



Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone (616) 833-4000

ANIMAL HEALTH
John W. Hallberg, D.V.M., Ph.D.
Director, U.S. Regulatory Affairs
9691-190-43
Kalamazoo, MI 49001-0199
Telephone: (269) 833-2482
Facsimile: (269) 833-2707
john.w.hallberg@pharmacia.com

13 December 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Re: Comments to FDA Docket No. 98D-1146, Draft Guidance for Industry #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"

Dear Dockets Manager:

The purpose of this document is to provide Pharmacia and Upjohn (P&U) Animal Health comments on or related to FDA Docket No. 98D-1146, Draft Guidance for Industry #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" for the Agency's review and comment.

P&U strongly supports the adoption of a risk-based assessment process to evaluate the possible human health impact from the use of antimicrobial drugs in food-producing animals. The risk-based assessment proposed by CVM in its Draft Guidance #152 is a major step forward. However, we do have some comments as itemized below and also support the comments by the Animal Health Institute, submitted previously to Docket No. 98D-1146.

General Comments:

As acknowledged by CVM in its draft Guidance document #152, the process of how resistance determinants are selected and transferred within and between the bacterial ecosystems of animals, plants and humans is highly complex and not well characterized. P&U believes that risk of transmission of antimicrobial resistant food borne pathogens is the most relevant component with regard to evaluating the risk(s) posed to human health from food-producing animals. However, flexibility is needed to design and conduct such a risk assessment and we endorse CVM's perspective in the Guidance that a sponsor can demonstrate the safety of its proposed product in other ways besides that proposed in Guidance 152.

98D-1146

C84

1. **State of Knowledge:** There are several areas where the state of knowledge is found substantially lacking and this has led to the use of conservative assumptions and speculations by CVM, many of which are oversimplified and may not have a database for support. As a consequence, there is a built-in tendency for overestimation of risk to human health. This is a major concern that clearly can have a negative impact on the animal health industry's investment in research and development regarding the safety of product line extensions of antimicrobials. Therefore, we encourage the Agency to suggest extensive use of pre-submission conferences with sponsors early in the drug development process to clarify the information needed to satisfy drug safety requirements for the potential approval of either a new chemical entity or new indication for an approved antimicrobial. Pre-submission conferencing will assist the sponsor in obtaining both appropriate estimates of the drug's perceived risk, and the cost and time for product development.
2. **Reasonable Certainty of No Harm:** The guidance should provide more clarity for the scientific rationale to be used to establish a "reasonable certainty of no harm" standard in this risk assessment. This is not explained currently in the document.
3. **Categorization:** The rankings (H,M,L) for release, exposure, and for categorization assessments are so broad that, in fact, there is little discriminatory power of the overall risk estimation for special cases. Examples are provided below within the commentary on each of the separate risk assessments.

Comments on Document 'Scope'

1. The provision in the scope of the document addressing certain supplemental NADA's (Category II) is difficult to interpret. It appears that Category II supplements will require a risk assessment regarding resistance emergence. Will the risk assessment need to address the original NADA as well as the supplement? If yes, this could be a major deterrent for sponsors to apply for product label extension. This could result in a broader (undesirable) consequence of less research to identify appropriate dose regimens of existing antimicrobials for treatment of infectious diseases in animals for which treatment options are limited or non-existent, thereby encouraging more extra-label use of existing drugs.
2. In the draft Guidance, CVM notes: "Microbial safety information is usually not needed for abbreviated new animal drug applications (ANADAs) for generic antimicrobial drugs but may be needed for supplemental applications seeking innovative extensions to the conditions of use for the approved pioneer product." P&U asks CVM to reconsider this statement, as the approval of a generic copy of any existing product may increase compound use in the same manner that a new supplemental approval for a new claim. CVM should insure that strict control over all extra-label promotion of generic copies to ensure only "label" approved use of these compounds and decrease

the likelihood that extra label use becomes potentially a means for increasing use of generic product in unapproved claims.

Comments on 'Risk Analysis Methodology'

1. For consistency with the definition given on page 11 for "boundaries of the release assessment", Figure 1 on page 7 should specify "at slaughter or when animal-derived food is collected" within the box to the right of the 'Release Assessment' box.
2. On page 8, CVM cites the requirements for data sources and data quality as it has been recently finalized in Guidance # 106. Is this standard applicable to the data used to generate the exposure assessment tables (Appendix B)? Data supporting any exposure assessment tables in Guidance #152 should meet the same standards drug sponsors are required to meet.

Comments on 'Release Assessment'

1. Given the information databases available and the state of the science at the time of the application, and also in terms of what can be accomplished, the Guidance Document should provide more clarity regarding what microbiological endpoint(s) should be examined for safety evaluations.

