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Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Comments to FDA Docket No. 98D-1146, Draft Guidance for Industry #152
“Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their
Microbiological Effects on Bacteria of Human Health Concern”

AHI provides these comments on CVM draft guidance document #152 to assess the microbiological safety of antimicrobial agents used in food producing animals. 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. AHI welcomes this draft guidance which follows a number of years of active debate and workshops on how to assess the safety of all antimicrobial agents used or proposed for use in food producing animals for microbiologic effects, in particular the selection of antimicrobial resistant bacteria that may be transferred to humans.

As has been said many times before, this is a complex issue that must be dealt with from a scientific, and not a legislative, standpoint. Calls for comprehensive bans on whole classes of products are clearly not consistent with existing laws and regulations and, if enacted, would seriously undermine the agency’s effectiveness and duty to direct its resources to those areas that might present the greatest public health impact. FDA has adequate authority and expertise to assess the safety of all antimicrobials and to act accordingly based on the scientific evidence presented. Furthermore, it is critical and in keeping with the Federal Food, Drug, and Cosmetic Act that a prioritized approach for the assessment of each antimicrobial agent and its specific use in a particular animal species should be used for assessing measurable human health impacts against the specific food-borne bacteria of most relevance.

We appreciate the progress that the FDA/CVM has made in addressing this problem on the basis of risk assessment as AHI, and other domestic and international organizations have been suggesting for some time. Indeed, the OIE, CVMP and the Australian NRA all have risk assessment procedures in place or in development. We believe the CVM draft guidance is a consistent step in the right direction and is a significant improvement over the “Framework” document concepts originally proposed in 1998. AHI commends the agency for its focus on food-borne pathogens, the deletion of pathogen load studies and the threshold concept from the

draft Guidance, and the substitution of NARMS in place of company-conducted post-approval monitoring programs as originally contained in the “Framework” document. AHI encourages CVM to further refine the draft guidance into a risk-based approach so that effective and safe antimicrobials can be made available or maintained for veterinarians and producers to use in keeping animals healthy, our food supply abundant and safe, while protecting the public health.

Specific comments on aspects of the document are organized against the following overall conclusions and recommendations:

- *The scope of the document, by requiring assessment of the potential transfer of resistance from animal enteric bacteria to the wide range of human commensals and pathogens suggested in the ranking of drugs important to human medicine in Appendix A, has not been justified by current scientific evidence. Without further justification by the agency of the connection between animal enterics and non-enteric human diseases, the scope should be limited to those drugs and pathogens, which are relevant to food-borne illness.*
- *AHI recommends inclusion of a fourth probability ranking and categorization element called “negligible” to more accurately describe those drugs and uses that are essentially of no risk to human health.*
- *The proposed methods for exposure assessment will overestimate the true exposure of consumers to resistant food-borne pathogens at doses sufficient to cause infection and illness.*
- *As written the risk management options would serve to preclude approval of virtually any herd or flock treatment of an antibacterial ranked at a medium risk category or higher. In particular, this could virtually block approval of any new therapeutic agent in poultry, even if it is not related to a human antibiotic.*
- *There is no guidance as to how CVM will make the final determination that a particular product and use has met the “reasonable certainty of no harm” standard. CVM needs to provide criteria as to how these final decisions will be made.*
- *The current guidance will serve as a disincentive for companies to add important new disease indications to currently approved antibacterial drugs.*

I. Resistance Determinants and Transfer

a. General Comments

The draft guidance suggests that resistance determinants (i.e. resistance genes) are a very important consideration in determining microbial safety. In fact, the hazardous agent has been defined as the resistant bacteria or the resistance determinant of human health significance. Categorization and release assessment evaluations as proposed in the draft guidance depend

heavily upon the presumed resistance determinant transfer. Although resistance transfer has been demonstrated *in vitro* and in experimental animal model systems, there is to our knowledge no documented evidence of resistance gene transfer events within the human intestinal tract from an “animal” to a “human” bacterium, nor between ingested food-borne bacteria and human non-foodborne pathogens (e.g. *S. pneumoniae*). References cited in the draft guidance supporting rather definitive statements that imply such data are available, in fact, are commentaries or reviews expressing opinions, conjecture or hypotheses that such events may occur. No definitive research results have been presented. What this really means for human health has been more a matter of speculation than hard facts. Nevertheless, the proposed risk assessment process asks sponsors to present data evaluating the occurrence and rate of transfer of resistance determinants (Section V.A.2.g, p.13).

Some initial questions that arise include:

- (1) What bacteria should be examined - are only human enteric bacteria of concern, or does this include other bacteria that could cause non-enteric infections?
- (2) How is it to be demonstrated that transfer could *not* happen?
- (3) How is a “rate” of transfer determined?
- (4) If transfer can be demonstrated *in vitro*, how can it be determined whether or to what extent this actually occurs *in vivo* and what would be the impact?

