data, there is clear evidence that the level of consumer risk of food-borne illness has indeed been reduced since those earlier studies.

We would also like to draw attention to a significant problem with the use of FoodNet in estimating the case incidence of *Campylobacter jejuni* due to poultry consumption. FoodNet 1998 reports that the case incidence for infants less than one year of age is three times that of older children and adults for *Campylobacter* and was even higher for *Salmonella*. Yet the total *Campylobacter* cases inclusive of infants was used as a baseline figure in finally arriving at the

“5000” expected cases due to poultry. The cases in less than one- year old infants could not have been due to consumption of undercooked poultry. While it is possible that cross-contamination from contaminated raw poultry to infants may have been the cause in some cases, it is more likely that other sources were at fault, such as contact with the family pet, consumption of unpasteurized dairy products, contaminated water, etc. CVM’s risk assessment however, examined poultry consumption as the only means of exposure. Unless the assessment is expanded to incorporate data and analysis on cross contamination as a likely cause of *Campylobacter* infections, the inclusion of infant cases in the database to extrapolate to the poultry consuming population is scientifically inappropriate.

Since these cases have no relationship to poultry consumption, it would seem appropriate to eliminate these cases from the calculations. To do otherwise biases the estimate of the number of cases that could have been from poultry consumption. This would have the effect of substantially reducing the risk of acquiring campylobacteriosis from poultry and would also change the current probability of harm, which was established on the basis of an artificially high estimate of infection rate.

These issues and others are addressed in more detail in subsequent sections of this document. In addition, AHI has sponsored an independent critique of the risk assessment from a more detailed statistical and mathematical viewpoint from Dr. Tony Cox of Cox Associates, Denver, Colorado. (A risk assessment expert invited by CVM to present comments at the December workshop.) (Attachment 1) We believe Dr. Cox has provided a particularly keen insight into the strengths and weaknesses of the risk assessment model and his review complements AHI’s concerns.

AHI has undertaken an in-depth review of this risk assessment because we believe it is critically important to make sure that the assessment and assumptions underlying the effort have been conducted as accurately and objectively as possible.

B. SPECIFIC COMMENTS ON RISK ASSESSMENT ASSUMPTIONS

Beyond the mathematical validity, it is extremely important to carefully evaluate the validity of each assumption of any risk assessment. In the following subsections, comments are provided concerning the evidence or rationale put forth by the CVM in justifying their assumptions. Although the Center has described the assumptions inherent in the model, AHI is providing comment on those assumptions for which we feel there is substantial data or knowledge to revisit or revise the assumptions which are critical to the model in assessing the potential risk to human health.

Priority 1

Assumption: The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those who took a fluoroquinolone prior

to culture and those for whom the time of taking the fluoroquinolone was unknown) is attributed to chickens.

Throughout the risk assessment document, the Center has acknowledged that there are several other sources from which humans can obtain *Campylobacter* infections. An additional reference that should be considered in the discussion of *Campylobacter* is a 1987 book titled “*Zoonoses and Communicable Diseases Common to Man and Animals*” which contains a section on campylobacteriosis (8). This book was published by the Pan American Health Organization and was authored by Pedro N. Acha and Boris Szyfres. In the article written by Acha, he references an article (9) which states that in developing countries, *Campylobacter jejuni* is isolated from 5 to 17% of persons without diarrhea and from 8 to 31% of persons with diarrhea. Although we realize that rate of exposure to *Campylobacter* may be quite different in developing countries vs. developed countries, it is fair to assume that residents in some households in developed countries share certain cultural traditions with those from developing countries and may not show signs of diarrhea, but at the same time be *Campylobacter*-positive on a fecal culture. This also gives credibility to the assumption that there are potential sources for *Campylobacter* other than poultry consumption, and that there is a significant percentage of human carriage (inapparent or apparent).

Assumption 1 excludes evidence that *Campylobacter* infections in humans have been linked to sources other than the consumption of chicken. The possibility that some of the fluoroquinolone resistant *Campylobacter* isolates from humans may have been obtained by other sources such as contaminated water and household pets must be part of the equation. The *New England Journal of Medicine* article referenced by CVM (10) to support their assumption, presents several other risk factors, yet does not include the consumption of chicken as a potential risk factor for infections with quinolone-resistant *Campylobacter*. Potential risk factors that were listed included human use of a fluoroquinolone, drinking untreated water, swimming and contact with pets. In addition, the study evaluated raw chicken carcasses for the presence of *Campylobacter* and did not consider that the potential risk from chicken is virtually eliminated if the chicken is prepared and cooked properly.

This assumption also fails to recognize and account for those *Campylobacter* isolates obtained from humans that were analyzed and found to be less susceptible or resistant to fluoroquinolones may have occurred naturally within the human reservoir. Reports in the published literature have shown that fluoroquinolone resistant *Campylobacter* strains existed in the late 70's through the 80's, well before the introduction of fluoroquinolone use in veterinary medicine (3, 11, 12). Another article by Lores-Salorio, et al. (13) states that person-to-person transmission is possible, but unusual. It documents a case that occurred in a Mexican hospital among children. It also stated that untreated patients may shed the organism from six weeks to a year.

As the Agency builds the model, these factors need to be taken into account and the possibility considered that although person-to-person transfer is unusual, it is not unlikely. If it can occur in a hospital environment it stands to reason that it can occur in a home environment given that shedding of *Campylobacter* has been demonstrated to occur for up to a year. Also, if

patients recover without treatment, it could be possible to shed the organism for 6 weeks up to 1 year. If the person who sheds the organism lives in a shared household, transmission to other people is a distinct possibility.

Conclusion

The risk assessment should look closely at sources other than poultry for *Campylobacter* infection and account for these within the model. The next version of the risk assessment should incorporate the fact that naturally occurring resistance to antibiotics occurs and fluoroquinolone-resistant strains of *Campylobacter* existed prior to the introduction of fluoroquinolone use as a veterinary product. Furthermore, CVM should consider that person-to-person transfer can and does occur. A more appropriate assumption to be made from the body of scientific knowledge would be:

Revised Assumption: The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those coming in contact with or ingesting untreated water, those who took a fluoroquinolone prior to culture, those for whom the time of taking the fluoroquinolone was unknown, and the estimated amount of naturally occurring resistance) is attributed to consumption of under-cooked or improperly handled raw chicken or other sources.

Priority 2

Assumption: The level of risk ascertained in studies in the 1980's represents the current level of risk.

The risk assessment model relies on data from three studies (14, 15, 16). The use of these studies in developing the risk assessment model emphasizes the fact that there is very little epidemiologic data in the literature that deals with the risks associated with obtaining a *Campylobacter* infection. The Agency does highlight the limitations of those studies, while at the same time using information available. While using the most current information available (15 + years old) may have been the only option to bring that type of data into the model, we believe the authors need to be more conservative in tying the three studies together. As stated by the author of the risk assessment model in the discussion of Priority 2, current data generated from the FoodNet case/control studies are essential to validate and accurately predict the risks at hand. It should be remembered that the lack of sufficient, current data does not validate the use of inappropriate data in this model. Specific concerns on the appropriateness of data from studies reported in the 1980's are as follows.

- We believe that the upper bound estimate of 70% is not a valid estimate. As stated by the author of the risk assessment model, the study population in Study #2 was not representative of the population at risk. The author of Study #2 did not calculate nor present this figure in the published/cited paper. This number was taken from a textbook chapter written by one of the co-authors seven years following the

referenced publication. The number does not lack validity because it was brought out later, but is not valid because it is not representative of the population at risk.

- The author of Study #3 did not calculate the etiologic fraction of 47% offered by the author of the risk assessment model. The 47% was calculated by the author of the risk assessment model. This 47% is not appropriate because it represents consumption of raw or undercooked chicken. It cannot be equated with the 48% calculated from the Study #1, since that number represents the etiologic fraction of all chicken consumed, i.e. not raw or undercooked chicken. In fact, the author of Study #3 stated that “exposure to undercooked chicken emerges as a possible risk factor” and that “chicken consumption is common in both cases and controls.” The author of Study #3 did not strongly implicate chicken as a risk factor.
- If the etiologic fraction could be calculated for chicken consumption for Study #3, it would be considerably less than the reported 47%. If that number could be calculated, and if it was averaged with the 48% from Study #1 (leaving out the 70% from Study #2), the resulting number of fluoroquinolone resistant *Campylobacter* infections from consuming chicken would be substantially less than the 48% reported for Study #1.
- We therefore believe the number on line 28 of Appendix B should be changed from 59% to 48% (which is still conservative and only is derived from Study #1) for the reasons outlined above. If the results of Study #3 are to be included in this model, they need to be re-calculated to include all chicken consumed, rather than just undercooked or raw chicken consumed.

(For specific comments on each of these three studies, refer to Attachment 2 to this letter.)

The author of Study #3 also states: “At least one-third of the cases in the study were potentially preventable by personal behavioral changes (avoiding drinking raw water or raw milk, cooking chicken thoroughly) and/or by public health measures (public education, prohibition of sale of raw milk for human consumption).” Therefore, we believe it would be appropriate to include a separate module, within the risk assessment model, to identify those food handling risk factors that may contribute to the exposure of consumers to *Campylobacter*. It seems reasonable that a portion of the human cases can be prevented if consumers and food handlers have a better understanding of how *Campylobacter* is transferred to other foodstuffs through mishandling. Consumer educational programs aimed at handling and cooking poultry that are initiated as a risk management tool provide a proven method for reducing the incidence of food-borne disease.

As the Agency re-evaluates how it might incorporate the data from the three epidemiologic studies (14, 15, 16) into the model, we suggest that a closer look be taken at a study conducted by Black et al. (17). In this study, Black indicated there was a wide variation in the percentage of people that became ill following various concentrations of the organism. A

carcass that is positive for *Campylobacter* doesn't necessarily represent a carcass that will potentially be infective. There was a wide variation in the potential for infection with the same dose, and in some instances a higher dose may be less likely to cause illness. If this is the case, the Agency should revisit the assumption that a positive carcass will cause disease in all instances; we suggest that this is unknown at this time. Level of potential exposure to *Campylobacter* organisms (exposure assessment) should be recognized as a part of this model. Dose-response assessment is crucial, not only for the determination of the number of organisms required to cause disease, but also to quantify the number of potentially infective organisms found on a serving of chicken.

Priority 4

Assumption: The rate of seeking care among persons with bloody stools is similar to the rate of seeking care among persons with campylobacteriosis with bloody stools. The rate of seeking care for diarrheal illness among persons with non-bloody stools is similar to the rate of seeking care among persons with campylobacteriosis with non-bloody stools.

