

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

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[Docket No. 93D-0398]

Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability for comment of draft guidance for industry entitled "Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora." This draft guidance is a revision of the guidance document no. 52 entitled "Microbiological Testing of Antimicrobial Drug Residues in Food," which was implemented in 1996. In this draft guidance, the agency recommends a pathway approach for assessing the microbiological safety of antimicrobial drug residues in food, rather than the approach described in the 1996 version of the guidance. The agency's decision to revise this guidance is based on new information available to the agency.

DATES: You may submit written or electronic comments at any time. However, the agency would like to use these comments during the next meeting of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Microbial Safety Task Force meeting. You should submit comments concerning this draft guidance by *[insert date 90 days after date of publication in the Federal Register]* to ensure the incorporation of your comments at that meeting.

Submit written or electronic comments on the collection of information by *[insert date 60 days after date of publication in the Federal Register]*.

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. All comments should be identified with the full title of the draft guidance and the docket number found in brackets in the heading of this document.

Submit written requests for single copies of the draft guidance to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855. Send one self-addressed adhesive label to assist the office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT:

For information regarding the guidance document: Haydee Fernandez, Center for Veterinary Medicine (HFV-150), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20850, 301-827-6981, e-mail: afernand@cvm.fda.gov.

For information regarding information collections and the Paperwork Reduction Act: Denver Presley, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1462.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of January 30, 1996 (61 FR 3043), FDA published a notice of availability for a guidance document entitled "Microbiological Testing of Antimicrobial Drug Residues in Food" (guidance no. 52). This guidance document stated that the agency would consider antimicrobial activity as a valid endpoint for establishing tolerances for antimicrobial drugs. The guidance also stated that antimicrobial residues present in food from food-producing animals should not cause any adverse effect on the ecology of the human intestinal microflora of consumers. The

guidance identified antimicrobial drugs that would be exempt from additional microbiological testing and those that would warrant testing. The reasons for exempting certain antimicrobial drugs from additional microbiological testing included "very low" residues present in the food, residues with limited antimicrobial activity, and drugs with no adverse effects on the intestinal microflora at therapeutic doses.

Guidance no. 52 stated that "very low" levels of antimicrobials present in food would not perturb the intestinal microflora or select for resistant microorganisms and, therefore, would be "safe" under Section 512 of the Federal Food, Drug, and Cosmetic Act. Based on the best information available at that time, FDA believed that a maximum Acceptable Daily Intake (ADI) of 1.5 milligram (mg)/person/day of microbiologically active residues present in the food qualified as "very low" residues and should not produce adverse effects on the intestinal microflora. After CVM established the maximum ADI of 1.5 mg/person/day in the 1996 version of guidance no. 52, CVM staff publicly (e.g., at a workshop sponsored by FDA on September 20 and 21, 1999, in Rockville, MD) stated that this threshold would need to be re-evaluated when additional information was obtained on the adequacy of this number for different classes of antimicrobial drugs.

The guidance recommended that additional microbiological testing be performed for those antimicrobial drugs for which sponsors were seeking an ADI higher than 1.5 mg/person/day. The guidance document identified the following areas for which antimicrobial residues present a potential public health concern. These endpoints are: (1) Changes in the metabolic activity of the intestinal microflora, (2) changes in antimicrobial resistance patterns of the intestinal microflora, (3) changes in the colonization resistance properties (barrier effect) of the microflora, and (4) changes in the number of microorganisms and composition of the intestinal microflora. The guidance recommended that sponsors characterize the product, identify its microbiological activity, and monitor the appropriate microbiological endpoints in order to establish the antimicrobial no-observed effect level (NOEL). Because no validated model systems were available at that time,

FDA announced its intention to validate model systems to evaluate the effect of low levels of antimicrobial drugs on endpoints of public health concern. The guidance also stated that in vitro microbiological inhibitory concentration data should not be submitted to establish the microbiological NOEL, because these data do not predict the level of drug residues that would elicit the potential public health concern. Sponsors were encouraged to consult with CVM to determine appropriate protocols before conducting studies.