The guidance indicates that in the absence of evidence to the contrary, an assignment of “High” is to be made for that particular situation. AHI is concerned that the requirements for conducting Release Assessment studies for resistance determinants cannot be realistically addressed as part of a pre-approval program. In fact, CVM indicated at the October 2nd Public Meeting that they themselves could not come up with a way to account for this potential route of resistance transfer. The likelihood of proving that resistance transfer never occurs in the myriad of commensal and pathogenic bacteria in the GI tract or that it will never present a human health concern is extremely small. The only other option available is to accept the default assumption that gene transfer is likely to occur, thereby biasing the assessment of certain antimicrobial agents to a more conservative status than is justified.

b. Specific Comments

The introduction section (page 1, paragraph 1) makes the proposition that presumably (all?) human illness caused by antibiotic resistant pathogenic bacteria is made more difficult to treat as a consequence of food animal antibiotic use. The papers cited as evidence do not contain definitive evidence that such is the case nor does the limited number of citations reflect the vast amount of information available to support a contrary conclusion. Yet in the next paragraph, it is stated that the attributable fraction is difficult to assess precisely. Nevertheless, the underlying assumption made throughout the document is that resistance gene transfer from ingested food-borne bacteria (presumably from salmonella, campylobacter, *E. coli*, enterococci, and

unmentioned other bacteria) to any human bacterial pathogen is a proven *in vivo* event and occurs frequently. In Appendix A (p. 32, item 2), as an example, it is inferred that the treatment of *L. pneumophila* pneumonia with erythromycin could somehow be compromised by the use of macrolides in food animals, a difficult scenario to rationalize. In fact, in a human volunteer study of ingested antibiotic resistant *E. faecium*, there was only evidence of transient passage and no resistance gene transfer from the “animal” challenge strain to the commensal “human” strains even though these strains were simultaneously present in the close confines of the GI tract (Sorenson). The type of information and rationale needed to substantiate hypothetical relationships between drug use in food animals and human health consequences needs to be provided. The goal should be to focus on measurable human health consequences, rather than theoretical or potential consequences. Thus, CVM should justify that the resistance gene transfer hypothesis is as significant as is assumed here. This is particularly critical to justify the ranking of antibiotics in Appendix A, a ranking that impacts not only other sub-assessments in the overall Risk Estimation process but also prioritization of review of currently approved drugs, as outlines in Appendix C.

2. Categorization of drugs important to treatment of human diseases (Appendix A)

a. General Comments

The ranking and categorization schemes in the document will vastly overestimate the potential risk of many compounds and uses. This is one of the most troubling aspects of the draft guidance. There is a serious disconnect between the assessment of those drugs important for treating human disease and the relevance to using drugs of the same drug classes for treating, controlling, or preventing common food animal infections. Many of the pathogen-antibiotic combinations given as examples for human drug use have absolutely no relationship to animal use (e.g. carbapenems, glycopeptides and oxazolidones, rifampin, etc.). In addition, overemphasis on resistance gene transfer has also contributed greatly to an inflation of prioritization of certain drug classes for specific bacteria, where human pathogens with no food-borne connection are given as examples for justifying importance (e.g. macrolides and *Legionella*, rifampin and *N. meningitidis*).

The appendix classifies a very large percentage of human use antibiotics as of high importance to human health which may be justifiable in considering human health per se but which, at least in some cases, is irrelevant with respect to considering the risk associated with use in food animals. If those (mis)-classifications are directly translated to the qualitative risk assessment process, it will have the effect of clearly biasing the assessment toward ranking most animal use antimicrobials as a high risk to human health. In reality, the classification of human drugs is not transparent because it fails to clarify how many of the important human uses are connected in any way with use in animals. The document continually stresses that exposure via the food pathway is the main concern of the agency, yet the classification scheme that will affect the overall assessment of risk from use of an animal drug is based on diseases where there has not been any scientific evidence of a connection with food animal use or food-borne illness.

For example, it is estimated that about 75% of all antimicrobials prescribed by physicians are for treatment of about a dozen respiratory tract pathogens, such as pneumococcus, streptococcus, haemophilus, and mycobacteria that are specific to humans. We believe medical experts would agree that the antimicrobial susceptibilities of these pathogens are not affected by antimicrobial use in food animals. The FDA needs to reconsider these rankings and base them on evidence of a clear association with animal use and not on mere speculation. Absent such evidence we believe, for the purposes of this document, that only those antimicrobials used in the treatment of a foodborne infection should be considered for classification as of high importance relative to animal uses.