Discussion: These estimates were for all diarrheal disease, and not specific to campylobacteriosis in the U.S. A recently published rate for seeking care for campylobacteriosis was not available from the literature or other sources.

The 12%-27% range value for care seeking (included into the Appendix B spreadsheet, at a weighted average overall frequency at about 13.9%) is based on extrapolations of rather limited surveys (Section 2, pages 2.3 and 2.4, Table 2.1). This represents an overestimate of the diarrhea cases seeking care. Contrary to the DISCUSSION statement, there are recent published estimates for enteric disease care seeking in FoodNet (1997 and 1998) and in The USDA/FSIS/OPHS Risk Assessment (18). These values are 8.0% and 6.04%, respectively. These published values also factor in susceptible subpopulations, which have a higher frequency of seeking care. They are based on much larger surveys, which are more appropriate for an analysis that uses the U.S. population as a starting point.

Looking at FDA's Foodborne Pathogenic Microorganisms and Natural Toxins handbook table; 'Onset, Duration, and Symptoms of Foodborne Illness' (19); the pathogens *Salmonella*, other *Enterobacteriaceae*, and *Campylobacter jejuni* all share the same predominant symptoms;

12-74 hour, mean 18-36 hours onset, symptoms of abdominal cramps, diarrhea, vomiting, fever, chills, malaise, nausea, headache. Sometimes bloody or mucoid diarrhea.

Salmonella infections cause significantly more hospitalization and mortality versus *Campylobacter jejuni*, and rank second in prevalence of foodborne enteric disease. It could be argued that the intensity of disease, and therefore the frequency of care-seeking will not be significantly greater for *Campylobacter* versus *Salmonella* or other pathogens sharing essentially the same symptoms. Further, a recently published synopsis (20) states that *Campylobacter* and *Salmonella* have the same multiplier (X38) when calculating the total number of cases. The

bloody pathogens *E. coli* 0157:H7 and *Shigella* utilize a lower multiplier (X20) due to higher rates of reporting. Since experts have previously categorized *Campylobacter* in the same class as *Salmonella* (in terms of symptoms and multipliers for estimating total cases), a question can be raised as to why *Campylobacter* has apparently been re-classified as a more highly reportable pathogen in the draft risk assessment. A possible explanation might be that those enrolled in the referenced special studies were more likely to seek care than the average U.S. resident. The care-seeking frequencies are therefore quite possibly overestimated (contrary to the statement on page 2.3 that they may be low). Since these care-seeking variables are extrapolated and are then used to estimate the total number of cases and total number of chicken-related cases seeking care in Sections 2 and 3, they should be questioned due to their very high influence on the total risk assessment. Other variables and calculation methods mentioned elsewhere in this review impact the results as well.

As pointed out elsewhere in our comments, we believe the risk assessment model as presented is not appropriate for the intended purpose without further modification and validation. For the purpose of illustration, however, we have provided two scenarios utilizing estimates we believe to be more representative of the real situation. The spreadsheets with these adjustments and new calculations are included as Attachment 3.

Priority 5

Assumption: The incidence rates for culture-confirmed Campylobacter infections in the FoodNet catchment are representative of incidence rates for culture-confirmed Campylobacter infections in the United States.

The Agency recognizes this statement as a limitation in the study and presents these data as preliminary. A three-fold increase in the incidence of cultured-confirmed *Campylobacter* infections between two of the catchment sites (MD and CA) creates some doubt in the above assumption. If the chicken consumption in both sites is similar, as indicated by the author, then there are likely significant differences in contamination levels, preparation methods, eating habits or socio-economic/ethnic backgrounds between the two sites that are contributing to the discrepancy in culture confirmed cases. If this is so, then the above assumption does not hold true and should be modified.

Assumption: Over-reporting by physicians of the proportion of persons with bloody diarrhea that are requested to submit stool specimens, compared to the proportion of stool requests reported from the persons with bloody diarrhea, is similar to physician over-reporting for persons without observable blood in their stools.

The discussion, by the author of the model about this assumption deals with sensitivity of culturing methods, which is unrelated to the stated assumption. We cannot comment on the assumption that over-reporting for bloody diarrhea versus no observed blood in stools is similar.

We do, however, question the assumption that the physicians over-reported any more than that the patients under-reported. The author of the model may have made the assumption

based on the idea that a physician might tend to over-report to add credibility to his/her standards of practice. But, a patient might have a strong tendency to under-report to validate their compliance with the doctor's order. The only way to validate the above assumption would be to examine not only the patient's record to see if the request was actually made, but also the participating laboratory records to verify that the stool was actually submitted. We therefore question the validity of using the 19% value on line 19 of Appendix B. This was modeled with information from 59 patient surveys that conflicted with the results of 18 physician surveys. We suggest that due to the conflicting nature of the data, a figure of 40% is more appropriate for the model than the 19% that was generated mathematically.

Assumption: The population survey proportion of cases of all acute diarrheal illness seeking care, not submitting a stool sample and receiving an antibiotic (40%) is similar to that for persons ill with campylobacteriosis.

The stated statistic of 40% was calculated from 41 patients (16/41). The sample size was very small compared to the overall estimated numbers of illnesses, presented in the model. We question if these numbers are representative of the standards of practice in the United States today. Without a definitive diagnosis, physicians today are less likely to prescribe an antibiotic to treat an undiagnosed case of acute diarrhea than they were just a few short years ago. Although the assumption that a physician may prescribe an antibiotic at the same rate for a patient with acute diarrhea, as for a patient with an undiagnosed case of acute *Campylobacter* diarrhea may be valid, the rate of 40% seems high given the awareness of today's informed medical community. Were investigators able to confirm that all patients, who stated they received an antibiotic, actually received an antibiotic? Could the patients have been confused about the prescription they received? Could the patients have thought they received an antibiotic, when in reality they may have received other medications that symptomatically treated their diarrhea?

C. ADDITIONAL COMMENTS ON THE MODEL

1. Pertaining to Appendix B (Block 1)

- The 10.4% value used in the model on line #37 of Appendix B could be revised to better reflect the data generated from FoodNet. As we analyzed the model, it was our best guess that the 10.4% was based on the estimated value taken from the equation on p.3.14. Since the outcome of the math was not shown, except in Appendix B, line 37, we were unable to follow the logic of its origin. The number that we think should be used is 6.9%, which represents the proportion of *Campylobacter* infections from chicken that are fluoroquinolone-resistant and was generated from the FoodNet data. The 6.9% represents a weighted estimate from all the FoodNet sites.

2. On page 5.17, under the discussion of the calculation of k , λ represents the mean number of people per year who will experience some human health effect as a result of consuming a

pound of fluoroquinolone resistant *Campylobacter* contaminated broiler meat. The risk assessment should also consider the number of people per year who will experience some human health effect as a result of consuming a pound of broiler meat that is contaminated with a fluoroquinolone susceptible *Campylobacter*. This is critical to determining the public health impact and putting the whole issue in perspective. Evidence to support any difference in human health outcomes as a result of differences in fluoroquinolone susceptibility should be considered in the model and should be rigorous enough to extrapolate the results to the population at risk. We suggest that the final model should be capable of evaluating all probable health consequences, whether dealing with disease caused by fluoroquinolone resistant, or fluoroquinolone susceptible *Campylobacter* isolates.

3. Dr. Charles Beard, vice president of research and technology, U.S. Poultry and Egg Association states that "...*Campylobacter* isn't able to replicate outside the host, a small amount on a kitchen counter won't grow to become a major source of contamination because it dies off in such settings. It even gradually loses viability at refrigerator temperatures so that a poultry carcass yields less and less *Campylobacter* with increasing storage time. Like other potential pathogens, it is readily killed by ordinary cooking temperatures. We know that 7-10 days in the refrigerator removes most, if not all, *Campylobacter*." (21) *Campylobacter* organisms most likely do not replicate on the carcass. If it doesn't replicate on the carcass, it would be important to not only quantify the number of potentially infective organisms per serving of chicken, but also the number of organisms required to cause disease.
4. The FSIS has established a new Division of Epidemiology and Risk Assessment within the Office of Public Health and Science. The re-organization also created an Office of Policy, Program Development and Evaluation that houses the food safety risk managers. This separation of risk assessment from risk management activities was done to ensure the scientific integrity of the process and the products of Agency conducted risk assessments. CVM should recognize the importance of this and consider the same policy.

In 1998, FSIS completed a risk assessment for *Salmonella enteritidis*. The risk assessment was conducted by a multi-disciplinary team with members from government and academia. A number of USDA agencies had members on the team, including the Agricultural Research Service, the Animal and Plant Health Inspection Service, the Economic Research Service, the Agricultural Marketing Service, and the Office of Risk Assessment and Cost-Benefit Analysis. From the Department of Health and Human Services, there were representatives from FDA and CDC. Two academic institutions were also involved: North Carolina State University and Delaware Valley College. Clearly there was a concerted effort to bring together many contributors so that the final document would be widely accepted.

5. On line #21 of Appendix B, 75% is used to estimate the sensitivity of culturing for *Campylobacter*. This number was primarily determined from personal communications with Drs. Angulo and Nachamkin. A recent publication by Engberg et al. (22) examined isolation rates from various media and found mCCDA medium recovery to be 95%. The medium was known to be used in the carcass NARMS study. If it was also used in the human studies, the

value of p(+) would likely be closer to 95%. Alternately, a beta distribution could be generated using 75% and 95% as lower and upper boundaries for this variable.

D. COMMENTS ON THE CVM RISK ASSESSMENT PROCESS AND HOW THE FINDINGS WILL BE USED

There was general agreement at the December Workshop that a risk analysis approach is an appropriate way to address public health concerns regarding antimicrobial resistance development in food-borne pathogens, the potential transfer of resistant determinants to humans, and the use of antimicrobials in food animals. Risk assessments in managing public health issues are used by a variety of other federal agencies; in fact, a similar approach was also recommended by the Joint Expert Technical Advisory Committee on Antibiotic Resistance in Australia. This approach is attractive because it is inherently scientifically based, which is what particularly interests most stakeholders in the U.S. In addition, depending how the risk assessment outcome is used in managing risk, decision-making from a regulatory perspective would not be dependent on building a consensus before taking action, thus the likelihood of legal recourse taken by those adversely affected from perceived unilateral decisions would be lessened.

We also recognize the difficulty in conducting such a risk assessment with something as complex as antimicrobial resistance development and potential interspecies transfer of resistance determinants, where data may be scarce and where experience in performing antimicrobial resistance risk assessments is non-existent. We were also enlightened at this workshop by clear messages from those with experience in risk analysis. Identified below are a few messages that we consider important to revisit before proceeding to the next step in the process.