In some cases the Guidance document refers to safety with respect to acquisition of resistance determinants *per se* and in other cases the document refers to resistance in specific food borne pathogens (e.g., *Salmonella* and *Campylobacter*). P&U acknowledges that it is possible for resistance determinants to emerge in bacterial ecosystems associated with animals, and to be transferred to bacteria associated with man (and vice versa) via many different routes, including food. However, it is clear that methodologies to quantify or qualify the risk of this occurrence are not developed (see "Research Needs" as recently outlined by the Academy of Microbiology [1]). Therefore, it is unrealistic to expect that even a qualitative risk assessment of potential exchange between animals and man can be developed with any accuracy or precision. If this were possible the Guidance Document should provide exposure tables for such an assessment. This is not the case, as evidenced by the exposure Tables provided only for *Salmonella* and *Campylobacter*. There are no national databases examining resistance determinants *per se* in food-animals or slaughter meats consistent with Guidance #106. There should be explicit recognition in the current version of the Guidance document that the technology is not available to quantify or qualify this risk of gene transfer between man and animals. To imply in the document that an assessment of gene transfer must be an inherent component of the overall risk assessment, or that the data gap regarding gene transfer from animals to man be filled, is unwarranted and opens up the possibility of the risk assessment to be based on speculation and not on a sufficiently robust, verifiable database.

2. The rankings (H,M,L) for release assessment do not allow for special cases. For example, if the drug is effectively not present in the gastro-intestinal tract of the treated animal (e.g., due to metabolism or lack of bioavailability), then it is reasonable that a "negligible" category ranking should be applicable. The inclusion of a "negligible" ranking at release would enable a fourth (very low) overall estimation of risk.
3. With regard to MIC testing, it is appropriate to use resistance breakpoints established for human medicine, not animal medicine (suggested on page 10 of the Guidance), since the question is whether the use of the antimicrobial in food animals affects human health and safety. NCCLS breakpoints established in veterinary medicine (and as cited in the NCCLS M37-A2 document) are based in part on efficacy of the drug for use in animals, not humans.
4. The extent-of-use evaluation is an integral component of the release assessment (page 14). It should not be re-evaluated a second time or considered alone in context of risk management (Page 25, Table 4 and Table 5 page 27). Extent of use should be examined only in the Release assessment, so that herd and flock administrations can be evaluated in context of key characteristics of the specific drug application, and not as a general basis for approval. For example, some drugs may be inactivated as a result of animal metabolism. Therefore whole herd or flock treatments should not be viewed as inherently providing an additional risk, even if the overall risk estimation was, for example, "Medium" (Category II). As currently written, by evaluating "extent of use" in terms of management options, it appears that the only drug approvals that would be available for treatment of poultry would be "Category III" drugs, since in modern poultry production practices, treatment occurs only by flock.
5. The term "first exposure effects" (page 13) is not defined, and should be included in the glossary. We are not familiar with this term, or the intent of this statement.
6. The relevance of determining the rate of resistance transfer is not clear. What parameters are to be measured, and under what conditions? In a test tube? In an animal? On the farm? What methodologies should be applied and what justification can be found that the methodologies and resulting rate data are predictive of resistance transfer from animals to man? Are there any models estimating rate of transfer that are applicable to prediction of resistance emergence in food animals? While it may be useful to review the pathways of potential gene exchange among bacteria qualitatively, we believe that at this time the technology is not available to estimate either the rate of transfer or rate of mutation in a manner or model that is predictive to addressing resistance emergence rates in the animal population at large.

7. P&U believes that the requirement for information regarding rate of resistance transfer may promote non-data based speculation, since the topic is so complex and the predictive value of monitoring resistance emergence *in vitro* among bacteria, or *in vivo* in animal models is unknown. This basic conclusion was reached at the end of extensive discussions in the CVM Public Workshop held 22-24 February 2000 addressing *in vivo* and *in vitro* models to estimate the rate of resistance emergence.
8. The release assessment is intended to estimate the "probability that factors related to the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the animal." The probability is assessed in a qualitative way as low, medium or high. However, the basis for these probability classifications is not clear. If a quantitative risk assessment were feasible and resulted in a numerical probability, then there should be some definition of what probability values result in low, medium or high release assessments. Although a quantitative assessment is generally a refinement of a qualitative assessment (i.e., the quantitative assessment results in a more precise estimate of the risk), both should be accurate to the limits of the qualitative scale. Therefore, it is necessary to be transparent in the meaning of the qualitative rankings. Table 1 of the Guidance lists "relevant parameters" for the release assessment, but it is not transparent how, for example, the mechanism of activity and spectrum of activity can be combined with other parameters to be translated into in any semi-quantitative summary of risk ranking for the release assessment. Knowing what the qualitative scale corresponds to quantitatively, and how the components of the assessment are summarized to "high, medium and low" needs fuller explanation.

