

November 26, 2002

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

Re: Comments to FDA Docket No. 98D-1146, Draft Guidance for Industry #152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”

Phibro Animal Health provides these comments on CVM draft guidance document #152 to assess the microbiological safety of antimicrobial agents used in food producing animals. Phibro Animal Health is an international manufacturer and distributor of animal health feed additive products. Phibro Animal Health welcomes this draft guidance and appreciates the progress that the FDA/CVM has made in approaching this problem on the basis of risk assessment.

As a member company of AHI, Phibro Animal Health endorses comments made by AHI on guidance document #152. Phibro Animal Health specifically endorses AHI’s overall conclusions and recommendations:

- 1. 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.*
- 2. AHI suggests CVM consider including a fourth probability ranking and categorization element called “negligible” to more closely describe those drugs and uses which are essentially of no risk to human health.*
- 3. 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.*
- 4. 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 was not related to a human antibiotic.*
- 5. 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.*

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6. *The current guidance will serve as a disincentive for companies to supplement current antibacterial applications to add important new disease indications.*

In addition to our endorsement of the AHI comments, Phibro Animal Health has the following comments on draft guidance document #152.

Resistance Determinants and Transfer

As outlined in the AHI comments, 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*). 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). Phibro Animal Health is concerned that *in vitro* models to generate such data do not truly assess the potential for *in vivo* transfer of resistance determinants, and that suitable *in vivo* models do not exist. In addition, based on the current list (Appendix A) of antibiotics “important to human health”, and the bacteria against which these antibiotics are effective, it would appear that numerous studies would have to be conducted to prove that transfer of resistance determinants does not occur between bacterial species. However, the limited data available on *in vivo* transfer of resistance suggests that even the same enteric bacterial species taken from different hosts do not readily transfer resistance determinants. 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 in the close confines of the GI tract (Sorenson).

The potential for *in vivo* transfer of resistance is theoretical and speculative and is not well supported by the literature. However, CVM has apparently accepted this hypothesis as significant, and requests in guidance document #152 that drug sponsors demonstrate that transfer does *not* happen. Phibro Animal Health believes that this would be near impossible, and thus, in the absence of evidence to the contrary, an assignment of “High” will almost always be necessary.

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

As it stands now the ranking and categorization schemes in the document will overestimate the potential risk of many compounds and uses, and, as mentioned in AHI’s comments, this is one of the most troubling aspects of the draft guidance. 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. Many of the antibiotics listed in Appendix A are prescribed for the treatment of respiratory diseases, while CVM has stressed in draft guidance #152 that exposure via the food pathway is the main concern of the agency. What is the connection between antibiotic use in animals, exposure of humans to enteric organisms (resistant or not) via the food pathway, and the potential lack of effectiveness of an antibiotic (due to resistance issues) when used against a respiratory disease?

Phibro Animal Health believes that CVM needs to re-consider these rankings and base them on evidence of a clear association with animal use and not on speculation. Absent such evidence we believe, for the purposes of this document, that only those antimicrobials used in the treatment of a foodborne disease should be classified as of high importance relative to animal uses. In addition, since there is no indication of food-borne disease rates associated with commensal bacteria such as *E. coli* and enterococci (Mead), until more definitive information is available on resistance gene transfer, these microorganisms and their associated human use antibiotics should not be listed in Appendix A as of high importance.

Phibro Animal Health is particularly concerned about reference made to linezolid and streptogramins (dalfopristin/quinupristin) as sole-use agents for VRE infections, and the resulting high-importance ranking on both of these products. How can two distinct products/antibiotic categories be listed as “sole-use”? In addition, due to its narrow spectrum of activity (effective only against *E. faecium* but not *E. faecalis*), its mode of administration (I.V.), and its lack of tolerance in patients, dalfopristin/quinupristin has already become poorly accepted by the medical community (as evidenced by drop in sales as reported by Aventis; in its 2002 annual report, Aventis lists its dalfopristin/quinupristin product Synercid as “no longer reported as strategic product”). Yet dalfopristin/quinupristin is listed as a high-importance human antibiotic in Appendix A of draft guidance #152, which would result in a similar ranking for virginiamycin, a streptogramin used in animals.