1. Risk assessment should be an iterative process involving all stakeholders.
 - This was clearly not the case with this fluoroquinolone-resistant campylobacteriosis risk assessment model. This model was developed in relative isolation and presented for public comment in near final form. Those interested parties that were not engaged in the process have been forced into a reactive, rather than supportive and cooperative position.
2. Risk assessments will only address the question they are designed (modeled) to answer.
 - In this model, only the risk of acquiring campylobacteriosis from chicken was addressed with further refinement to fluoroquinolone-resistant infections, and further defined for different populations that are at increasing risk of greater health consequences. Because the Vose model views this hazard from a static perspective, it will not provide risk managers any indication of what impact changing conditions such as prescription rates would have on resultant

fluoroquinolone-resistant *Campylobacter* populations, and subsequent impact on public health.

- As was mentioned by several panelists, the risk assessment model developed by Dr. Vose did not consider the impact that other interventions already have or could have on the probability of acquiring fluoroquinolone-resistant campylobacteriosis from chicken. Such interventions include HACCP procedures at processing facilities, proper storage, cooking and food preparation, and irradiation of poultry carcasses. The entire continuum of “farm-to-fork” needs full consideration for meaningful conclusions to be drawn.
 - To summarize, the effects of fluoroquinolone management policies on public health cannot be predicted by looking at fluoroquinolone use in chickens alone. Other decisions and behaviors, from food preparation to physicians’ prescribing practices, affect the outcome. The current model quantifies the health risk (attributed entirely to fluoroquinolone use in chickens) while holding these other factors constant. Yet, the best way to manage the risks of *Campylobacter* infection cannot be decided while artificially holding most of the variables that affect the outcome constant. Instead, the likely changes in “all” of the key factors following a change in fluoroquinolone policy, communication programs, and so forth must be realistically accounted for. The current model provides an initial framework for doing so, but needs substantial further expansion for it to be truly useful in risk management.
3. Critical to this model, and for monitoring levels of fluoroquinolone-resistance in chickens and campylobacteriosis in people, are the NARMS and FoodNet surveillance systems.
- Antimicrobial susceptibility characteristics of *Campylobacter* have not been well defined, nor have quality control standards been established by the NCCLS for the testing of this organism from animal sources. Building a model with data that is currently tenuous will not build confidence in the outcome.
 - Correlating NARMS to FoodNet findings will be difficult if not impossible to do. Given geographic variability to findings and drug use patterns, the broad distribution systems through which food animal products are delivered to consumers, sample size and sample time limitations of the FoodNet system, meaningful correlations are unlikely. Any associations proposed will not bear the scrutiny of sound epidemiologic principles.
4. Risk assessments are just a tool to help manage risk. In establishing mitigation strategies, risk managers should use this information, along with a detailed evaluation of the impact of decisions based on the risk assessment will have for all concerned, political implications not withstanding.

- Decisions implemented to reduce risk of the hazard potentially could have other negative consequences. A simple example of this is the negative impact on animal health and welfare, the economic fall-out for the producer, and the potential public health consequences of diseased birds entering the food chain, should effective products be unduly restricted.
 - Furthermore, if the question the risk assessment was designed to answer does not address the issue from the proper perspective, mitigation strategies may be misdirected and ineffectual. For example, with fluoroquinolone-resistant genes already apparent in human Gram (-) enterics, will restricting fluoroquinolone use in poultry have any impact on the ability of physicians to treat the campylobacteriosis with fluoroquinolones, given the empirical prescribing practices of physicians when faced with a possible *Campylobacter* infection, and given the reduction of food-borne pathogens in poultry carcasses through HACCP intervention and even irradiation practices?
5. It is unclear how such a risk assessment may be used to establish thresholds of resistance prevalence, which will trigger intervention activities designed to reduce the level of resistance and hence risk to public health.
- Setting thresholds of resistance prevalence, which will trigger corrective action, is an inappropriate approach to managing risk in this context. Thresholds are more appropriate for managing risk to public health due to contaminants, pesticides and other direct cause-and-effect scenarios. In such cases, reaching a threshold, which triggers restrictive actions, will likely have a direct and profound effect on prevalence rates of the hazard. Effectively managing antimicrobial resistance genes is a vastly more complex task. Thresholds established simply on the basis of assessing risk of transfer of resistant organisms from food animals to man is an oversimplification of the issue.
 - It is important when managing public health risk not to overlook the impact of other causes of resistance development such as misuse and over-prescription of antibiotics, or prolonged antimicrobial therapy for the immuno-compromised patient. It must also be kept in mind that when using antimicrobials, it is the mere presence of resistance determinants in the microbial environment that is the critical factor, not necessarily the level of resistant organisms or determinants that will effect the efficacy of these drugs. In all likelihood, when a resistance threshold is reached it is likely too late for an abatement strategy to be effective in reducing the threat of resistance development and ultimate utility of human use of the antimicrobial compound. Restricting human or animal use of an antimicrobial will in some cases result in falling resistance prevalence levels; however the resistance genes are still present in the environment. Resistant bacteria may proliferate in the presence of selective pressure/amplification due to exposure to the selective antimicrobial. Such a response is independent of the number of resistant bacteria initially present, thus makes managing this risk by thresholds a

meaningless exercise. Using resistance thresholds that are created to restrict use of antibiotics in animals or in people may have little if any impact on limiting the presence of resistance genes. A more appropriate approach would be to design more effective safeguards for the judicious use of antibiotics in both the animal and human contexts, in addition to better management of the potential of food animal to human transfer of these genes.

6. What is the legal basis for setting Risk Standards that pertain to resistant food-borne pathogens?
 - CVM has a unique opportunity to set risk standards pertaining to antibiotic resistant food-borne pathogens. The complexity of the task is clear, and the resources required to base such standards on sound science and legal principles are considerable. Furthermore, there is no legal precedent for managing such risk on a “zero risk” basis, or even on a “reasonable certainty of no harm” basis, which in effect widens the purview for the Agency. Risk standards that are set in due course by CVM must, however, by law be rational. In addition, applicable case law demonstrates that a risk/benefit analysis is inherent in the decision-making process.
 - FDA must evaluate the safety of a new animal drug (NAD) with respect to both the health of the target species and man. Neither the Federal Food, Drug, and Cosmetic Act (FFDCA) nor the Code of Federal Regulations (CFR) provides the standard for determining the safety of a NAD. Case law indicates that the standard is determined *ad hoc* by FDA, and that a risk/benefit analysis is inherent in the process. Historically, FDA has taken the position that the FFDCA does not allow it to evaluate the benefits of an NAD, and only allows a consideration of the risks. This position has been overruled by the U.S. Court of Appeals for the D.C. Circuit. In reality, the standard is whatever CVM decides it is on a case-by-case basis. The only constraint is that under the Administrative Procedures Act (APA) there must be a rational basis for the decision. Conspicuously absent from the case law is any discussion or reference by either the courts or FDA regarding “reasonable certainty of no harm.”

(The AHI evaluation of Risk Standards as presented by Kent McClure, DVM, JD, at the December workshop is included here as Attachment 4.)

We strongly encourage CVM to revisit risk analysis planning for fluoroquinolones and other antimicrobials used in both human and animal medicine. Risk management must consider this issue in a broader context, and also over changes in time, geography, and human and animal drug use patterns. The complexity of managing resistance gene development and transfer requires a novel and scientifically valid approach, rather than one built on simple, static terms. One place to start would be a review of the recommendations of the Australian Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) on the use of antibiotics in food-

producing animals (23). Another source would be the recommendations of the European Agency for the Evaluation of Medicinal Products (24).

With respect to the specific risk analysis process under discussion, we urge CVM to extend and refine its risk assessment further before using it as a basis for decision-making. We would like to help in this process, and are willing to work quickly to do so. Possible next steps, in rough order of priority, are as follows.

1. Have Dr. Vose run validation tests to determine whether the model is internally consistent and produces mathematically correct results.
2. Convene a two-day working meeting of no more than 10 food scientists, biostatisticians, and modeling experts (plus as many observers as want to participate) to agree on the best ways to extend the model and analysis to address the following key issues:
 - a. Put **COMPETING RISKS** into the model. (These will recognize that chicken is not the only source of *Campylobacter* contamination or fluoroquinolone resistance and that the existence of other sources affects the benefits that can be expected from controlling fluoroquinolone administration to chicken.)
 - b. Expand the **MODEL SCOPE** to link fluoroquinolone decisions to all of their likely public and animal health consequences, taking into account the roles of other decision-makers (consumers, patients, physicians, producers, etc.).
 - c. Incorporate **RELEVANT DOSE-RESPONSE INFORMATION** to quantify the relation between contamination and illness (rather than just contamination and infection, as in the current model).
 - d. Refine **DATA AND PARAMETER VALUES AND ASSUMPTIONS**, as outlined in our preceding comments. Even if complete agreement is not reached, identifying a range of values of interest to be examined in sensitivity analyses may go far toward resolving unimportant disagreements and clarifying any important ones.
3. Extend the risk analysis model to include the results of the working meeting. Create a final model that is scoped and designed to evaluate alternative fluoroquinolone usage policies taking into account all causal paths leading from fluoroquinolone use to health impacts. Validate that model, which will be an outgrowth of the current one. Then, use it to evaluate the likely effects of alternative risk management policy options. Present the results of these evaluations, as well as the model, in a final document.

In the end, we recognize that we are all interested in achieving the same goals of maintaining a safe, wholesome food supply, while minimizing the risk of antimicrobial

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resistance development which might compromise public health by limiting the utility of antimicrobials which are considered essential for human therapy. These goals are best achieved through a collaborative effort among the stakeholders from the start, not unlike what has been accomplished by JETACAR in Australia. We encourage the CVM to work cooperatively throughout the process with those organizations which represent the companies, health professionals and producers that are responsible for the availability and use of antimicrobial compounds in animal agriculture.

E. CONCLUDING REMARKS

Risk assessment is a powerful tool used to organize the information necessary to assist the public policy process. It should not be a biased tool used to punish stakeholders or drive policy to a pre-determined outcome. A well-developed risk assessment should be an instrument that helps us arrive at an informed decision. Politics are an element of the process, but public values, economics, and the law also play critical roles in the process. The challenge of developing a workable risk assessment model is to characterize the risks in a way that is scientifically sound, useful to the decision making process, and understandable/credible to the stakeholders and public.

