

Background:

Food-producing animals are administered antimicrobial drugs for therapeutic, preventive, and production purposes. With the use of antimicrobial drugs in food-producing animals, bacteria may become resistant to drugs or drug classes that may also be used to treat human illness, potentially making human illnesses more difficult to treat.

In January 1999, the FDA published a concept paper titled, “Proposed Framework For Evaluating And Assuring The Human Safety Of The Microbial Effects Of Antimicrobial New Animal Drugs Intended For Use In Food-Producing Animals” (Framework Document). The Framework Document discussed possible strategies for managing the potential risks associated with the use of antimicrobial drugs in food-producing animals. The strategies included: 1) revision of the pre-approval safety assessment for antimicrobial resistance for new animal drug applications to assess all uses; 2) categorization of antimicrobial drugs based upon the importance of the drug for human medicine; 3) post-approval monitoring for the development of antimicrobial drug resistance; 4) the collection of food animal drug use data; and 5) the establishment of regulatory thresholds for the development of resistance.

After holding several public meetings to obtain comments and feedback from various stakeholder groups, FDA developed draft Guidance for Industry to implement the various strategies and concepts discussed in the Framework Document. In developing the draft guidance, FDA considered all relevant comments recorded at the public meetings on the subject as well as all relevant comments received in writing. The draft guidance titled, “Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern” was published in September 2002 and was the subject of a public meeting in October 2002. This guidance is presented as part of this background package. The focus of the guidance is on antimicrobial drugs intended for use in food-producing animals and the potential for human exposure to resistant bacteria through the ingestion of animal-derived foods. The guidance is included as part of this background package.

This guidance uses a qualitative risk assessment approach to evaluate the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. This risk assessment process includes: a consideration of the potential for resistance to emerge in the animal as a consequence of the use of an antimicrobial drug (release assessment); the potential for humans to be exposed to that resistance (exposure assessment); as well as the potential consequences of that exposure to human health (consequence assessment). A fourth component of the risk assessment, referred to as the risk estimation, integrates the results of all components of the risk assessment into an overall qualitative estimate of risk. The risk estimation serves to characterize the overall level of concern that antimicrobial resistance would emerge and cause an unacceptable impact on human health. This risk assessment conclusion would then be used for determining the appropriate risk management steps.

The importance of the particular drug in question to human medicine is the key factor for characterizing the human health consequence component of the risk assessment. The ranking of drugs according to their importance in human medicine is included in Appendix A of the guidance document. The added benefits of an antimicrobial drug product may be important in making decisions on drug approval particularly when there is a safety concern with the drug. However,

the ranking of drugs according to their importance in human medicine is not a regular part of the Center for Drug Evaluation and Research (CDER) approval process for antimicrobials.

A joint team composed of members of CDER and the Center for Veterinary Medicine (CVM) developed the following criteria for ranking drugs according to their importance in human medicine:

Factors related to drug efficacy

- 1) sole therapy/limited available therapies for treatment of human infections
- 2) therapy of choice for human infection(s)
- 3) spectrum of activity of particular importance
- 4) importance as an oral (rather than parenteral) therapy
- 5) importance in treating food-borne infections
- 6) unique mechanism of antimicrobial action

Factors related to development of antimicrobial resistance

- 7) cross-resistance within drug class
- 8) cross-resistance across drug classes
- 9) ease of transmissibility of resistance determinants
- 10) cross resistance between animal and human drugs

Representatives of CDER presented these criteria as part of an open public hearing held by CVM in October of 2002. Members of CDER and CVM will present these criteria again for comment at this meeting of the Anti-Infective Drugs Advisory Committee. The committee members will be asked to comment on the appropriateness of the criteria used to rank the drugs, keeping in mind the balance of preserving drugs for use in human medicine and the impact of the availability of such drugs in veterinary practice. The committee will not be asked to specifically comment on the rank assignment for particular drugs or drug classes.