

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

[Docket No. 00D-1677]

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Certifier	Ramon Ower

**Discussion Paper: An Approach for Establishing Thresholds in Association With the Use of Antimicrobial Drugs in Food-Producing Animals; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a discussion paper entitled "An Approach for Establishing Thresholds in Association With the Use of Antimicrobial Drugs in Food-Producing Animals (discussion paper)." This discussion paper reflects the Center for Veterinary Medicine's (CVM's) current thinking on one concept for establishing resistance thresholds for antimicrobial drugs used in food-producing animals. The concept will be presented for discussion at a public meeting on January 22 to 24, 2001. CVM wants to receive comment on scientific and policy issues regarding this concept, as well as suggestions for alternative approaches.

**DATES:** Submit written comments on this discussion paper by April 9, 2001.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

See the **SUPPLEMENTARY INFORMATION** section for electronic access to the discussion paper. Persons without Internet access may submit written requests for single copies of this discussion paper to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send one self-addressed adhesive label to assist that office in processing your request.

**FOR FURTHER INFORMATION CONTACT:**

*For general inquiries:* Sharon R. Thompson, Center for Veterinary Medicine (HFV-3), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 301-827-4514. e-mail at [sthompso@cvm.fda.gov](mailto:sthompso@cvm.fda.gov).

*For technical inquiries:* William T. Flynn, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-7570, e-mail at [wflynn@cvm.fda.gov](mailto:wflynn@cvm.fda.gov).

## **SUPPLEMENTARY INFORMATION:**

### **I. Background**

In the **Federal Register** of January 6, 1999 (64 FR 887), FDA announced the availability of a discussion paper entitled "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial Drugs Intended for Use in Food-Producing Animals" (the Framework Document). FDA made the Framework Document available to the public to initiate discussions with the scientific community and other interested parties on the agency's thinking about appropriate underlying concepts to be used to develop new policy for evaluating and ensuring that antimicrobial drug use in food-producing animals is safe for the public health. The Framework Document discussed several strategies for addressing concerns regarding the development of antimicrobial drug resistance associated with the use of antimicrobial drugs in food-producing animals. These strategies covered both preapproval and postapproval approaches and included: (1) Revision of the preapproval safety assessment for antimicrobial resistance for new animal drug applications to consider all uses of antimicrobial drugs in food-producing animals, (2) categorization of antimicrobial drugs based upon the importance of the drug for human medicine and upon which preapproval and postapproval requirements would be based, (3) postapproval monitoring of the development of antimicrobial drug resistance, and (4) elaboration of resistance and monitoring thresholds.

The Framework Document discussed the concept of two thresholds, the resistance threshold and the monitoring threshold, that would be established prior to the approval of an antimicrobial

new animal drug for use in food-producing animals to ensure that food products derived from the animal species treated with the drug are safe for consumers. The resistance threshold would be established in humans to represent the upper limit of resistant bacteria that can be transferred from animals to consumers. The Framework Document discussed the possibility of establishing resistance thresholds based on human data, animal data, or both.

The Framework Document noted that monitoring thresholds also would be established to guide the postapproval monitoring of resistance development in animals. According to the Framework Document, a monitoring threshold would need to be determined for each antimicrobial drug prior to approval, and the threshold could vary depending on the human or animal pathogen of concern. Monitoring thresholds would be established in animals so that they would serve as an early warning system, signaling when loss of susceptibility or resistance prevalence is approaching the resistance threshold.

If a monitoring threshold were reached, the drug sponsor could implement mitigation actions to address the loss of susceptibility or the increasing resistance trend. According to the concepts described in the Framework Document, if mitigation actions were found to be unsuccessful, and resistance levels exceeded the resistance threshold, withdrawal of the approval of the drug for the use(s) of concern would be warranted.