Again, we commend CVM for undertaking this task and for encouraging feedback pertaining to the draft risk assessment on fluoroquinolone use in poultry and campylobacteriosis in humans. We look forward to open dialogue and a cooperative effort that will lead to a final document which can be endorsed by all stakeholders.

Sincerely yours,



Alexander S. Mathews

Attachments

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Attachment 1 – ANIMAL HEALTH INSTITUTE

Comments to FDA Docket No. 98D-0969, “Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken”

COMMENTS ON FDA CVM RISK MODEL FOR CAMPYLOBACTER

Prepared by Dr. Tony Cox

COMMENTS ON FDA CVM RISK MODEL FOR CAMPYLOBACTER

The following comments are divided into a macro level and a micro level. The macro-level comments address the suitability of the current FDA risk model (Vose 99) for use in risk management decision-making. The micro-level comments are concerned with technical details of the modeling approach.

Overall, the current model and document do an excellent job of spelling out key assumptions and uncertainties. However, not all of the key assumptions have been subjected to uncertainty and sensitivity analysis. For example, uncertainties about the basic model form (a product of factors modeled as independent random variables) have not been fully addressed in the current draft. Moreover, whether the model is ready for use in guiding practical risk management decision-making must be decided.

I believe that the model should be extended and carefully validated before it will be fully ready to use in supporting decisions. Extensions are necessary to support good policy-making by linking *all* of the action variables that should be considered to *all* of the consequence variables that should be considered. Validation is necessary to assure that the model performs as intended.

MACRO COMMENTS: IS THE MODEL FRAMEWORK SUITABLE FOR DECISION-MAKING?

Section 5 of the December draft report proposes the following approach to using the model for risk management decision-making purposes.

1. Determine unacceptable human health impact in probabilistic terms (e.g., "There is a 10% probability that more than 5,000 people will become infected per year by fluoroquinolone resistant *Campylobacter* as a result of domestic consumption of domestically reared poultry".)
2. Estimate values for k in the equation $\lambda = knp$.
3. Use the above equation to infer a p_{max} value for all bacteria in question.
4. Monitor broiler production and institute action when the first p_{max} is reached.

In Step 2,

- λ = mean number of people per year who will experience some human health effect as a result of consuming a pound of Fluoroquinolone resistant *Campylobacter* contaminated broiler meat;
- n = quantity (lbs.) of broiler meat consumed in a year in the US; and
- p = prevalence of the Fluoroquinolone resistant *Campylobacter* in the meat.
- k = an aggregate potency constant, estimated from the model via the following equation:
 $k = N37/V_i$, where:
 - $N37$ = "the total number of human fluoroquinolone resistant infections from domestically reared chicken that sought care in 1998 (*sic*) and were prescribed fluoroquinolone"
 - V_i = "total consumption in 1998 of boneless domestically reared chicken that were contaminated at the slaughter plant with fluoroquinolone resistant *Campylobacter* in US (lbs.)"

Before acting on this framework, good policy analysis requires that one should evaluate whether doing so it is likely to lead to better decisions, i.e., to choices of risk management options that protect human health better than alternatives.

COMMENT 1: The model's scope 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 fluoroquinolone (FQ) requires coordinating multiple decisions and policies.

In assessing any model offered to support policy and risk management decision-making, it is worth being explicit about the decisions that the model is designed to support. One way to do this is to classify the variables in the model into three groups, as follows:

- *Decision variables*, i.e., variables that the decision-making agency intends to control or constrain. An example in the above framework might be p_{max} .
- *Outcome and value variables*, i.e., variables that describe the outcomes of interest. Typically, the goal of decision-making is to maximize or minimize a value variable, or to keep it (or them) within an acceptable set of values. In the Vose model, N_{3T} might be an example of such a variable.
- *State variables*. These variables affect the outcomes of interest but that are not directly controlled by the decision-maker. Examples could include many of the input parameters in the model.

The general causal structure of the model is then:

decisions → outcomes ← states (Decision support model structure)

In words, the probability distribution of outcomes is determined by the values of the decision variables and the state variables. One may use such a model, together with estimates of the probabilities of different states, to seek values for the decision variables that lead to preferred probability distributions of outcome values.

This framework is roughly consistent with the approach to decision-making outlined in Section 5 of the current draft. Specifically, allowed FQ prevalence in poultry may tentatively be identified as a decision variable. Consumer behavior (e.g., care taken in food preparation, medical care-seeking, compliance with doctor's instructions, etc.) and physician and lab behaviors may be identified with the state variables. The number and duration of cases of illnesses prolonged by FQ-resistant *Campylobacter* from poultry (broilers) may be regarded as the outcome variables of interest. However, the current draft does not explicitly identify decision, state, and outcome variables. Doing so would clarify the appropriate uses of the model and help to identify the decision and policy issues that it can support as well as those that it cannot.

If the tentative identifications just made are correct, then the model addresses only a subset of the decision and outcome variables that are essential for assessing how different FQ usage strategies will affect human health risks. Such a partial model, while perhaps addressing exactly the scope of concerns that the FDA requested, does not

provide a fully adequate basis for policy-making. For example, it models the following input parameters as random variables with distributions and/or point estimates estimated from data:

- p_{ca} = Proportion of *Campylobacter* infections relating to domestically consumed chicken
- p_{nm} = Proportion of *Campylobacter* non-bloody diarrhea enteric infections seeking medical care
- p_{bm} = Proportion of *Campylobacter* bloody diarrhea enteric infections seeking medical care
- p_{bc} = Proportion of enteric bloody diarrhea infections seeking care who are requested to supply stool sample and comply
- p_{FQ} = Proportion of those who are treated who are prescribed Fluoroquinolone

Yet, depending on the goals of the model, these might instead be considered decision variables and/or quantities that can be affected by advertising, warning labels, publicity, physician advisories, and other means. Modeling consumer and physician behaviors more realistically as variables that can be controlled or influenced by allocating resources, instead of as random variables that cannot be affected, could produce more effective prescriptions for how to manage the risks of FQ-resistant *Campylobacter*.

In summary, if this model is intended to support policy decisions that will optimize the net benefits achieved from FQ usage and control, then *its inputs should be modified to include more decision variables* and perhaps fewer random variables. Specifically, the input side of the model should be capable of representing the impacts of risk management intervention decisions such as the following:

- (a) Warning labels about the hazards of eating undercooked chicken;
- (b) Public health messages about safe cooking and food safety and sanitation behaviors, perhaps especially among cat owners;
- (c) Public health messages about appropriate care-seeking behavior, especially when infants and elderly are ill;
- (d) Physician advisories about the appropriate use of different fluoroquinolones;
- (e) Changes in FQ usage (and/or prevalence of FQ-resistant strains) in food sources other than chicken, such as raw milk, water, other meats and poultry, and so forth.

On the output side of the model, potential outcomes of interest for FQ include the following:

- Total cases (or total days) of prolonged illness due to prescription of FQ to patients who are ill with FQ-resistant strains of *Campylobacter* or other microorganisms.
- Total cases or days of illness due to *Campylobacter* or to other microorganisms.

If medical use of FQ as a human antimicrobial is restricted because of concerns about resistant strains due to *Campylobacter*, then not only *Campylobacter* patients may be affected. Patients ill from *E-coli*, mycobacteria, or other microorganisms for whom FQ might otherwise be prescribed will also be affected by changes in FQ prescription practices. Conversely, if FQ medical usage, reflected in the model parameter p_{FQ} , is reduced for reasons not related to *Campylobacter* in chicken, e.g., to avoid intra-hospital development of resistant strains, then patients with illness from *Campylobacter*-contaminated chicken would also be affected. The health impacts of different patterns of FQ use in poultry, other animals, and human patients include the health effect externalities created by the fact that changing p_{FQ} for any reason has consequences for patients ill from a variety of sources or causes. Focusing on how changes in the model's inputs affect *Campylobacter*-related illness alone looks at only part of their health impacts. To fully assess the public health impacts of different FQ usage patterns, it is necessary to consider their impacts on prescriptions for non-*Campylobacter* illnesses as well as on prescriptions for *Campylobacter*-related illnesses.

In summary, the current model has clearly been designed to help the FDA make some decisions about fluoroquinolone use. However, *the model's scope, meaning the set of inputs and outputs considered, is not broad enough to address the total impact on human health of different FQ usage policies.* Considering only some of the health consequences of some of the decision variables will in general tend to lead to sub-optimal decision-making. Therefore, the scope of the model should be broadened to include all the health consequences of concern that may be affected by changes in FQ usage and to include all of the inputs and decision variables that jointly determine the health risks from FQ-resistant *Campylobacter*.

COMMENT 2: FQ resistance and FQ development are dynamic processes. Realistic modeling of the risks of FQ-resistant microorganisms requires a dynamic model.

The current model uses the following input parameters to describe the prevalence of FQ-resistant *Campylobacter* (CP) infections from chicken and physician prescription practices, respectively:

- p_{rh} = Proportion of *Campylobacter* infections from chicken that are resistant to Fluoroquinolone
- p_{FQ} = Proportion of those who are treated who are prescribed fluoroquinolone

Both parameters are modeled as having fixed but uncertain true values. Both treat fluoroquinolone as if it were one substance, rather than an entire family of related drugs. These modeling simplifications ignore the dynamics of FQ use and of FQ resistance.

The model as a whole is a *comparative statics* model rather than a dynamic model. In other words, the outputs are calculated from the inputs via a series of static formulae. In effect, any time lags between changes in input values and resulting changes in output values are ignored. But such lags, and other dynamic responses, may be important in calculating the responses of infection and illness rates to changes in inputs. Simplifying the modeling of dynamic phenomena to more clearly reveal essential relations and to achieve useful, robust results is often commendable. Dr. Vose has

been meticulous in simplifying the model as much as possible while striving to retain its usefulness and while allowing relevant data to be included to reduce uncertainties. In this case, however, the dynamics of FQ use and of survival or extinction of resistant strains may be too important to ignore in assessing the incremental risk from FQ use in chickens. In other words, using a comparative statics model rather than a dynamic model may be an over-simplification because the phenomena being modeled are inherently transient.

A typical dynamic model for FQ resistance might have the following features (e.g., Jaffe 97).