In 1995, CVM funded two extramural research contracts to study the dose-response effects of antimicrobial drugs on human intestinal microflora endpoints that could be of public health concern. In a workshop sponsored by FDA on September 20 and 21, 1999, in Rockville, MD, information from the two research contracts was presented. Data on the effect of low doses of different classes of antimicrobials on several microbiological endpoints of the human intestinal microflora were discussed. After reviewing and discussing the data, FDA concluded that the threshold ADI discussed in guidance no. 52 is not appropriate for all classes of antimicrobials. Different classes of antimicrobials affect, to different degrees, microbiological endpoints that could be of public health concern. Therefore, FDA has decided to modify guidance no. 52 to recommend that sponsors use a pathway approach (described in the draft guidance) for addressing human food safety of antimicrobial drug residues, rather than the approach described in the 1996 version of the guidance. The scientific rationale for this decision is provided in the appendix of the draft guidance document.

Guidance no. 52 may be further revised at a later date according to the recommendations from VICH concerning proper tests and model systems and standard protocols for addressing endpoints of public health concern. VICH also needs to address how to calculate ADIs using NOELs obtained from microbiological testing models. However, the agency believes that it is in the best interest of the regulated industry and public health to revise guidance no. 52 now, instead of waiting for the VICH recommendations to be completed.

This level 1 guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). This draft guidance, when finalized, will represent the agency's current thinking with regard to the approach that should be used to assess the microbiological safety of antimicrobial drug residues in food of animal origin. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternate method may be used as long as it satisfies the requirements of applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction act of 1995 (the PRA) (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed collection of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing a notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora

Description: Sponsors of new animal drugs must meet certain statutory requirements for new animal drug approval under section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b). Among other things, the sponsor must demonstrate that the use of the drug is safe. Thus, when CVM reviews new animal drug applications for drugs that will be used in food-producing animals, it must determine whether residues of the drug that may remain in human food derived from those animals would be harmful to humans. One possible harmful effect of residues of antimicrobial drugs that CVM considers in this determination is the possible effect of residues on human intestinal flora.

This draft guidance document describes the recommended pathway approach for assessing such effects. An assessment of the safety of antimicrobial drug residues in food is a major issue that should be addressed by the sponsor of a new animal drug. For residues determined to have no antimicrobial activity against representatives of the human intestinal flora, an ADI should be calculated based on traditional toxicology studies. The burden hours required are reported and approved under OMB Control No. 0910-0032. However, the draft guidance recommends that additional information be provided for certain drugs. This additional information should be provided if an assessment of microbiological safety determines that a new animal drug produces residues in foods that are microbiologically active in the human colon. The likely respondents to this collection of information are sponsors of antimicrobial new animal drugs that will be used in food-producing animals.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

Guidance	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Assessments (including studies) of safety of antimicrobial drug residues that are microbiologically active in the human colon	5	1	5	14,110	70,550

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

The estimates in table 1 of this document resulted from discussions with sponsors of new animal drugs. The estimated burden includes studies, analysis of data, and writing the assessment. The number of respondents provided is based on current experience, however, the number may change in the future.

III. Comments

This draft guidance document is being distributed for comment purposes only and is not intended for implementation at this time. Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this draft guidance document. Submit written or electronic comments by *[insert date 90 days after date of publication in the Federal Register]* to ensure adequate consideration by the VICH Microbial Safety Task Force and in the development of the final guidance. Two copies of any comments are to be submitted, except that individuals 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 draft guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

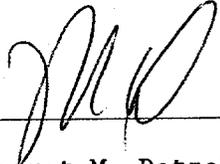
Submit written comments concerning the information collection requirements to the Dockets Management Branch by *[insert date 90 days after date of publication in the Federal Register]*. A copy of the document and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

V. Electronic Access

Electronic comments may be submitted electronically on the Internet at <http://www.fda.gov/dockets/ecomments>. Once on this Internet site, select *[Insert Docket Number for this publication]* "Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the

Human Intestinal Flora” and follow the directions. Copies of the draft guidance entitled “Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora” may be obtained on the Internet from the CVM home page at <http://www.fda.gov/cvm>.

Dated: 12/18/01
December 18, 2001.



Margaret M. Dotzel,
Associate Commissioner for Policy.

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