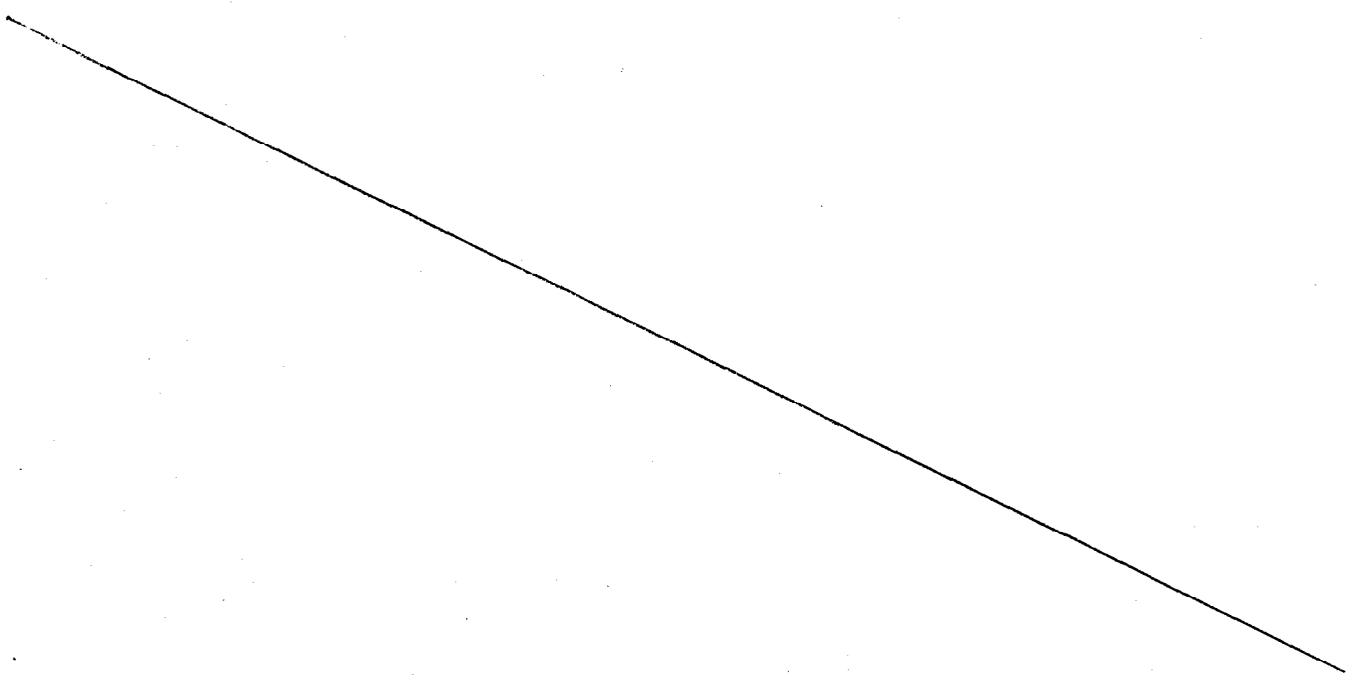
The discussion paper, which is the subject of this notice of availability, further describes an approach for establishing thresholds intended to limit the emergence and spread of antimicrobial resistance in human pathogens attributed to antimicrobial drug use in food-producing animals. The discussion paper attempts to describe the possible complexities of this approach to establishing thresholds in order to encourage discussion before, during, and after the January public meeting mentioned above. A notice of the public meeting was announced in the **Federal Register** of September 26, 2000 (65 FR 57820).

The discussion paper discusses the use of two types of thresholds, a human health threshold and a resistance-in-animals threshold. The human health threshold represents the level at which

there is no longer a reasonable certainty of no harm to human health associated with antimicrobial resistance development as a consequence of antimicrobial drug use in food-producing animals. The resistance-in-animals threshold represents the upper limit of acceptable levels of antimicrobial resistance in a food-producing animal species. This resistance threshold is derived through a risk assessment model that builds a link between the human health threshold and the resistance levels in animals. Therefore, exceeding the resistance threshold would be considered an unacceptable human health risk.

## **II. Comments**

This discussion paper is being distributed at this time for consideration by the public in anticipation of the January 22 to 24, 2001, public meeting. Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this discussion paper by April 9, 2001. Two copies of any comments are to be submitted, except that an individual may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the docket including transcript and comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.



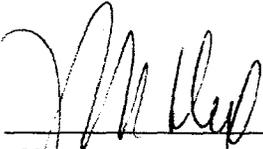
**III. Electronic Access**

Copies of the discussion paper may be obtained on the Internet from the CVM home page at <http://www.fda.gov/cvm/>.

Dated: 12/21/00  
December 21, 2000.

**CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL**

Domeni Oliver

  
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Margaret M. Dotzel,  
Associate Commissioner for Policy.

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

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