- The prevalence of resistant strains of microorganisms in the FQ-exposed population tends to increase while FQ is being used and to decrease while FQ is not being used.
- The rate of increase in prevalence of resistant strains is a *non-linear* function of current prevalence and additional FQ use. In the simplest case, it would be described by an equation such as $dp(t)/dt = f[p(t), q(t)]$ where $p(t)$ = prevalence in a population, $q(t)$ = current intensity of FQ exposure, and f is a non-linear function. (More realistically, the dynamics should be modeled as a controlled stochastic process.) Prevalence only increases if $q(t)$ is greater than a critical level that depends on $p(t)$.
- In the chicken population, $q(t)$ depends on FQ usage. In the human population, $q(t)$ depends on FQ exposure from *all* sources (e.g., from undercooked chicken among those who eat it, from untreated water, raw milk, etc.) Thus, to keep prevalence acceptably low or decreasing, one must limit the sum of the contributions from all sources.
- Physicians confront a population of patients (or several sub-populations, e.g., those with and without blood in stools) having uncertain values of $p(t)$. They also have a variety of FQs to draw on, with new ones being introduced from time to time (e.g., Gemifloxacin in 1999). The effectiveness of any specific FQ will depend on what FQ-resistant strains (if any) a patient is afflicted with.

Against such a changing background, the physician's best choice of prescription may depend on the current prevalences of various FQ-resistant strains of microorganisms in different sub-populations. By avoiding prescribing FQs for which the current prevalence of resistant strains is unacceptably high, the physician may be able to both serve the patient's best interests and, perhaps, help to limit or reduce the prevalence of resistant strains. To back-calculate the levels of FQ use in poultry (for specific FQs) that will keep the prevalence of FQ resistant strains from increasing unacceptably among human patients, one would presumably need to consider (a) physician prescription practices, (b) availability of new FQs, (c) the current prevalence of resistant strains in the human and poultry populations, and (d) the intensity of FQ exposures from various sources in the human population. A fully realistic model might also allow for the fact that FQs may be prescribed in conjunction with other agents.

In summary, a realistic dynamic model could show how to coordinate FQ restrictions in chickens with control of these other inputs to achieve desired prevalence

levels. Modeling the relevant parameters as static random variables does not support such coordinated risk management. Nor does it allow for usage patterns in animals and for prescription patterns among humans that are deliberately varied over time and among specific FQs to reduce the risk of resistant strains. In practice, however, sensible risk management may involve such adaptive control strategies. To allow for these possibilities, the current model should be extended to make p_m and p_{FQ} dynamic variables instead of static parameters.

COMMENT 3: The current comparative statics model does not support predictive modeling of the health impacts of changes in some of its inputs. Formulas in the model have been used to interpret past data and to estimate key quantities, often under the implicit assumption that formula inputs and outputs are in equilibrium (so that transients can be ignored, as discussed above). This sharply limits the appropriate uses of the model's formulas in predicting how outputs will change if inputs are changed – the most important use for many decision-making purposes.

As an example, consider the following model formulas:

- $N2_{eb} = N1_{eb}/(p_m * p_{bc} * p_t * p_+) =$ Estimate of expected number of people in US population ill with enteric *Campylobacter* infection and bloody diarrhea in year
- $N2_{en} = N1_{en}/(p_m * p_{nc} * p_t * p_+) =$ Estimate of expected number of people in US population ill with enteric *Campylobacter* infection and non-bloody diarrhea in year

The parameters are defined as follows:

- $p_+ =$ Proportion of infected stool specimens that test positive
- $p_t =$ Proportion of submitted stool specimens that are tested by the laboratory
- $p_{nc} =$ Proportion of enteric non-bloody diarrhea infections seeking care who are requested to supply stool sample and comply
- $p_{bc} =$ Proportion of enteric bloody diarrhea infections seeking care who are requested to supply stool sample and comply
- $p_m =$ proportion of *Campylobacter*-infected victims seeking medical care (later divided into p_{mb} and p_{mn}).

These formulas are used to estimate $N2_{eb}$ and $N2_{en}$ from historical data. But, suppose they were used instead to predict the health impacts of changes in the parameters. Taken at face value, the formulas would imply that if either p_+ or p_t (or both) approach zero, e.g., due to changes in lab test procedures, then the estimated expected number of people in the US population ill with *Campylobacter* infection will approach infinity – clearly not a causally reasonable prediction.

Of course, the model is not intended to be used this way. The above formulas are intended for use in estimating past illnesses, not for predicting future ones. Yet, there is nothing in the model to prevent it from being used for prediction. Indeed, it will only be useful for risk management if it can be used to predict future illnesses as a function of its inputs. (Moreover, the extreme example of zero values for some of the parameters in the denominator raises the question of whether the estimates for $N2_{eb}$ and $N2_{en}$ are unbiased. This detail should be covered in the final report.)

In summary, it appears that the predictive value of the model could be improved by (a) Using formulas that do not assume equilibrium between inputs and outputs, in keeping with the above recommendation that dynamics be modeled; and (b) Providing a clearly identified set of formulas to be used for prediction, as opposed to estimation of past parameter values.

COMMENT 4: The risks attributed to FQ-resistant *Campylobacter* reflect implicit policy judgments. These judgments and their policy consequences should be made explicit.

It has become traditional in health risk assessment to try to clearly distinguish between scientific and factual data or evidence, on the one hand, and policy judgments on the other. The definition of λ in the decision framework outlined in Section 5 of the December draft report contains a subtle but important violation of this principle. The definition given is " λ = mean number of people per year who will experience some human health effect **as a result of consuming** a pound of Fluoroquinolone resistant *Campylobacter* contaminated broiler meat (emphasis added)." Thus, behind the mathematical symbol lies an important policy decision: that the risk to be quantified will be attributed solely and specifically to consumption of contaminated broiler meat.

The reality of food science and health protection is that the health consequences of FQ-resistant *Campylobacter* arise from the interaction of multiple decisions and behaviors by several different parties. A partial list includes:

- Producers' level of care
- Consumer's behavior and level of care in food preparation and sanitation
- Behavior of consumers who become infected (e.g., care-seeking, compliance behaviors as patients)
- Doctor's behaviors (e.g., in deciding what tests to order, what prescriptions to give, whether to prescribe specific FQs, etc.)
- Lab's behavior in handling samples, running tests, and so forth.

Attributing all of the health risks resulting from this set of interactions to the first component only is a policy decision not dictated by science. Moreover, doing so suggests that CP contamination is the only relevant factor. For contrast, suppose that λ were defined as follows:

" λ = mean number of people per year who will experience some human health effect as a result of inadequately cooking FQ-resistant CP-contaminated broiler meat."

This equally valid description emphasizes a different aspect of the same phenomenon, but might suggest different countermeasures.

Wording aside, defining the risk to be quantified as the risk attributable to FQ-resistant CP-contaminated broiler meat may have consequences that are not conducive to good policy-making and risk management. For example, based on the above

definition of λ , each of the following actions would presumably *reduce* the risk estimated via the proposed methodology:

- Consumers seek less medical care when infected and ill. (If they never seek medical care, then the incremental risk from FQ prescriptions to patients with FQ-resistant infections would be zero.)
- Doctors less often diagnose infections correctly and prescribe antimicrobials. (If FQ is never prescribed, then the incremental health risks due to FQ resistance would be zero.)
- Labs use less sensitive tests for *Campylobacter* infection. (If they never detect CP infection and the result is that FQ is less often prescribed, then the incremental health risks due to FQ resistance would be reduced.)
- Patients less often comply with their doctors' prescriptions to take antimicrobial medications following infection. (If patients never take FQ, then the incremental health risks due to FQ resistance would be zero.)

Conversely, improvements on any of these four dimensions would presumably lead to more frequent violations of p_{max} and hence to more frequent "institution of action" in Step 4 of the decision process outlined in Section 5 and reproduced above. A definition of risk that shows positive risk reduction benefits for counter-productive activities, while triggering increased intervention when consumers and doctors act to decrease or mitigate the health consequences of infection, may not be the most appropriate one for guiding policy decisions.

A more useful definition of the risk of CP infection might instead focus on the total expected cases of CP illness experienced by the U.S. population per year, without incorporating policy judgments about how that risk should be apportioned among the multiple factors that contribute to it. In this case, the relevant risk model for supporting decisions about the most beneficial coordinated use of FQ in poultry, livestock, and human patients would emphasize how different usage policies would affect the *total* burden of illnesses (or, perhaps, total illnesses from CP infection) per year in the U.S. population.

More generally, beneficial risk management and policy decisions can only be expected if the total risks and benefits of different alternative options are identified and compared. A framework that attributes all of the estimated risks from an interaction of causes to FQ alone, while ignoring health benefits of FQ use, provides incomplete information on which to base decisions.

COMMENT 5: The acceptable-risk decision framework in Section 5 of the December draft report is not compatible with many normative frameworks for public risk management decision-making. Any framework that requires acceptability of risk to be determined on an absolute scale (as in Step 1 of the proposed approach), rather than comparing the net health risks from different alternative risk management decisions, will violate principles of rational decision-making. (After all, presumably no

positive risk would be acceptable if it could be eliminated for free without increasing other health risks or incurring other losses.) In general, criteria of the form "There is an x% probability that no more than y people will become infected per year by fluoroquinolone resistant *Campylobacter* from domestic poultry", suggested in the draft document, fail to distinguish among many prospects that are not all equally desirable. Such criteria also violate prescriptive principles of decision-making, such as those captured in Expected Utility theory and many of its generalizations.

The decision-making framework outlined in Section 5 is currently less completely developed than the rest of the model. Yet, it has strong potential implications for how the model is used and for what actions it appears to justify. It is therefore highly desirable to spend more effort on the decision framework component of the document. It should be revised and extended to:

- (a) Conform to normative principles of decision-making, e.g., by including an explicit value function, utility function, or objective function, perhaps with adjustable value weights, as an output to be maximized or controlled; and
- (b) Allow the probability distributions of total *Campylobacter*-related illnesses per year to be compared for different risk management options.

The options to be considered should, at a minimum, include various strategies for allocating FQ treatments and alternatives to poultry, other animals, and human patients. The goal should be to identify the probable net change in human health risks per year associated with different choices and to identify the options yielding the best (undominated) probability distributions of outcomes.

COMMENT 6: Infection is not illness: the necessity of dose-response modeling. A potentially valuable contribution of the draft report is its attempt to use historical data to circumvent the need for quantitative dose-response modeling. This is certainly a desirable goal, insofar as dose-response relations are uncertain. However, it appears to be mathematically necessary to make some assumptions about the dose-response (or exposure-response) relation, either implicitly or explicitly, both to correctly interpret historical data on exposures and responses (i.e., illnesses) and in order to predict the health consequences of future changes in exposures.