The appendix makes no provision (at least no transparent one) for ranking the likelihood or severity of “harm” that might be associated with an antibiotic resistant food-borne disease. Although estimates of food-borne disease are frequently cited (Mead), FoodNet surveillance provides other statistics on actual incidence of food-borne disease trends (<http://www.cdc.gov/foodnet/default.htm>). These two documents provide coverage primarily of salmonella and campylobacter (zoonotic pathogens) and do not provide information on enterococci or non-*E. coli* O157 strains (indicator/commensal strains). Additionally, there is no description of the “harm” that might be attributable to a resistant salmonella or campylobacter infection, such as more days of diarrhea, mortality, etc. A mere ranking of human medical importance solely on the basis of “bug-drug” cross-resistance (this is really the bottom line for the proposed ranking) not only oversimplifies reality, it leads to erroneously conservative results with tremendous impact on the Risk Estimate and Appendix C prioritization.

b. Specific Comments

Categorization should be based on the importance of antibiotics to human medical treatment of zoonotic bacterial infections as the first criterion. Indicator bacteria, such as *E. coli* and enterococci, should not be considered in this ranking until more definitive information is available on resistance gene transfer, especially since there is no indication of food-borne disease rates associated with these microorganisms (Mead). Ranking of an antibiotic’s importance to human medicine without ascribing an animal-origin relationship is not justified.

Appendix A lists 10 factors considered in the ranking process; we offer the following comments on each of those factors:

1. Sole or limited available therapy. Reference is made to linezolid and streptogramins as sole-use agents for VRE infections. However, it would seem by the label claims on these agents that there are indeed two therapeutic options. In addition, waiting for resistance to develop in the human pathogen population will unduly delay development of products for veterinary therapy, and by default, circumvents the very risk assessment process that the Guidance Document seeks to use to assess safety. In essence, this is the application of the Precautionary Principle, which the US government has vigorously rejected in numerous international fora.

2. Therapy of choice. The list of examples given appears to be based on human clinical value of an agent to treat a specific human pathogen rather than on the importance for treatment of zoonotic disease.
3. Spectrum of activity. While the spectrum of activity is important, many of the examples given are not relevant to this issue as explained above. Additionally, a discussion of antibiotics that are broad-spectrum vs. those with a narrow spectrum, with respect to food-borne pathogens is required. For example, while fluoroquinolones target both Gram positive and Gram-negative bacteria, macrolides target campylobacter, but not *E. coli* or salmonella, and bacitracin targets only Gram-positive bacteria. Moreover, within the spectrum assessment, a consideration of genotypes, serotypes or species of food-borne bacteria needs to be made. For example, serotypes of salmonella isolates from food animals obtained *after* slaughter differ from those of isolates found in humans (Sarwari). Moreover, an epidemiological study reported at the 2002 ICAAC meeting (W. A. Gebreyes, et al. Abstr. 42nd Intersci. Conf. Antimicrob Agents Chemother., abstr. C2-1286) analyzed 484 multi-drug resistant *Salmonella enterica* serovar *typhimurium* strains isolated from swine, comparing them with 293 clinical human strains. It was found that the most common MDR types found in healthy swine are distinctly different from genotypes commonly found in humans. A virulence factor gene (*spvA*) was lacking in the most common MDR swine isolates. Furthermore, antibiogram and PFGE patterns showed a clear difference between human clinical isolates and those that may colonize healthy swine.
4. Important oral therapy. While the convenience of oral delivery to outpatients is important, it is unclear as to how this is relevant to ranking drugs used in food animals.
5. Important for treating foodborne infection. This section appears to be the most relevant means to evaluate antibiotics for importance, particularly as it later is used to prioritize the review of currently approved drugs in Appendix C.
6. Drug with unique mechanism of action. The automatic exclusion of drugs with unique mechanisms of action invokes the Precautionary Principle. This exclusion becomes a disincentive to novel drug discovery and development efforts for animal health products.
7. Cross resistance within drug class. The cross-resistance default to the highest category within-class agent should not be automatic. While cross-resistance can occur, strict application of this factor would place practically every antibiotic into the High category, in effect, making it a key component for Importance Ranking. This is somewhat redundant and tends to artificially inflate the value of the overall Risk Estimate process since it will affect the evaluations made in both Release and Consequence Assessment components. The Importance ranking should be used just once in the overall estimation, not twice.

8. Cross resistance across drug classes. The cross-resistance (co-resistance) default to the highest across-class ranking should also not be automatic. Other selection pressures can be operative, but unknown, and thus mistakenly attributed to the presence of a second antibiotic (Heinemann). As above, the High category could be easily assigned to most drugs, once multiply resistant bacteria are identified.
9. No comment.
10. Cross-resistance between drugs used in animals and drugs used in humans. This was essentially addressed in Factors 5 and 7 and is redundant.

Table A1 needs to be fully justified as to why an “X” was placed in each box and the final determination of importance made for the entire class. Emphasis should be on food-borne zoonotic pathogens only and not take into account antibiotic use against infections not associated with food animal origin. It would be beneficial to state that polyether ionophores, arsenicals and other non-human use antimicrobial agents are outside the scope of Appendix A, or they might be re-listed in a new separate Category, Negligible, as we are proposing.

