AMERICAN
SOCIETY FOR
MICROBIOLOGY

Public and Scientific Affairs Board

July 26, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 99D-3028

Draft Guidance for Industry and FDA on Premarket Approval Applications for In Vitro Diagnostic Devices Pertaining to Hepatitis C Viruses (HCV): Assays Intended for Diagnosis, Prognosis, or Monitoring of HCV Infection, Hepatitis C, or Other HCV-associated Disease

The American Society for Microbiology (ASM) is the largest educational, professional, and scientific society dedicated to the advancement of the microbiological sciences and their application for the common good. The Society represents more than 42,000 microbiologists, including scientists and science administrators in academic, industry and government institutions working in a variety of areas, including biomedical, environmental, and clinical microbiology. In response to the notice published April 27, 2001 in the Federal Register, ASM would like to comment on the draft Guidance for Industry and FDA on Premarket Approval Applications for In Vitro Diagnostic Devices Pertaining to Hepatitis C Viruses (HCV): Assays Intended for Diagnosis, Prognosis, or Monitoring of HCV Infection, Hepatitis C, or Other HCV-associated Disease.

The ASM commends the FDA for proposing guidance for premarket approval (PMA) applications for assays pertaining to hepatitis C viruses. The guidance document is extremely detailed and complete and should be of significant assistance to manufacturers in the design of studies for review of data and preparation of PMAs, as well as for the FDA staff in assisting manufacturers in their review of PMAs. In support of this guidance document, we would like to offer the following comments:

We agree with the recommendation that detection of anti-HCV antibodies requires confirmation; however, we disagree with the recommendation that the strip immunoassay (SIA) is the appropriate test. The SIA is not an independent marker of infection because the "SIAs use the same or similar HCV antigens as EIAs." This is supported by the observation that virtually all positive EIAs are confirmed as positive or determined to be indeterminate by SIAs in all patient populations with the possible exception of screening tests performed with very low prevalence populations. We would also disagree with the recommendation that EIAs should be confirmed with repeat duplicate testing. This

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should be unnecessary if the test is demonstrated to be reproducible and accurate. Whereas it is reasonable to expect the manufacturer of an assay to demonstrate accuracy and reproducibility, it is not reasonable to expect clinical laboratories to confirm positive EIA tests with duplicate EIA tests and SIA. We believe the appropriate confirmatory test for a positive EIA test is an assay that demonstrates active viral replication; that is, a HCV-RNA assay should be performed.

The guidance document recommends that "quantitative assays should have at least two controls, negative and positive, at appropriate points within the clinically defined range of the assay." We believe three controls should be used – a negative control, a low positive control, and a high positive control that defines the upper limit of linearity for the assay under evaluation. The range of linear values should correspond to the anticipated range of clinically significant values observed for patients with acute disease and chronic disease.

In the comparison of an assay under evaluation with an acceptable standard, presentation of the study findings should include all original observations, as well as an analysis of discrepant results. Discrepancies should be resolved using an independent assay and sufficient clinical and analytical data to eliminate interpretive bias.

Thank you for the opportunity to comment on this guidance document.

Sincerely,

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