The main assumption made in the report is that *risk of response is proportional to exposure*, as captured in the relation $\lambda = knp$. This is the most important technical assumption in the analysis. It is highly uncertain, since λ could well be (and, according to the preceding references, probably is) a non-linear function of (np) . The sensitivity analyses reported so far do not reveal what would happen to the risk estimates if this very strong assumption about model form were incorrect.

The equation $\lambda = knp$ implies that halving the prevalence of FQ-resistant *Campylobacter* in broiler meat should halve the annual risk of adverse health effects of interest (i.e., λ), other things being held equal. However, as noted by Teunis et al. (1999), "In order to judge the significance of exposure to a certain pathogen, insight into dose response relations is indispensable... Probability of *illness* changes with dose in a manner different from that of the probability of *infection* (not always monotonically

increasing, but a decrease at very high doses in some cases)." (Emphases added.) The December draft does not always maintain a clear distinction between infections and illnesses.

The relevance of quantitative dose-response relations for interpretation of past data on contamination and illnesses may be illustrated as follows. Suppose for purposes of discussion that the mean rate of infections (in units of expected infections per exposed person per year) satisfies the postulated equation $\lambda = knp$. But, suppose that illness only occurs in people for whom the *magnitude* or *intensity* of infection exceeds some tolerance threshold reflecting host defense capacity. Then the past data on observed confirmed cases constitute a *left-censored version* of the (only partially observed) past history of infections. In other words, only sufficiently severe infections lead to illness and detection. In this case, the key formula

$$k = N37/V_i,$$

used to estimate k will be incorrect.

In place of the simple Poisson process in the current draft, a more realistic probabilistic model for infections, based on observed illnesses, might be a *compound Poisson* process with left-censored observations. The statistical analysis and interpretation of past data could then differ significantly from the analysis and interpretation in the draft report, which seems to assume that all infections lead to illness (or have the same probability of leading to illness), without regard for intensity. (A hidden Markov model (HMM) approach to data analysis and prediction might be even more appropriate, with illnesses that lead to consulting a doctor being the observed components and infections in the rest of the population being the unobserved components.)

As a practical matter, use of a compound Poisson process with heterogeneous individual exposures (and/or response thresholds) may have important qualitative and quantitative implications for the effectiveness of different risk management strategies. For example, the true exposure-response relation may look more like

$$\lambda = knp^2$$

or contain other important non-linearities if the upper tail of the annual frequency distribution of individual infection intensities contributes disproportionately to the observed history of cases. This seems biologically plausible. Indeed, there is evidence *against* the draft report's implicit hypothesis that acute illnesses from *Campylobacter* follow a single-hit model (Teunis *et al.*, 1999, p. 1254.) If the one-hit model is rejected, then the most likely alternative is that some bunching of "hits" (either at the same time or across time) is needed to trigger an illness with high probability. The main practical consequence of this type of model is that a comparatively small reduction in (np) may yield disproportionately large reductions in risk of illness, in contrast to the $\lambda = knp$ model's prediction of an exactly proportionate reduction in risk.

In summary, the current model should be expanded to include the following four additional components.

1. *Appropriate dose-response (or exposure-dose and dose-response) models for individuals.* Since the most appropriate model is unknown, this dose-response component should be created as a separate module, so that different plausible alternatives can be tried and the results included in the sensitivity and uncertainty analyses. Specific alternatives to be evaluated might include non-linear dose-response relations such as the Beta-Poisson exposure-infection model and Poisson-Gamma infection-illness model developed by Teunis *et al* (*ibid.*, p. 1256). Another possibility might be the Weibull-gamma model advocated for *Campylobacter jejuni* and other pathogens by Holcomb *et al.*, 1999. Without appropriate dose-response models, the entire risk assessment and the use of particular formulae such as $k = N_3/V_i$ are subject to question.
2. *An estimate of the population frequency distribution of individual parameters (e.g., tolerance thresholds, scale parameters) for the dose-response function.*
3. *An estimate of the population frequency distribution of exposures in past data, taking into account the likely censoring of observed cases of exposure by non-response (i.e., successful host defense) in cases where the exposure was not sufficient to trigger illness.*
4. *A new sensitivity analysis showing how total annual risk of illnesses (per person per year) varies with np when an appropriate dose-response model is used to interpret past data, as outlined in 1-3.*

If the most appropriate dose-response relation is uncertain, then the sensitivity analysis should explicitly include model uncertainty. The risk assessment could use a technique such as Bayesian model-averaging to help reconcile and combine risk estimates made under different plausible assumptions.

COMMENT 7: Population heterogeneity should be modeled more fully. The model details in Sections 1-4 make repeated use of beta and gamma distributions to express uncertainty about key parameters, usually proportions and mean rates, respectively. These distributions are motivated by Bayesian theory for models in which each individual has the *same* (uncertain) probability or mean rate of occurrence of an event. They are not necessarily adequate when different individuals have very different probabilities or mean rates. For, instead of quantifying uncertainty about a population mean or proportion, it then becomes important to quantify uncertainty about the *population frequency distribution* of means or proportions. This is not done in the current model. If the simulation technique used were changed from Monte Carlo propagation of distributions to discrete-event simulation of individual behaviors, exposure histories, and responses, then it would be relatively easy to properly account for the heterogeneity in individual exposure and response parameters.

To see why this matters, consider the following simple example. Suppose that a population of 3 individuals is exposed to contaminated broiler meat. For simplicity, suppose that individuals A, B, and C receive levels 2, 3, and 1 of contamination, respectively. Suppose that their respective tolerance levels for exposure (i.e., the maximum intensity that they can tolerate without becoming sick) are 1.5, 2.5, and 3.5, respectively. Then A and B would become ill. Now, the (false) assumption that all 3 individuals have the same exposure and response parameters would lead to an estimate

for their common response probability of about 2/3, perhaps with a beta distribution around it. But, in reality, the true mean risk should be found by considering the six different ways in which exposures can be assigned to individuals, i.e.,

A, 1.5	B, 2.5	C, 3.5	Illnesses
1	2	3	0
1	3	2	1
2	1	3	1
2	3	1	2
3	1	2	1
3	2	1	1

If it is equally likely that any individual will receive any of the three intensities of exposure (i.e., 1, 2, or 3) next time the experiment is performed (e.g., next year when a new harvest of broilers is consumed), then the true mean risk is 1/3. The assumption that all three individuals have the same risk parameters leads to an incorrect point estimate of the mean and to an inappropriate uncertainty distribution around it. The beta distribution for the mean does not deal with this type of uncertainty, which may well swamp the uncertainty due to sampling variability that it does deal with. Similar comments apply to the gamma distribution for the unobserved true mean rates of illnesses in various populations discussed in the report.

In summary, *the statistical estimates of proportions and mean rates in the report should not rely on gamma and beta distributions, but instead should take into account the likely joint frequency distribution of exposure-response parameter combinations.* As indicated above, this need not be burdensome. A discrete-event simulation model (e.g., implemented in SIMUL8™) will handle the required calculations quite easily. The potentially hard part, i.e., estimation of the population frequency distribution of dose-response characteristics, should be undertaken anyway (see previous comment) in order to correctly interpret past data, distinguish between infections and illnesses, and predict impacts of changing exposures on future illness rates.

An especially tractable approach that could address several of these concerns about heterogeneity and non-linearity might be to replace the model $\lambda = knp$ with a model of the form:

$$\{\lambda_j = k_j n_j p_j, \pi_j\},$$

where j indexes sub-populations, π_j is the estimated proportion of the population in sub-population j , and k_j is allowed to have different values for different ranges of the value ($n_j p_j$). Such a mixture-distribution model might provide a reasonable compromise between excessive complexity and excessive simplicity.

COMMENT 8: Statistical interdependencies among components of risk should be modeled. One of the main probability techniques used in the draft report is the decomposition of the exposure-illness process into a sequence of steps. A typical model of this type might be expressed as follows:

$Pr(\text{prolonged illness} \mid \text{prevalence of FQ-resistant CP in the meat is } p) =$

$Pr(\text{consumption of contaminated meat} \mid p) * Pr(\text{illness} \mid \text{consumption of contaminated meat}) * Pr(\text{seek help} \mid \text{illness}) * Pr(\text{help is ineffective due to FQ-resistance} \mid p).$

In fact, the report uses a somewhat different logical chain and divides it into several different parallel sub-chains for different specific illnesses. (Throughout, “|” means “conditioned on” or “given”.) However, the same idea of decomposition of a conjunction of conditions into components is used.

However, the report does *not* condition each parameter on all of its relevant predecessors, as proper methodology requires (unless all parameters are thought to be statistically independent). Instead, parameters such as care-seeking or doctor or lab behaviors are modeled as being statistically independent across different variants of the illness. In other words, *correlations among uncertain quantities have been ignored* in the present analysis. This may not be very realistic. For example, if public health messages raise consumer or doctor awareness of microbial hazards, this could affect several of the parameters simultaneously. Therefore, *a refined model might incorporate possible correlations among the input parameters* (e.g., using Bayesian copulas between marginal distributions.) Other examples of possible dependencies among model quantities include:

- p_+ = Proportion of infected stool specimens that test positive, and p_t = Proportion of submitted stool specimens that are tested by the laboratory. (Is it not possible that one could affect the other, e.g., because reports or many recent positives lead to increased testing, or because increased number of specimens tested leads to increased likelihood of observing small proportions, e.g., by increasing the expected number of positives well above 1?)
- p_c and p_p (Could use of FQ in poultry affect prevalence of CP in chicken carcasses at end of slaughter process?)
- p_{ab} and p_{FQ} (Might not introduction of a highly effective new FQ for which resistance is low stimulate prescriptions of the new FQ, and hence increase the proportion of patients treated with medication?)

Treating these and other quantities as statistically independent random variables may be less useful and less realistic than treating them as dynamic variables that change together as physicians and other decision-makers respond to available information and treatment options.

Similarly, the last term, $Pr(\text{help is ineffective due to FQ-resistance} \mid p)$, can only be quantified accurately if the probability that help will be ineffective anyway (e.g., due to natural resistance, misdiagnosis, failure to comply, or other competing risks) is known. The current model focuses on failures due to FQ resistance, but does not provide a full, credible quantification of competing risks.

In summary, the probabilistic framework adopted in the current report should be extended to include

- (a) Conditioning of each random variable on its predecessors; and

(b) Modeling of causal interdependencies among variables.

Until the probabilistic framework incorporates realistic dependencies among variables (possibly also including stochastic dynamics via a discrete-event simulation) the results of analyses based on it may be hard to interpret.