3. Assessment Ranking and Risk Categorization

The Qualitative Risk Assessment process used by other regions may offer alternative approaches worthy of consideration. For example, the CVM prefers the use of 3 X 3 matrix boxes and a High, Medium, Low categorization to drive the process. The Australian NRA and OIE qualitative risk assessment guidelines both include a category of negligible, in addition to High, Medium and Low. The inclusion of a category of negligible should be explored because it offers the advantage of more closely describing a particular assessment component's effect, thereby removing the potential for developing an overly precautionary and conservative outcome. Inclusion of this fourth category offers many additional opportunities for assessment and risk management. For example, categorization of drugs important to human health could be more closely aligned to how animal health products might actually relate to them (e.g. ionophores and topical-use or non-human use agents would be Negligible, older drugs like tetracycline and some B-lactams would be Low, drugs used for food-borne disease treatment of multiple zoonotic pathogens might be Medium to High Exposure Assessment would benefit from application of this category since Zero Tolerance for listeria and *E. coli* O157 are strictly enforced by the USDA, and pasteurization of milk and other products effectively lowers exposure to milk-borne contaminants, making exposure to these bacteria “negligible.” Risk Management options could be adjusted to re-label the proposed Category 3 as Category 4 (Negligible). Category 2 could be split into a Medium Category (as it is currently proposed) and a new Category 3 (Low) that would allow OTC use and High extent of use options.

An additional factor included in the NRA assessment is a section on the benefits to animal health from the use of the product as well as those groups that bear the risk. For example, the concept of a “drug of last resort,” so frequently mentioned in the human medical area, might

just as easily apply to veterinary medicine. Specific applications of this factor would need to be worked out in terms of Guidance 152 considerations.

The VICH Expert Working Group on Antimicrobial Resistance has advanced guidelines that are incorporated to a certain extent within the release assessment. The main focus of the proposed guidelines is food-borne pathogens. It would be advisable to construct the guidance document with the expectation that the VICH process will provide specific details to enable a sponsor to develop the type of information that can be used on a global basis.

4. Exposure assessment

a. General Comments

AHI supports CVM's recognition that food-borne routes of exposure are more relevant than other routes. Even this pathway is, however, exceedingly complex given the commercial production systems operative in the U.S. and the great variety of foods of animal origin available to consumers.

Accurately assessing exposure to consumers from food-borne pathogens is of great importance in arriving at an accurate risk potential estimate. The document attempts to simplify exposure assessment by using per capita consumption of specific commodities and USDA/FSIS estimates of the percentage of carcasses contaminated with specific food-borne pathogens. The problem with such an approach is that it assumes that all meat or poultry products presented to consumers are of equal risk potential. Food safety risk assessors have outlined the complexity of the exposure assessment and provided approaches to address it (Lammerding).

Relying only on per capita consumption fails to consider that a large percentage of raw meat and poultry is further processed (cooked, cured) before reaching the consuming public. USDA estimates that about 50% of all chicken is further processed before being distributed to supermarkets or restaurants (USDA NASS 2002). Proper processing and cooking effectively destroys food-borne bacteria such as Salmonella, Campylobacter, *E.coli*, and enterococcus, therefore presenting a near-zero risk to consumers from susceptible or resistant bacteria.

At the October 2nd CVM public meeting, the agency explained that the reason per capita consumption and carcass contamination data were used for the assessment of exposure was that "good data" were available. Unfortunately, the assumption that risk exposure is a direct product of these two factors is flawed, therefore erroneous conclusions will result. A clear example of this error is revealed by the exposure risk associated with pork. According to the draft Guidance for Industry #152, per capita pork consumption and swine carcass campylobacter contamination rates are High (Tables B1 and B3). Consequently, the probability of human exposure to campylobacter in pork is considered to be High (Table B4). This conclusion contradicts epidemiological studies, which do not find a significant association between pork consumption and enteric illness (Harris et al., 1986; Altekruse et al., 1998). In fact, the FDA's sister agency (CDC) within the Department of Health and Human Services does not consider pork consumption to be an important risk factor for campylobacter infection (Altekruse et al., 1998;

CDC, 2002). The reason for the disconnect between risk determined as the product of consumption by contamination versus risk as assessed by epidemiologic study is unknown. The former does not account for the relative level of carcass contamination, the more thorough food handling practices used for the preparation of pork, and the known presence of non-pathogenic strains in livestock and meat samples (Sarwari et al., 2001). The net effect is an overestimation of the exposure to campylobacter from pork and a higher ranking than is warranted.

The CVM approach also fails to consider dose-response information that can further characterize human exposure. Simply relying on percentages of carcasses contaminated does not take into account the actual number of colony forming units (cfu) of bacteria on the carcass, which in general is exceedingly low for USDA inspected and passed products. The CVM approach assumes that even 1 cfu is an infective dose for food-borne pathogens when, in fact, studies have shown that the infective dose is likely several hundred to thousands of times greater. Such assumptions also have the effect of overestimating actual exposure and skewing the final assessment in the direction of high overall risk. The National Academy of Sciences clearly defines dose response assessment as a key element of risk assessment (Risk Assessment in the Federal Government: Managing the Process 1983). In its effort to simplify the process we feel CVM has overlooked important criteria that are critical in truly understanding the real risk. We believe FDA/CVM needs to adhere to these principles in order to arrive at an accurate assessment of the risk from using an antimicrobial in food animals.