Phibro Animal Health believes that Table A1 needs to be made more transparent, i.e. fully justified as to how an “X” was placed in each box and the final determination of importance made for the entire class. Using the example above, why were streptogramins ranked high while they are not considered sole therapy (in the table, although they were on page 32), are not orally active, and in reality are not used to any great extent due to poor tolerance in patients? If the final guidance document contains similar rankings as currently listed in Appendix A, we believe that most, if not all, antibiotics used in animal health will receive a medium or high importance ranking.

Assessment Ranking and Risk Categorization

Phibro Animal Health believes that the use of many animal health products will have no or negligible impact on usefulness of human health antibiotics. If, for example, an antibiotic used in animals is shown to cause resistant organisms in animals, but these organisms are shown not to colonize in man (as in the Sorensen example cited above), then the net effect of the antibiotic use in animals would be negligible on the impact on human health (regardless of the importance to the same or a similar antibiotic in human health). A negligible ranking in any category would then result in low potential for harm (i.e. if an animal antibiotic doesn't cause resistant bacteria in the animal **or** if resistant bacteria in the animal are not transferred to man **or** if there are no important uses of the same class of antibiotic in man, then the use of the antibiotic in animals will have no or negligible impact on human health). Yet, CVM prefers the use of 3 X 3 matrix boxes and a High, Medium, Low categorization to drive the process, which excludes the possibility of a negligible ranking. In addition, as shown in Table 3, use of the 3 X 3 matrix will almost always result in an overall risk estimation of medium or high. And in fact, if a sponsor is unable to conduct resistance transfer studies as discussed above, and accepts the high ranking in this category, then an overall risk estimation of low is impossible. Even if resistance transfer studies are conducted and demonstrate a low risk of transfer, antibiotic rankings in Appendix A assure that virtually all

antibiotics of importance to animal health will be ranked at least medium in the overall risk estimation. This will have a tremendous impact on risk management options as discussed later.

Phibro Animal Health believes that CVM should include an additional factor in the risk assessment, the benefits to animal health from the use of the product as well as the potential benefits to humans and the environment. For example, virginiamycin use at growth promotion levels is known to help control necrotic enteritis in poultry. In addition, because the poultry are more feed efficient, less excreta is produced when virginiamycin is used. Less excreta means less negative impact of poultry waste on the environment, while less necrotic enteritis means less exposure of humans to potentially harmful bacteria (necrotic enteritis can lead to more gut breakage during processing, resulting in higher potential for contamination of carcasses with salmonella and campylobacter). These known benefits may very well outweigh any theoretical (and as yet unproven) harm due to antibiotic resistance, however, they are not considered in the risk assessment proposed in draft guidance #152.

Exposure assessment

Phibro Animal Health believes that CVM has oversimplified 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 doesn't take important criteria, such as level of contamination and further processing of foodstuffs, into consideration. Simply relying on percentages of carcasses contaminated does not take into account the actual number of colony forming units of bacteria on the carcass, which in general is exceedingly low for USDA inspected and passed products. Based on the scientific literature, these low levels of contamination will not result in illness in humans. In addition, most animal protein is either further processed before it reaches the consumer, or is cooked before it is consumed. 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. However, using per capita consumption values presented in Table B1 will result in medium or high human exposure ranking (Table 2) for the 3 major meat sources (beef, pork and chicken).

Phibro animal Health does not know how to obtain national data on commensal enterococci or *E. coli* as there is no USDA baseline survey available for these bacteria that is comparable to the salmonella or campylobacter criteria. This omission of baseline data reinforces our contention that the commensal bacteria should not be included within the risk assessment.

Risk Management Options

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. Given that it will be impossible for an antibiotic used in cattle, pigs or chickens to have an exposure assessment (based on the current Table B1 and Table 2) of low, and given the "default" ranking of high if resistance determinants transfer cannot be disproven, draft guidance document #152 virtually assures that no new antibiotics will be approved for whole herd or flock treatment. In addition, as proposed in Appendix C, all antibiotics currently approved will eventually be assessed under this

guidance document, and risk management measures will be required. A quick evaluation indicates that virtually all antibiotics currently approved for whole herd or flock disease prevention and control, or growth promotion, will be restricted to low or medium extent of use. In effect, application of guidance document #152 in its current form will effectively “ban” the low-level, long-term use of antibiotics in the US beef, pork and poultry industries.