Comment 9: The current model has not been validated. Several kinds of validation should be carried out before the model is used to guide or support risk management decision-making. These include:

- (a) *Internal validity.* The model can be subjected to "black-box testing" in which known risk processes are simulated, sample data are supplied to the model, and the model's risk estimates are compared to the correct values.
- (b) *External validity.* The dose-response models and other assumptions used in the final model should be tested to determine how well they predict data from human exposure experiments and other data not used in building them.

Until the model has been extended and carefully validated, it would be premature to start using it as a guide for policy making and risk management decision-making.

MICRO-COMMENTS

The following comments address technical details of the model.

Comment 10: The modeling of p_{ca} (proportion of Campylobacter infections relating to domestically consumed chicken) does not reflect the full plausible range of uncertainties about this variable. It is not clear why a uniform distribution between two point estimates is used to model uncertainty about this crucial parameter. For example, the lower point estimate at 47.0% had a reported associated 95% CI of 0-75.2%. So, why is 0 not included as a possible value for the lower point estimate? More generally, why is the report's usual strategy of surrounding point estimates with distributions based on a prior and conditioned on data abandoned for this parameter? Risk estimates appear to be sensitive to this parameter, and therefore departures from the methodology used elsewhere in the report should be especially well justified.

Other sources of uncertainty for this parameter include (a) Omitted covariates and confounders in the original studies; (b) Use of a logistic regression model to analyze the data without adequate model diagnostics; (c) Treatment of possible measurement errors and errors in variables in the original studies; and (d) Failure to explain differences in point estimates of source-specific risks across studies. Moreover, the etiologic fraction calculations may not be appropriate if sources interact (e.g., if raw water, raw milk, house pets, and consumption of under-cooked chicken jointly act to create CP illness risk.) Finally, Table 3.2 of the report shows that the odds ratio for living in a household with cats is less than that for eating chicken, while the original reference shows the reverse relation. Table 3.2 would benefit from a footnote in which any transformations made in the original numbers are explained.

Comment 11: Estimating quantities by taking products and ratios of random variables is a somewhat non-standard alternative to both Bayesian inference (i.e., conditioning priors on data) and conventional statistical methods. Potential biases from this approach should be quantified. It might be helpful to compare the results presented to corresponding estimates from more standard approaches, e.g., for estimating confidence intervals for ratios of exponential or Poisson variables. Also, exact analytic expressions are known for the products of independent random variables, and these formulas could be used to help validate the accuracy of the simulation-based estimates.

Comment 12: Structural vs. reduced-form modeling. It may be statistically more efficient to estimate some of the products using only some of the data and fewer unknown parameters. For example, suppose that the structural (causal) model equations of interest are as follows: $z = ay$, $y = bx$, $x = cw$, corresponding to the causal diagram: $w \rightarrow x \rightarrow y \rightarrow z$. Rather than estimating a from observations of z and y , b from x and y , and c from x and w , it might be more accurate to simply estimate the relation (reduced equation) $z = dw$ from observations of z and w . In this case, $d = abc$ is a reduced parameter. More generally, it may be possible to factor a product (or ratio of products) in such a way that the error variance of the quantity to be predicted is minimized, given the data, by representing it as an appropriate product of reduced parameters. Applying this insight to the formulas of the current model, most of which involve ratios or products, may further reduce the uncertainty in quantities to be estimated or predicted.

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Jaffe K, Issa S, Daniels E, Haile D, 1997. Dynamics of the emergence of genetic resistance to biocides among asexual and sexual organisms. *J Theor Biol* Oct 7;188(3):289-99

Teunis PFM, Nagelkerke NJD, Haas CN, 1999. Dose response models for infectious gastroenteritis. *Risk Analysis* Dec; 19(6):1251-1260.

Vose, D., 1999. Draft Report to FDA: Risk assessment on the human health impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken.

Attachment 2 – ANIMAL HEALTH INSTITUTE

Comments to FDA Docket No. 98D-0969, “Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken”

COMMENTS ON INDIVIDUAL STUDIES

Comments on Individual Studies

(Note: Reference numbers included in this section refer to the CVM Risk Assessment.)

Study #1: "The Role of Poultry and Meats in the Etiology of *Campylobacter jejuni/coli* Enteritis" by Noreen V. Harris, DVM, PHD et al., AJPB April 1986, Vol. 76, No. 4.

- Those without telephones and those that did not speak English were eliminated from the study. Could this have biased the study in comparison to the FoodNet data?
- Only 4 of 25 controls that reported mild diarrhea in the week prior to interview were cultured and found negative for *Campylobacter*. Was this enough of a sample to assume that the other 21 were negative for *Campylobacter*?
- The statement is made that because CJC infection is rare in asymptomatic individuals in the USA, the chances of interviewing a control who was infected were small. What if they had interviewed a Mexican who had returned from a trip to Mexico in the last 6 weeks? Interviewees were only asked about travel in the week previous to the diarrhea episode since the incubation period for campylobacter is 5-8 days. Since people can shed the organisms for 6 weeks or longer, could some of the controls had a positive stool for campylobacter but had another cause for the diarrhea?
- Infants were excluded from all analyses unless their parents indicated they ate foods other than baby foods and formula. The FoodNet data included all infants. A fairer comparison would have included infants in both studies.
- Controls scored higher on the average than did CJC cases with regard to the "cutting board scale" (indicating safer practices). This supports the concept that focusing on chicken consumption for campylobacter disease may be overrated. Instead we should be focusing on handling procedures with possible contamination of other foodstuffs.
- People who traveled to undeveloped countries and consumed raw milk were not removed from this study. The authors of this particular study indicated that removal of this data did not impact the association of CJC enteritis with unprocessed poultry, fish, or processed turkey consumption. (31, 1986) The summary in the RA model included further information, from an apparent follow up article using the same data, that quantitated the risk of foreign travel. (64, 1993)
- The etiologic fraction was calculated as being 48%. This was calculated from chicken consumption (OR of 2.4 with 95% CI of 1.6-3.6), not from eating raw or undercooked chicken.
- The table, 3.1 presented in RA model, was adapted from a different article (64) than the body of the referenced paper (31). Apparently there was another paper written on this same study at a later date. (1986 vs. 1993). The original paper did not provide an analysis of foreign travel, raw milk consumption etc....

Study #2: Campylobacter Enteritis at a University: Transmission from Eating Chicken and From Cats by Michael S. Deming et al., American Journal of Epidemiology, Vol. 126, No. 3, 526-534.

- The citation for the article was incorrect (22). It was cited as being in the American Journal of Public Health, but was actually in the American Journal of Epidemiology.
- None of the cases drank raw milk or traveled outside the United States during the week previous to the sickness.
- The etiologic fraction calculated for this study of 70% was not reported in this article (22). It was reported in a chapter of a textbook on campylobacter published in 1993 (74).
- CVM's discussion on the limitations of the study indicates that the study population was not representative of the US population. In spite of that, the 70% was used in the calculations. If the 70% was not averaged with the 48% to get the 59%, a lower figure would have been used to calculate the chicken associated cases.

Study #3: Endemic Campylobacter jejuni Infection in Colorado: Identified Risk Factors, by Richard S. Hopkins, MD et al, AJPH, March 1984, Vol. 74, No. 3.

- This study only looked at eating raw or undercooked chicken as opposed to consuming chicken, as a risk factor.
- Drinking raw water, raw milk, or having a cat in the household presented a greater risk than consuming raw or undercooked chicken.
- The etiologic fraction, of 47%, was not calculated as a part of the paper. It was calculated and offered by the author of the RA document.
- The author of the study paper stated: "Exposure to undercooked chicken emerges as a possible risk factor in this study, but chicken consumption is common in both cases and controls." The author isn't that anxious to strongly implicate chicken.
- The author also states: "At least one-third of the cases in the study were potentially preventable by personal behavioral changes (avoiding drinking raw water or raw milk, cooking chicken thoroughly) and/or by public health measures (public education, prohibition of sale of raw milk for human consumption)."
- If the etiologic fraction could be calculated for chicken consumption for this study, it would be considerably less than the reported 47%. That averaged with the 48% from study #1 (leaving out the 70% from study #2) would bring the numbers of FQ resistant infections from consuming chicken down even more.

Attachment 3 – ANIMAL HEALTH INSTITUTE

Comments to FDA Docket No. 98D-0969, “Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken”

SPREADSHEETS – TWO SCENARIOS UTILIZING AHI ESTIMATES

Appendix B(1): Alternative Values for Draft RA Variables

Note: bold italics denote suggested corrections or alternative.

Key: data, assumption, calculation, link, model output, section result

Section 1		Nominal observable confirmed cases of campylobacteriosis in US			
n(us)	US Population	270,298,524			
n(FN)	Catchment site population	20,723,982			
O(i)	Observed FoodNet invasive cases of Campylobacteriosis	43			
O(e)	Observed FoodNet enteric cases of Campylobacteriosis	3,985			
lambda(l)	Expected observed invasive disease in catchment	43			
lambda(e)	Expected observed enteric disease in catchment	3,985			
N(i)	Nominal observable mean population invasive infections	561			
N(e)	Nominal observable mean population enteric infections	51,976			
p(b)	Proportion enteric infections with bloody diarrhea	46%			
			Enteric	Invasive	
			Non-bloody	Bloody	
N1(en),N1(eb),N1(i)	Nominal mean Culture Confirmed Cases reportable to health department	28,077	23,898	561	
Section 2		Total nominal expected number of Campylobacter infections in a year in US			
p(nm),p(bm)	P(seek care)	12%	26.70%	100%	
p(nc),p(bc)	P(stool requested and submitted)	40%	55.40%	100%	
p(l)	P(lab tests for organism)	94.5%	94.5%	100.0%	
p(+)	P(culture confirmed given tested)= test Se, assumes Sp=1]	95%	95%	95%	
N2(en),N2(eb),N2(i)	Illness in population	651,559	179,964	591	
N2(T)=N2(en)+N2(eb)+N2(i)	Total cases (bloody+non-bloody+invasive)	832,114			
Section 3		Number of FQ-resistant infections, from domestic chickens			
p(ca-min)	Lower bound estimate	n/a			
p(ca-max)	Upper bound estimate	48%			
p(ca)	Therefore chicken associated (<i>estimate</i>)	48%			
	Chicken associated cases	312,749	86,383	283	(Total) {weighted %}
p(nm), p(bm)	Proportion seeking care	12.20%	26.70%	100%	399,415
	Number seeking care	38,155	23,064	283	61,503
p(an),p(ab),p(ai)	Proportion treated with antibiotic	47.9%	63.7%	100.0%	54.1%
	Number treated	18,276	14,692	283	33,252
p(FQ)	Proportion receiving FQ treatment	55.08%	55.08%	55.08%	
	Number of chicken related cases treated with FQ	10,067	8,092	156	
p(rh)	Proportion of Campylobacter infections from chicken that are FQ-resistant	6.90%			
N3(en),N3(eb),N3(i)	Number of FQ-resistant infections from chicken seeking care, get FQ	695	558	11	
N3(T)=N3(en)+N3(eb)+N3(i)	Total Number of FQ-resistant infections from chicken, seeking care, get FQ	1,264			
Section 4		Number of FQ-resistant Campylobacter-contaminated carcasses consumed annually			
p(c)	Total prevalence of Campylobacter	88.1%			
p(rc)	Prevalence of FQ-resistant Campylobacter among Campy. Isol./slaughter	11.8%			
p(p)	Est. prevalence of FQ-resistant Campylobacter in broiler carcasses	10.4%			
c	Consumption of boneless domestic-reared ck. In US per head (lbs.)	51.40			
V(c)	Total consumption of boneless domestic-reared ck. In US (lbs.)	1.39E+10			
V(l)	Total consumption of boneless domestically-reared chicken contaminated at slaughter w/FQ-resistant Campylobacter in US (lbs.)	1.45E+09			
	Denominators	Value	Probability	Eq. To 1 in:	
P1	US citizen	270,298,524	0.00047%	213,888	
P2	Person with campylobacteriosis	832,114	0.15187%	658	
P3	Person with campylobacteriosis seeking care	128,131	0.98629%	101	
P4	Person with campylobacteriosis seeking care and prescribed antibiotic	69,274	1.82425%	55	