b. Specific Comments

An apparent contradiction is noted in the boxed section on page 16 of GFI #152 that focuses the Exposure Assessment on the ingestion of animal-derived foods as opposed to the Release Assessment that stops at the time food animals are presented for slaughter. At the time of presentation for slaughter, the edible tissues of the animal are considered sterile; only the hide, feathers or intestinal/coloacal contents have viable bacteria. Indeed, lairage of commingled animals prior to slaughter can result in the exchange of various bacteria among animals (Small). Through inadvertent contamination during slaughter and processing, the meat can be exposed to these bacteria, or other bacteria from within the processing plant itself. In some cases, post-processing interventions and storage conditions will reduce the bacterial load (e.g., forced cooling at low humidity), whereas in others they may actually increase the level of cross-contamination (e.g., the chill tanks). Thus, the actual amount of bacteria on a food of animal origin will vary depending on many factors outside the immediate control of CVM or the drug sponsor, as noted on Page 17, and may even vary depending upon such factors as when in the processing scheme a carcass is sampled or the microbiological methods used for detection. Nevertheless, the CVM has chosen to “assume that the probability that bacteria *in the animal at slaughter* will be resistant may be used as an estimate of the probability that the same bacterial species would be resistant *in the food commodity* derived from that animal” (page 17-18).

Appendix B provides tables that are meant to guide an evaluation of the amount of meat consumed, its likelihood of having bacterial contamination, and the likely percentage of those bacteria that are antibiotic resistant. AHI has a number of concerns regarding this evaluation process, as follows:

- The proposed qualitative ranking system in Table B1 is naturally biased toward ranking beef, pork and chicken as High for consumption, making table B4 essentially limited to an outcome of High or Medium with respect to probability of human exposure from these commodities (since even a Low probability of food commodity contamination will not change the final outcome). Inserting this ranking back into Table 2 (page 18), using the High column, results in a High or Medium outcome, no matter what the probability that bacteria of interest are resistant (from the Release Assessment). This outcome is improperly skewed toward the High or Medium outcomes, based on several flawed assumptions (noted above for p. 17-18).
- Tables B2 and B3 provide USDA FSIS baseline meat contamination prevalences that have been arbitrarily ranked into Low, Medium or High by CVM. The CVM has overlooked the fact that >85% of all-sized establishments sampled were in compliance with (i.e. passed) the USDA salmonella safety criteria for “A” sets in 2001. Looking only at large establishments, the percentage of sample sets that passed the criteria was even greater. If the establishments are in compliance with USDA criteria for salmonella contamination, then it becomes incumbent upon CVM to explain how the meat contamination prevalence can be considered contaminated at High or Medium levels.
- Other surveys provide different estimates of meat contamination based on sampling at the point of retail sale and could provide a local exposure assessment baseline. For example, a recent survey of retail poultry and meats in the Washington, D.C. area revealed that only 1.7% of pork samples tested positive for *Campylobacter* (Zhao). Similarly, a year-long weekly survey of retail meat samples in Iowa found only 2/167 (1.2%) pork samples positive for this pathogen (Carter). Nevertheless, Table B3 assigns a qualitative ranking of High to *Campylobacter* contamination of market hogs, based on slaughter data, as an indicator of potential human exposure to this pathogen from pork consumption. Clearly there is the likelihood of a significant overestimation of potential exposure that derives from use of the slaughter data.
- No particular attention appears to have been paid with respect to the wide variety of serovars, biotypes, clones, or species, of salmonella or campylobacter. By narrowing the focus of the assessment appropriately, a more accurate representation of the exposure can be obtained. An example of how this might be done is provided in an examination of *Salmonella* DT104 in retail ground beef (Zhao, 2002). This study also points out that national trends can be highly skewed by local “hot spots.”
- Table B4 does not provide the opportunity to account for cooking and processing effects that minimize or eliminate bacterial contamination. Indeed, most food-borne risk assessments incorporate this critical control point as well as an estimate of infectious dose (Cassin, Buchanan, Walls, Oscar).

- Appendix B does not contain prevalence contamination rates for the commensal enterococci. There is no USDA baseline survey available for this bacterium that is comparable to the salmonella, *E. coil*, or campylobacter criteria. Thus, it is unknown how a sponsor is to obtain this kind of national data. Neither does there appear to be any indication of food-borne disease rates associated with this microorganism (Mead). This omission of baseline data reinforces the contention that this commensal bacteria should not be included within the risk assessment.

Dr. Craig Hedburg, at the Pork Quality and Safety Summit meeting in June 2002, used CDC data to evaluate the role of pork as a vehicle for confirmed food-borne disease outbreaks in the U.S. from 1990-1997. Only 4% of 1,692 outbreaks with a known etiology were due to pork or pork-containing foods. Pork was calculated to be associated with 3% of all confirmed salmonella outbreaks and was associated with just 2% of the total number of campylobacter infections reported. These CDC numbers, if inserted into the Exposure/Consequence assessment sections, would give an entirely different interpretation than do the proposed values.

