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SOCIETY FOR  
MICROBIOLOGY

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Public and Scientific Affairs Board

March 27, 2002

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852.

Re: [Docket No. 93D-0398]; *Federal Register*, Vol 66, 66910-66912; Assessment of the Effects of Antimicrobial Drug Residues From Food of Animal Origin on the Human Intestinal Flora; Availability, Notice.

The American Society for Microbiology (ASM) would like to comment on the draft guidance for industry, "Assessment of the Effects of Antimicrobial Drug Residues From Food of Animal Origin on the Human Intestinal Flora," published December 25, 2001, in the *Federal Register*.

The ASM is the premier educational and scientific society dedicated to the advancement of microbiological research and its application for the common good. The Society represents more than 40,000 microbiologists, including scientists in academic, industrial and government institutions, working in a variety of areas, including medical, genomic, molecular, environmental and food microbiology, and public health. The ASM's Public and Scientific Affairs Board Committee on Agricultural and Food Microbiology has developed the following comments.

The ASM commends the Food and Drug Administration (FDA) for developing an assessment process on the effects of antimicrobial drug residues on the human intestinal flora. The Society supports the concept of quantitative microbiological assessments, such as this Assessment, which provides an additional series of tests to supplement the current toxicology-based tests for industry sponsors and regulatory authorities to evaluate the potential health risk that antimicrobial drug residues might exert on human intestinal microflora. Furthermore, the Assessment provides a reasonable review of the subject from both a historical and contemporary point-of-view. The Assessment also provides a strong and convincing justification for a "pathway approach" for establishing a NOEL (no-observed effect level) endpoint that can then be used to set the Allowable Daily Intake (ADI) for determining concentrations of antimicrobial drugs residues in human food of animal origin.

#### **General Comments**

The purpose of conducting microbiological safety studies of antimicrobial drug residues in food is to ensure that there are no adverse effects on human health. This is a

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requirement by the sponsor of an antimicrobial animal drug. ASM supports the value of conducting human food safety studies and their review by regulatory authorities. ASM is also committed to ensuring that an appropriate microbiological approach is taken that is fair and workable for all stakeholders.

The ASM supports the initial portion of the pathway approach to determine whether there is any microbiologically active drug present when tested against a representative panel of intestinal bacteria (lines 212-216 and 270) and secondarily, whether microbiologically active residues actually enter the colon (217-223 and 276). If no microbiological activity is detected, then the standard toxicological ADI is used. This approach allows the sponsor and the regulatory authority to assess with a high degree of certainty, whether the bacteria of interest, in the presence of an antimicrobial drug or its microbiologically active metabolites, actually have antibacterial activity.

The ecology of normal (i.e. non-pathogenic) intestinal microflora, of both animals and humans, is incompletely understood. Indeed, not all genera or species have been cultivated or identified. In fact, one must consider what is actually meant by "normal" microflora. Against this background, the predictive value of test systems for determining the effect of an antimicrobial drug at very low concentrations in the human intestinal tract must be questioned (lines 291-297). If subtle changes in bacterial populations are detected in a model test system, are they necessarily related to a potentially adverse human health effect? While a correlation can be drawn between therapeutic effects of antimicrobials in models and in humans, their predictive value in identifying an antibiotic ingested residue concentration that has no effect on the intestinal flora has not been determined. The Assessment notes that studies on therapeutic concentrations of antimicrobial agents are difficult to interpret due to the tremendous individual test variations. Given that residue concentrations (milligram amounts at most) will be investigated in the proposed model systems, the proposal suggests sponsors may wish to conduct a batch culture to obtain a preliminary idea of which endpoint is of concern. Batch cultures can be replicated so as to account for variability and thus provide valuable information at an early stage in drug evaluation schemes. Given the microbiological complexity of developing *in vitro* model test systems that are relevant and predictive of human health impacts, the ASM supports the logical progression of the proposed pathway approach. Furthermore, the ASM believes the FDA should develop model systems that can statistically account for the inherent variability within individuals and normal intestinal microflora.

The Assessment (lines 80-81; 191-195) allows sponsors to bring forward, in consultation with the regulatory authorities, alternate approaches. This option provides flexibility and will allow new technological advances and research approaches to be brought into play for establishing an acceptable ADI value. Given that the current test systems may not be able to identify NOEL of low concentrations of an antimicrobial, the ASM believes it would be appropriate for the final evaluation to take into account new test system(s) appropriate to the drug in question, so that reviewers can make a scientifically sound final recommendation on an acceptable ADI. In either case, there remains some question of the predictive value to human health impact from conducting *in vitro* tests.

The FDA's Center for Veterinary Medicine (CVM) draft Assessment document has been developed through public workshops, research studies, and other expert input (line 203). It must also be recognized that the Assessment also has international "counterparts" and an international regulatory harmonization aspect, too, as reviewed in Appendix E (line 835). The contributions of many ASM members to the meetings and discussions on this topic should not go unrecognized. ASM is supportive of these efforts and urges the CVM (and other national authorities with similar regulatory requirements) to work toward a unified approach within the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products. In this way, the world's experts can be brought together to achieve the best path that ensures a level playing field for all stakeholders.

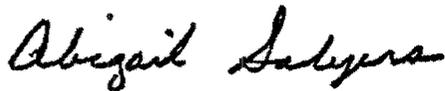
### **Specific Comments**

In contrast to the barrier effect and resistance selection studies (Lines 307-314), the use of endpoints that measure change in the metabolic activity of the microflora should be abandoned. Of the multiple genera in the human intestinal microflora, each one will have slightly different metabolic pathways that enable them to occupy a particular niche. Differences in oxygenation, depth of niche occupation, and competitiveness with other microflora are further factors that will affect metabolism. Additionally, differences in the substrates (i.e. diet) of the host will alter the metabolism in unknown ways. It must also be considered that there is no particular metabolic trait that has been associated with an adverse human health effect. Therefore, the ASM recommends that additional research be conducted in this area in order to determine whether alterations in microbial physiology are warranted in establishing ADI.

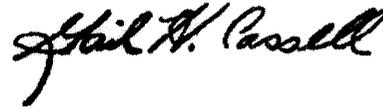
The Assessment document has reviewed the literature on various model test systems and the interpretation limitations. It is accepted that other *in vitro* model test systems can and will be designed that are extremely sensitive and can detect small biological changes in normal intestinal flora (e.g. PCR-based gut flora profiling, DNA chips, etc.). As noted above, the Assessment allows flexibility in applying these new approaches. However, the attribution of any observed change in these model systems must be related to the significance to public health. Since an observed change could be beneficial, detrimental or inconsequential, a determination will need to be made by the model system. The assessment of effect and establishment of NOEL requires the application of modern scientific methods that take into account the complexity of the model biologic systems involved and the need to measure changes at the most fundamental level possible (e.g. genetic).

The ASM is pleased to have the opportunity to provide comments in response to the draft Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora and hopes that these comments and recommendations are of assistance to the FDA.

Sincerely,



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President, ASM



Gail Cassell, Ph.D  
Chair, Public and Scientific Affairs Board



Anne Vidaver, Ph.D  
Chair, Committee on Agricultural and Food Microbiology

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