Consequence assessment and reasonable certainty of no harm standard

Phibro Animal Health does not understand how CVM will make the final determination of safety based on the standard continually referred to as “reasonable certainty of no harm.” Even after following draft guidance document #152, we will still not know whether or not the product is approvable. Even if drug resistance occurs, it is unknown if treatment outcomes will be negatively impacted. There must be some measurable human health consequence, not merely a potential one; otherwise, guidance document #152 is no more than justification for a “precautionary principle”. The consequence assessment should include a component on the likelihood that bacteria (from meat) will colonize in the human and subsequently cause some type of illness. In addition, Table 3 lists overall risk estimations of medium even in light of low consequence rankings. Even if an animal use antibiotic causes resistance in a bacteria, and even if man is subsequently exposed to this bacteria, if there is no negative consequence, there is no risk.

Consequences of application of draft guidance document

Phibro Animal Health strongly agrees with the AHI statement that the risk assessment process proposed in guidance document #152 will serve as a further deterrent to the drug sponsor to seek the addition of new claims to existing products. Additionally, as it is currently drafted, Phibro Animal Health believes that the guidance would virtually eliminate 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.

Miscellaneous Remarks

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. In addition, CVM should incorporate comments made at the public meeting that results from quantitative risk assessments would outweigh results from following the qualitative risk assessment outlined in guidance document #152.

In section C, page 4, listed are “antimicrobial NADAs for food-producing animals that may not be subject to this guidance”. Phibro Animal Health has specific questions about a few of these:

- Page 5, #3. Would new combinations of “old” (previously approved) antibiotics trigger a risk assessment on the old products?
- Page 5, #4. If a generic sponsor applies for approval against a pioneer product, would a risk assessment on the pioneer product be triggered?

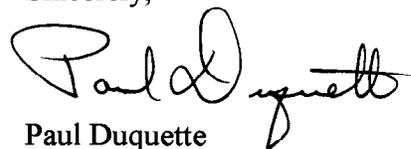
On page 25, #3, CVM states, “In general, it is believed that increasing the extent to which an antimicrobial drug is used will increase selection pressure for resistance.” Taking this argument one step further, products that have been used for many years and have been fed to billions of chickens, such as virginiamycin, would be expected to have already “saturated” the resistance pool due to selection pressure. However, Synercid resistance data collected at the time of its approval (more than 25 years after the introduction of virginiamycin use in animals) indicated 0.2 % resistant *E. faecium*, suggesting that either the general belief on use effects on selection pressure is incorrect, or that resistance in *E. faecium* from animals does not become an *E. faecium* resistance issue in man.

Concluding Remarks

Phibro Animal Health believes that CVM should seriously consider the consequences of finalization of guidance document in its current form. We believe that the document could virtually eliminate any research on future antimicrobials for animal use, and also eliminate many of the products currently on the market.

Risk assessment should take into account the benefit of the products being assessed. Antimicrobials have been used in animals in the US for 30 years, helping the US to be a leader in production of a safe and adequate food supply. In addition, these products are beneficial to the environment (in decreasing the feed requirements of the animals, decreasing the excreta, decreasing the number of carcasses of diseased animals, etc.) and have many unrecognized advantages. For example, the EU wholesale ban of growth promotants resulted in an unexpected consequence in increased necrotic enteritis in poultry. Increased necrotic enteritis results in more gut breakage during processing, which can result in a higher level of carcass contamination, and more exposure of man to bacteria on the carcasses. Thus, CVM must weigh these known benefits against an as yet unproven potential risk of antibiotic resistance.

Sincerely,

A handwritten signature in black ink that reads "Paul Duquette". The signature is written in a cursive style with a large, looped initial "P".

Paul Duquette
Director, Global Regulatory Affairs

Literature Cited

Mead, PS, LS Slutsker, V Dietz, et al. 1999. Food-related illness and death in the United States. *Emerg Infect Dis* 5:607-625.

Sorenson, TL, M Blom,, DL Monnet, et al. 2001. Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. *N Engl J Med*. 345:1161-1166.