5. Risk Management Options

a. General Comments

According to Table 5 of this guidance, all new claims for Medium (Category 2) risk products would be restricted to Low to Medium extent of use, thereby eliminating any use of an antimicrobial in feed for flocks or herds for longer than twenty-one days, or as an OTC product. We believe that extent of use has no direct connection to risk management for food-borne illness, and therefore should not be a prime determinant of risk management. Moreover we note that extent of use is already included as a factor to consider in the release assessment under (h) on page 14. Applying extent of use under risk management as well will result in a double jeopardy and an overly conservative approach. CVM must re-evaluate this issue, so that artificial restrictions are not imposed on products such as feed additives that might be used for more than 21 days.

Since it is now extremely unlikely that a totally novel antibacterial agent would first be introduced into veterinary medicine rather than human medicine, the decision to engage in the development of a new analog in an existing class would require a company to determine the likelihood of success. Part of this determination would be to look at the antibiotic class, dose, and duration of treatment needed for efficacy. Risk management limitations described in Table 5 for Category 1 and 2 will have the effect of specifying *a priori* the duration of treatment and the type of populations of animals that can be medicated, potentially eliminating the development of alternative treatments before they even leave the discussion phase within a company.

The categorization combined with the risk estimation of Table 3 does not appear to reflect true resistance concerns nor does it differentiate products to any extent; essentially everything falls into the medium exposure category. For example, a novel antimicrobial class with no human use might be presented for development as a treatment of mycoplasma infection in poultry. Assume that it readily selects for resistance to itself in campylobacter, which equates

to “high” for the release assessment. From Appendix B, one concludes that poultry are “high” for the exposure assessment for both campylobacter and salmonella. Since this is a novel agent, it would automatically be placed in the “high” category for consequence assessment. Therefore, the overall risk estimation would be high. In Section VI of the guidance, the agency indicates that a high risk estimation would be treated as a Category 1 drug. In Table 5, the extent of use for a Category 1 drug is restricted to low extent of use. In practice, poultry can only be treated as a flock, which according to Table 4 equates to high extent of use. Therefore, the guidance indicates that a drug such as this might not be approved, even though there would be no human health consequence if resistance to it were to become widespread in human isolates of campylobacter. This type of guidance gives industry little incentive to develop drugs that are not important in human medicine, thus we question its relevance for protecting human health.

As noted above, the Release Assessment is likely to result in a ranking of Medium to High for most antibiotics, and the Exposure Assessment (as proposed), will also most likely result in a High ranking. Thus, the sponsor’s Risk Estimate scenario will be artificially forced toward Category 1. The consequences for existing products to comply with the Risk Management options given for this category are severe, as noted elsewhere, and will fundamentally cause a change in the manner in which veterinary medicine is practiced as well as compromising animal health.

b. Specific Comments

Duration of use has been arbitrarily categorized on the basis of days of administration. However, no justification has been provided in the draft guidance, or prior workshops, to show that duration of use result in different prevalences of antibiotic resistant enteric bacteria. The ‘Duration of use’ assumption (Table 4, p.25 of the Guidance) assigning an implicit ‘high’ risk category at applications of >21 days, is questionable. For example, an empirical study of longer duration application was reported by the UK Veterinary Laboratories Agency (Ridley, A.M. et al 2002. Abstr. 42nd InterSci. Conf. Antimicrob. Agents Chemother., abstr. C2-120). A generic chick model applied an oral gavage of 5 representative types of bacteria to day old chicks along with 3 growth promoting/antimicrobial agents and followed the resistance (as well as PFGE patterns to confirm strain identity) over a 5 week (=35 day) duration. Administration of the growth enhancing agents according to the manufacturer’s recommended dosing levels showed no increase in MIC of recovered isolates in this model. Given the results of this and numerous sponsor studies demonstrating lack of increase of MIC, the assumption that longer duration applications are inherently more hazardous remains an unproven (yet popularly reported) axiom, and needs to be addressed on a case-by-case rather than broadly applied basis. Some studies in fact point to examples of *declines* in prevalence of resistant bacteria due to some growth promoting agent applications (flavophospholipols) (Van den Bogaard, et al). If this is the case, the agency should include these favorable studies in assigning risk as a function of duration of use. The idea of including favorable combinations aimed at reducing resistance development over longer durations could also be considered as a management option instead of relying solely on restrictions.

The application of the VFD for feed additives ranked in Category 2 should be further explored, particularly with regard to the practicality of implementation on a national scale for many additional products and the anticipated positive consequences on resistant enteric bacteria prevalence (e.g. reduced prevalence of antibiotic resistant bacteria). No matter whether the feed additive product is used per VFD or OTC, the fact that it is used at all will result in the selection of antibiotic resistant bacteria, which may or may not impact human health.

Similar concerns are raised for Category 1. The key constraints on products are that they can only be used <6 days, for individual animals, and under prescription (not VFD). This effectively eliminates the oral routes of feed and water administration that are necessary to maintain herd or flock health. The ultimate effect will be to eliminate water soluble product use (or consideration for development) in swine and poultry for products in Category 1.