Appendix B(2): Alternative Variables and Calculation Methods

Note: **bold italics** denote suggested corrections or alternative.

Key: data, assumption, calculation, link, model output, section result

Section 1		Nominal observable confirmed cases of campylobacteriosis in US	
n(us)	US Population	270,298,524	
n(FN)	Catchment site population	20,723,982	
O(i)	Observed FoodNet invasive cases of Campylobacteriosis	43	
O(e)	Observed FoodNet enteric cases of Campylobacteriosis	3,985	
lambda(l)	Expected observed invasive disease in catchment	43	
lambda(e)	Expected observed enteric disease in catchment	3,985	
N(i)	Nominal observable mean population invasive infections	561	
N(e)	Nominal observable mean population enteric infections	51,976	
p(b)	Proportion enteric infections with bloody diarrhea	46%	
		Enteric	
N1(en),N1(eb),N1(i)	Nominal mean Culture Confirmed Cases reportable to health department	51,976	
Section 2		Total nominal expected number of Campylobacter infections in a year in US	
p(nm),p(bm)	P(seek care)	n/a	
p(nc),p(bc)	P(stool requested and submitted)	n/a	
p(t)	P(lab tests for organism)	n/a	
p(+)	P(culture confirmed given tested)= test Se, assumes Sp=1	n/a	
N2(en),N2(eb),N2(i)	Illness in population	n/a	
N2(T)=N(e)X38	Total cases (bloody+non-bloody+invasive)	1,975,088	
N(FB)=N2(T)X0.8	Total Foodborne Cases	1,580,070	395,018 non-foodborne cases
Section 3		Number of FQ-resistant infections, from domestic chickens	
p(ca-min)	Lower bound estimate	n/a	
p(ca-max)	Upper bound estimate	48%	
p(ca)	Therefore chicken associated (estimate)	48%	
	Chicken associated cases	758,434	821,637 non-chicken foodborne
p(nm), p(bm)	Proportion seeking care	8.00%	8.00%
	Number seeking care	60,675	97,332 total non-chicken seeking care
			158,007 Total No. Cases seeking care
p(an),p(ab),p(ai)	Proportion treated with antibiotic	51.6%	51.6%
	Number treated	31,290	50,223 total non-chicken treated with AB
			81,513 Total No. Cases treated with AB
p(FQ)	Proportion receiving FQ treatment	55.08%	
	Number of chicken related cases treated with FQ	17,235	
p(rh)	Proportion of Campylobacter infections from chicken that are FQ-resistant	6.90%	
N3(en),N3(eb),N3(i)	Number of FQ-resistant infections from chicken seeking care, get FQ	1,189	
N3(T)=N3(en)+N3(eb)+N3(i)	Total Number of FQ-resistant infections from chicken, seeking care, get FQ	1,189	
Section 4		Number of FQ-resistant Campylobacter-contaminated carcasses consumed annually	
p(c)	Total prevalence of Campylobacter	88.1%	
p(rc)	Prevalence of FQ-resistant Campylobacter among Campy. Isol./slaughter	11.8%	
p(p)	Est. prevalence of FQ-resistant Campylobacter in broiler carcasses	10.4%	
c	Consumption of boneless domestic-reared ck. In US per head (lbs.)	51.40	
V(c)	Total consumption of boneless domestic-reared ck. In US (lbs.)	1.39E+10	
V(l)	Total consumption of boneless domestically-reared chicken contaminated at slaughter w/FQ-resistant Campylobacter in US (lbs.)	1.45E+09	
	Denominators	Value	Probability
P1	US citizen	270,298,524	0.00044%
P2	Person with campylobacteriosis	1,975,088	0.06021%
P3	Person with campylobacteriosis seeking care	158,007	0.75261%
P4	Person with campylobacteriosis seeking car, prescribed antibiotic	81,513	1.45888%
			Eq. To 1 in:
			227,298
			1,661
			133
			69

Attachment 4 – ANIMAL HEALTH INSTITUTE

Comments to FDA Docket No. 98D-0969, “Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken”

AHI EVALUATION OF RISK STANDARDS

**Presented by Kent McClure, DVM, JD
as presented at December 1999 CVM Workshop**

WHAT IS THE APPROPRIATE LEGAL STANDARD TO APPLY TO THE EVALUATION OF RESISTANCE FOOD-BORNE PATHOGENS?

- The nutshell answer is that the FFDCFA does not mandate a legal standard
- The statute requires that an NAD be shown to be safe [21USC § 360b(d)]
- Safe is defined as referring to the health of man or animal [21 USC § 321(u)]
- The statute provides no further guidance. The statute does provide some factors to consider, but does not provide the standard against which to evaluate the factors [21 USC § 360b(d)]
- In this context, the regulations promulgated by FDA parrot the statute and provide no guidance as to the standard. [21 CFR 514.111]
- In cases in which the FDA has been a party, they have not argued that promulgated rules set a standard for determining safety in the context of evaluation of an NADA. The DC Court of Appeals noted this and stated that was because “the only ones relevant add little to the statute.” *American Cyanamid Co. v. FDA*, 606 F.2d 1307, 1310 and n.16. (D.C. Cir. 1979).
- Federal Courts that have attempted to determine the standard against which the FDA must evaluate safety for a New Animal Drug, have determined that no standard is mandated.
- “The Food, Drug, and Cosmetic Act does not indicate the standard an applicant must meet to demonstrate a new drug’s safety or the evidence upon which the FDA must base its safety determination.” *Stauber v. Shalala*, 895 F.Supp. 1178, 1191 (W.D. Wis 1995)
- *American Cyanamid Co. v. FDA*, 606 F.2d 1307, 1313-1314 (D.C. Cir. 1979)(The FFDCFA contains no provision delineating the nature of the evidentiary showing required to prove the safety of a new drug).
- The courts have made several other points that are of interest to this discussion:
- The DC Court of Appeals has at least twice rejected the Agency’s argument that the Legislative History behind the Animal Drug Amendments of 1968 set the particular standard that must be used to evaluate the safety of a new animal drug in a food producing species.
Hess & Clark v. FDA, 495 F.2d 975, 993 - 994 (D.C. Cir. 1974);
Rhone-Poulenc, Inc. v. FDA, 636 F.2d 750, 754 (D.C. Cir. 1980),
- The DC Court of Appeals has held that a risk / benefit analysis is inherent in the process of safety evaluation for NADs in food producing animals.
Hess & Clark v. FDA, 495 F.2d 975, 993 - 994 (D.C. Cir. 1974);
Rhone-Poulenc, Inc. v. FDA, 636 F.2d 750, 754 (D.C. Cir. 1980),

- Conspicuously absent from the decisions addressing safety standards for NADs is a discussion of “reasonable certainty of no harm.”
- The take away message is that the Agency has flexibility to craft a reasonable and workable standard that will appropriately protect public health.

WHAT IS AN APPROPRIATE RISK STANDARD TO APPLY TO RESISTANT FOOD-BORNE PATHOGENS?

- We agree with CVM (statement in the introduction to the Risk Assessment, p.I-8) that there are significant differences between considerations of traditional chemical based residues and resistance issues.
- Attempting to regulate resistance in the context of residues is like trying to fit a square peg in a round hole.
- The USDA and FDA standards for the regulation of pathogens should be the same. The USDA standard is the most appropriate, as it takes into account the HACCP program of pathogen reduction and the fact that raw meat and poultry is intended to be cooked prior to consumption. In fact, packages of raw meat and poultry sold in supermarkets are labeled with specific handling and cooking instructions. The USDA standard revolves around the quantity of pathogen. The Poultry Inspection Act and the Meat Inspection Act standards do not consider a pathogen, resistant or otherwise, to make a carcass adulterated if the quantity does not ordinarily render it injurious to health. This standard should be explored by FDA
- [21 USC § 453 – Poultry – 21 USC § 601(m) – Meat]
- Resistant pathogens are not treated as “added poisonous or added deleterious substances” by the USDA.
 - Why? – pragmatic reasons – can’t culture every carcass, would have to condemn any carcass with a resistant pathogen
 - Scientific – antibiotic doesn’t create the pathogen or create resistance*
- It is important to ask where in the process will the standards be used. At the heart of the matter is the monitoring of the true incidence of resistance in slaughter isolates. This is a post approval function. The approval process for an NADA and post marketing surveillance are distinct entities.
- AHI is in favor of post marketing surveillance and applauds the NARMS program.
- However, it would be wrong, and not legally justified, to hold the approval process hostage by attempts to require manufacturers, as a condition of approval, to agree to remove a product from the market when some arbitrary threshold is crossed. The FFDCA has provisions for removal of a product from the marketplace based upon scientific evidence. It

would be wrong for the Agency to attempt to circumvent the provisions of the FFDCA when formulating a standard.

- The bottom line is that: The standard for regulation should be in accordance with the USDA, the Agency has flexibility in addressing this issue, the approval process should not be held hostage to post approval activities, action in response to post approval monitoring should be handled under the provisions provided in the FFDCA and not via the standard itself.