Comments on 'Exposure assessment'

1. We strongly suggest that an additional public workshop on exposure should be convened to enable additional peer review and refinement of this part of the document. Further dialog is needed with stakeholders to assist in developing the methodology for determining the ranking mechanism. There should be further dialog from the public regarding each food commodity and its relative contribution to human exposure. Following input from a public workshop, the Agency may revise the Guidance to better reflect the current "best thinking" regarding the ranking of exposure, and how data bases may be used, rather than using data from one year to determine the ranking. We believe that further refinement of the proposed exposure assessment will strengthen the Guidance Document itself as well as the quality of the resulting applications by the sponsors.
2. Do the overall rankings in Appendix B agree with available data? For example, beef has a high consumption level and a low salmonella prevalence, which results in a ranking of medium for human exposure. Turkey, on the other hand, has a medium consumption level and high salmonella prevalence resulting in a high probability of

human exposure. The conclusion is that the average person is more likely to attain a salmonella infection from turkey than from beef. However, in data reported by Olsen et al [2]) in "Surveillance of Foodborne Disease Outbreaks – United States, 1993-1997" there were 31 salmonella outbreaks designated due to consumption of beef, chicken, turkey or pork. Of the 31 outbreaks, 14 were from beef and 6 were from turkey: this study contradicts the predicted outcomes in the Appendix. Given the complexities of the food chain, the utility and predictive value of this type of outcome is in need of a broader scientific review (as could occur in a Public Workshop), before the Tables become a component of the Guidance Document and future submissions.

3. The rankings (H,M,L) for exposure assessment do not allow for special cases. For example, if a food commodity is typically pasteurized (e.g., milk) or is processed in such a way as to essentially sterilize it, then it is very reasonable that a "negligible" category ranking be applicable. The inclusion of a "negligible" ranking at release would enable a fourth (very low) "category of concern" (Table 5 on page 27)
4. The procedure for ranking needs to be transparent, and a method should be set in place by which these rankings can be systematically updated as data continues to be generated via US surveillance programs. The rankings listed for Campylobacter and Salmonella in Appendix B are based on US data that are generated periodically, and thus there should be a transparent basis by which these data are reviewed and updated.

Comments on 'Consequence Assessment'

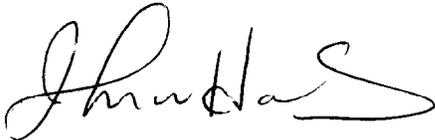
1. The relative importance of individual drugs to human health changes with time. Therefore a mechanism needs to be in place to allow the basis for the rankings to be transparent, and systematically updated. We recognize that the Guidance makes the conservative assumption that (p.8) "risk" is (defined as) "the probability that human illness is caused by a specified antimicrobial resistant bacteria, is attributable to a specified-animal food commodity and is treated with the human antimicrobial drug of interest". However, in practice not all human illnesses are equally attributable to food animals, not all food-borne bacteria cause disease, and not all resistance in bacteria in man are due to the use of antimicrobials in animals.
2. We recognize that all antimicrobials can be considered important (or potentially important) to human health in their own right. However, the maintenance of animal health and food safety is also important to the health and welfare of humans, and thus all factors regarding human health consequence as a result of antimicrobial use in animals can not be equal, or there would be no need for Appendix A in the first place. While all factors listed may be taken into consideration in the final ranking, the basis for their inclusion and the relative importance of these factors in the final ranking of importance to human health should be understandable and transparent to the public and the sponsors. Such transparency will also provide a basis for future updates of the

appendix as human (and animal) health management change and new and more effective antibiotics become available for human medicine. It is certainly not clear at this point why the natural penicillins that have been available for use in animals and humans for decades receive in Appendix A, a "high" ranking, equal to the "high" ranking given to the oxazolidones, a new class of antimicrobials which has only recently become available as a new drug class within the past 5 years. Moreover, it appears not all drugs listed in Appendix A were systematically reviewed. For example, it appears that the fluoroquinolones were individually reviewed, and reviewed as a class. Aminoglycosides were reviewed individually but not as a class. Third generation cephalosporins are reviewed as a class, but only a subset of the individual third generation cephalosporins were reviewed individually. Why is this review so inconsistent?

As mentioned in the opening of this letter, P&U supports CVM's adoption of a risk-based approach for the evaluation of the human health impact of animal antibiotic use in food producing animals. P&U fully supports the use of a science and data based risk assessment for the evaluation of the potential effect that a new antibiotic used in food animals may potentially have on resistance in food borne pathogens that can infect people. We look forward to broader, continued review of this topic, with input from the human and veterinary health communities, to better define and refine the factors under consideration, and the relative weight they should have in the final ranking. If CVM has any questions on the comments in this letter, please contact me at (269) 833-2482.

Sincerely,

PHARMACIA & UPJOHN COMPANY



John W. Hallberg, D.V.M., Ph.D.
Director, U.S. Regulatory Affairs

JWH/cs
Enclosures

REFERENCES

¹ American Academy of Microbiology. 2002. The role of antibiotics in agriculture. Report from the American Academy of Microbiology. www.asmusa.org.

² Olsen, SJ; MacKinon, LC; Goulding, JS; Bean, NH; Slutsker, L. Surveillance for Foodborne Disease Outbreaks. United States, 1993-1997. CDC MMWR Surveillance Summaries, March 17, 2000/49 (SS01); 1-51.