6. Consequence assessment and reasonable certainty of no harm standard

a. General Comments

The document provides little guidance to companies as to how CVM will make the final determination of safety based on the standard continually referred to as "reasonable certainty of no harm." It is evident that a company could conduct the qualitative risk assessment proposed here, categorize their product, apply risk management restrictions suggested in the document, and still not be in position to know whether or not the product is approvable. While the guidance proposes to assess the risk, it appears that a "second" risk assessment on top of the proposed scheme is necessary to determine whether or not the product meets the stated standard. The agency has not provided any criteria on how this "second" assessment will be conducted for determining safety from antimicrobial effects. Some have gone so far as to suggest the standard should be zero risk, which is clearly an impossible standard to meet. It appears, based on actions CVM has taken over the last several years, that the standard has been determined on an *ad hoc* basis. The agency's rationale has not been transparent. While we accept that FDA must have flexibility in decision-making, it is also vitally important that FDA provide its criteria, possibly in the way of a decision tree, as to how they will go about determining that the product is or is not safe.

The Consequence Assessment on page 19, Section C, appears to suggest that Appendix A be checked to find the drug of interest and the associated ranking for it. In essence, the consequence assessment makes no attempt to consider any sort of human disease consequence from resistance! It is clear that for the 10 factors described in the ranking scheme in Appendix A none has factored in the human medical impact from resistance, only whether the antibiotic may be used to treat food-borne disease or not, or is medically important for some reason other than treatment of a food-borne disease. This oversimplification does not provide the necessary basis for assessment and is an inappropriate application of Consequence Assessment in the Risk Assessment process. The CVM should provide information or references related to treatment failures of antibiotic resistant foodborne bacteria. If CVM cannot direct the sponsor to such information or if it is not available, then perhaps the issue of antibiotic resistant food-borne disease is not as much of a problem as stated.

b. Specific Comments

Attribution of “harm” as indicated by morbidity or mortality above some baseline norm is difficult to determine. Even within the human medical community, there is disagreement on whether drug resistance affects treatment outcomes (Bishai, Amsden, Garbutt). There must be some measurable human health consequence, not merely a potential one.

7. Consequences of application of draft guidance document

a. General Comments

According to the draft guidance, proposed changes to an existing approval may trigger a re-examination of an animal antimicrobial based on the new criteria. While sponsors have always lived with the possibility of FDA re-opening their NADA when a significant supplement is proposed, there is now another area of uncertainty for a sponsor in deciding on whether or not to pursue product enhancements. This process will serve as a further deterrent to the drug sponsor to seek the addition of new claims to existing products, which may be needed to combat critical animal diseases. Clearly it is in the interest of animal and public health to have FDA-approved indications. As it is currently drafted, the guidance would discourage many companies from investing in new indications due to the uncertainty that products that have presented no public health problems could suddenly be placed into an artificially high-risk category, jeopardizing not only the proposed new indication, but the existing claims as well. CVM should reconsider the scope of the approvals that are encompassed within Guidance 152 and provide exclusions for minor label claim additions (e.g. addition of another target pathogen in the same anatomic site of the same animal species, such as the addition of another respiratory disease pathogen to an existing respiratory disease claim).

b. Specific Comments

Appendix A gives an importance ranking for antibiotics that includes both food-borne and non-food-borne disease indications. The ranking is then applied to Appendix C to prioritize the drugs for further review. It is suggested that a separate prioritization list be used that avoids the stigma of associating a High, Medium or Low category to a given class of antibiotics. Further, it might be useful to focus only on salmonella and campylobacter as the two most important food-borne pathogens (Mead). Prioritization could be done on the basis of listing those agents used to treat both salmonella and campylobacter, followed by those used only for salmonella, and then those used only for campylobacter. Prioritizing antibiotics for review based on their utility in human food-borne disease treatment seems to be a more relevant approach than simply using the same ranking in Appendix A. An authoritative guide to antibiotic treatment of bacterial food-borne diseases, for example, the Sanford Guide (Gilbert), might be useful for developing the list. CVM should note that the listing of antibiotics does not necessarily mean that these products do not meet the reasonable certainty of no harm criterion; only that because they are used to treat zoonotic food-borne disease are they prioritized for review according to Guidance 152. CVM should notify sponsors of their preliminary Guidance 152 assessment and

the potential risk management actions that are considered. The sponsor should have the opportunity to respond to the agency to address the findings and the proposed actions.

8. Additional Remarks

a. The CVM alludes to "alternative approaches" that could be used to satisfy the requirements for addressing antimicrobial resistance (page 1 and 6). Additional clarification on what constitutes an acceptable alternative approach would be useful.

b. The CVM makes note of the applicability of Guidance Document #106 that describes the conditions for use of published literature in support of NADAs. The guidance allows for the agency to request raw data and other key pieces of information that may not be contained within the publication. Strict application of this guidance document could, however, undercut the use of valuable information that a drug sponsor could or would not be able to generate independently. This is not to say that any or all reports should be accepted at face value, or that the author's interpretations are valid, but rather to note that the situation of using literature for this section of the submission is different than that for an efficacy section; thus, some reasonable latitude in the allowance of literature use must be maintained.

c. The inclusion of NCCLS document M31-A2, as the recommended methodology for conducting antimicrobial susceptibility testing is more appropriate for target pathogens listed on the product label. The ultimate focus of the qualitative risk assessment is on food-borne bacteria and human medical use of antibiotics, so it is more appropriate to use the NCCLS documents designated for human clinical laboratories.

d. Various portions of the Release Assessment "package" may require sponsors to conduct specific studies to obtain the data; with the default being that the Release Assessment is simply rated High if such information is not provided. Moreover, most of the studies requested appear to have the unstated concept that it is meat, not milk or eggs, or other animal-derived products that need to be evaluated.

e. Page 13, 2d: Zoonotic pathogens and commensal bacteria of animal origin will need to be collected and tested for susceptibility to the test article and (by extension with subsequent requirements) with related compounds for cross- and co-resistance. [It is presumed, but in need of clarification, that the word pathogens refers to zoonotic pathogens and not target animal pathogens which should not be the focus of this Guidance.] While NARMS data may be of some use, it is quite possible that it may not be available from that source, or for the specific animal-use antibiotic in question.

f. Page 13, 2c: Although metabolism studies done in support of residue food safety sections of the dossier might provide some information on pharmacokinetics of the drug, up until now there has been no requirement to determine antimicrobial activity in colonic contents. Unless the sponsor chose to assume that 100% of administered activity was present in the gut, this requirement would require additional studies to be done.

Specific issues are:

- Why are colon contents required instead of feces?
- Why are various treatments required?
- How does CVM recommend that antimicrobial *activity* be determined in colonic (or fecal) material?

Finally, it is not clear what value first-exposure effects (what are these?) or post-antibiotic effects will have for commensal or zoonotic bacteria in terms of the overall evaluation.

g. Page 13, 2f and g: Unless literature citations can be used for known antibiotic classes, it will be costly to develop this kind of information. For novel agents, the elucidation of novel resistance mechanisms is a laborious process.

h. Page 14, 2h: The scope of the risk assessment is mainly limited to the sponsor's own product. Yet there can be multiple within-class antibiotics, or those with cross-resistance that are competitors with the sponsor's product. To what extent can one sponsor be expected to address this aspect? It is entirely possible that the risk assessment could miss the "big picture" in terms of cumulative selection pressure or improperly attribute more "resistance contribution" to one product than another. The CVM should recognize that other selection pressures are exerted besides antibiotics (Heinemann).

i. Page 14, 2i: It should be clarified whether the baseline resistance prevalence data is from the actual veterinary use candidate or the human counterpart analog that would be used in human medicine. Additionally, it is not clear whether human or food animal (or both sources) bacteria are to be tested in developing a baseline. The guidance document states in the next section that information is of most interest from the time animals are presented for slaughter, a condition that is not met by much of the NARMS database. It would seem that a common panel of NARMS isolates might be made available to sponsors to conduct baseline testing, thus ensuring consistency of isolate origin.

j. Page 14, 2j: Additional clarification is needed on "rate of resistance development and decline after treatment" and "bacteria of human health concern". How does this differ from section g (mutation frequency) and e (post-antibiotic effect)?

It would appear that an animal "microbiological withdrawal study" is considered as relevant to addressing these issues. There are no validated procedures for conducting and interpreting such studies. One component of "558.15" pathogen load studies, which were concluded as non-predictive by the VMAC in January 2002, was a coliform resistance study. Yet, it appears that CVM is retaining that very concept by suggesting the need for an animal study to evaluate this issue. In essence there could be a need to conduct multiple such studies, each done for different "bacteria of human health concern," which may not even be present in

sufficient quantities in the animals selected for testing. AHI strongly recommends that this requirement be deleted.

k. There is no evidence that in vitro studies to evaluate resistance development or transfer will predict what will happen from the standpoint of resistance development in vivo. In the miraclemycin scenario that was presented at the Public Meeting on October 2, antimicrobial characteristics that would be predictive of a low rate of resistance emergence were defined, e.g., chromosomal-based resistance. Classes of antimicrobial drugs with similar traits exist, and in some cases resistance has emerged readily, theoretically jeopardizing the continued use of the antimicrobial. After investing a great deal of effort, manufacturers and producers will still be faced with the likely prospect of product withdrawals in these cases.

Concluding Remarks

AHI would welcome the opportunity to participate in workshops to further understand and refine the qualitative risk assessment process and the type of data that CVM will need to make decisions on each of the components of the risk assessment. A collaborative effort between the regulated industry and the regulators is important so the process is transparent and the most informed decision is made with regard to food animal antibiotics.

Sincerely,

A handwritten signature in cursive script, appearing to read "Richard A. Carnevale".

Richard A. Carnevale, VMD

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