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December 23, 2004

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

Re: *Docket No. 2004D-0385 – Comments on Draft Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Hepatitis A Serological Assays for Clinical Laboratory Diagnosis of Hepatitis A Virus*

Dear Sir or Madam:

AdvaMed respectfully submits these comments to the Food and Drug Administration (FDA) in response to a September 30, 2004 notice requesting comments on the Agency's draft guidance document "Class II Special Controls Guidance Document: Hepatitis A Serological Assays for Clinical Laboratory Diagnosis of Hepatitis A Virus."

AdvaMed, the Advanced Medical Technology Association, represents more than 1,200 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Its members produce nearly 90 percent of the \$75 billion in health technology products consumed yearly in the United States and nearly 50 percent of the \$175 billion purchased around the world annually. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually. A number of our member companies market hepatitis A serological assays, the subject of FDA's request for comments.

GENERAL COMMENTS

Thank you for the opportunity to comment on FDA's special controls guidance document developed to support the reclassification of hepatitis A virus (HAV) serological assays in to class II. We applaud FDA for acknowledging that its knowledge and understanding of these products, as well as that of the industry, warrants down classification of hepatitis A assays. We support FDA's efforts to ensure the continued safe and effective use of diagnostic tests

for the detection of anti-HAV IgM, IgG and total antibody by issuance of a special controls guidance document.

SPECIFIC COMMENTS

I. Scope

On page 8, section 4, paragraph 2 states, “Hepatitis A virus serological assays are devices that consist of antigens and antisera for the detection of hepatitis A virus-specific IgM, IgG, or total antibodies (IgM and IgG), in human serum or plasma. These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis or for determining if an individual has been previously infected with the hepatitis A virus. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by hepatitis A virus in conjunction with other clinical laboratory findings....”

We suggest that individuals who are susceptible to infection by hepatitis A also be included in the Scope and descriptions of hepatitis A serological assays. We believe this is warranted as the testing of vaccination panels is suggested in section 7, Performance Evaluation; General Study Recommendations.

We recommend that the scope be revised as follows:

“Hepatitis A virus serological assays are devices that consist of antigens and antisera for the detection of hepatitis A virus-specific IgM, IgG, or total antibodies (IgM and IgG), in human serum or plasma. These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis or for determining if an individual has been previously infected with the hepatitis A virus. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by hepatitis A virus in conjunction with other clinical laboratory findings *or as an aid in the identification of HAV-susceptible individuals for vaccination....*”

II. Performance Characteristics: General Recommendations

On page 10, section 7, paragraph 1, FDA’s general study recommendations state, “We recommend you test specimens from individuals that have been vaccinated against HAV. You should evaluate a baseline specimen (prevaccination) and a post vaccination specimen collected two to four weeks post vaccination from individuals aged two years and greater. In your study, you should include all vaccines that are currently U.S. licensed.”

We agree that testing panels from immunized individuals vaccinated with vaccines representative of those currently licensed in the U.S. is reasonable. Differences between the source antigen materials and inactivation methods used are likely to result in the greatest differences between vaccines. Therefore we believe selecting and evaluating samples from patients vaccinated with representative vaccines should be adequate.

With regard to collecting samples beginning at 2-4 weeks, this requirement seems overly burdensome. The Advisory Committee on Immunization Practices (ACIP in its 1999

recommendation pertaining to HAV stated “post-vaccination testing is not indicated because of the high rate of vaccine response among adults and children.” Thus, we question the need to conduct the post-vaccination study suggested in section 7. The ACIP does address pre-vaccination serologic testing for susceptibility when it is cost effective. However, this recommendation pertains to immunity because of prior infection and not to immunity due to vaccination.

In any case, if a post-vaccination study is required published antibody profiles support the emergence of anti-HAV antibodies by 4 weeks post vaccination. Pre-vaccination samples of seronegative individuals would supply a negative baseline value. Post vaccination samples should be collected at a point in time (i.e. at least 4 weeks post vaccination) when a known antibody response would be expected. A sample obtained sooner than 4 weeks could result in a negative result. Seroconversion panels will address the emergence of the immunological response to the presence of a viral immunogen.

We recommend that the language in this section be revised as follows:

“We recommend that you test specimens from individuals that have been vaccinated against HAV. You should evaluate a baseline specimen (prevaccination) and a post vaccination specimen collected *from individuals aged two years and greater*. In your study, you should include vaccines that are representative of those currently U.S. licensed, *based on the antigen source materials and inactivation methods used*. If the assay’s capture antigen is different than the vaccine strain, you should explain why this will not produce a false negative result when testing for immunity due to vaccination.”

III. Performance Characteristics: Reproducibility

In the section on reproducibility on page 11, paragraph 2 FDA’s states, “If your device is indicated for use in matrices other than serum, we recommend that you establish the reproducibility of the assays in each matrix, e.g., EDTA anticoagulated plasma.”

There is no reason to believe that the performance characteristics would differ significantly in the serum and plasma matrices. Manufacturers who claim that their assays can be used with multiple sample matrices provide data supporting the use of their assays with all claimed sample types in their premarket notification 510(k) submissions. Equivalence is established during pre-clinical testing and support of sample matrix studies. However, demonstration of reproducibility is generally performed using a pool of test material that is divided into separate aliquots and then stored for subsequent testing. The physical characteristics of plasma (fibrinogen content, lipids, etc) could induce a lack of homogeneity between aliquots in the test material. As a consequence, the results maybe skewed. A manufacturer should demonstrate that the assay performance across the claimed matrices and that the assay has demonstrated reproducibility using serum only. We recommend deleting the sentence. We also recommend that only one type of heparin anticoagulant (either sodium or lithium) be evaluated. It is not necessary to do both.

IV. Performance Characteristics: Interference

In the section on interference beginning on page 11 FDA states, “Potential sources of interference can include compounds normally found in serum, such as triolein (triglycerides), hemoglobin, bilirubin, and serum albumin, as well as potential serum-based interference by rheumatoid factor (RF), anti-nuclear antibodies (ANA), and heterophilic antibodies.”

Later, in the section on cross reactivity beginning on page 12 FDA states, “For HAV IgM assays, we recommend that you include performance in the presence of such factors as rheumatoid factor, anti-nuclear antibodies, and human anti-mouse antibodies.”

We recommend deleting the reference to ANA, RF and heterophilic antibodies from the interference section as they are more appropriately identified in the section on “cross-reactivity”. These samples are obtained with test results that indicate that they are above the normal range and are tested in the assay undiluted to represent the worst clinical case. This is the same analysis that would be performed in the cross-reactive subgroup testing. Hence, testing for these substances in both sections would be redundant.

We recommend modifying the language in the section on cross-reactivity:

“For HAV IgM assays, We also recommend that you include performance in the presence of such factors as rheumatoid factor, anti-nuclear antibodies, and ~~human anti-mouse~~ heterophile antibodies.”

V. Prevalence (Expected Values)

We suggest FDA clarify the study population for prevalence determination. The prevalence of HAV is variable based on outbreak, location and socioeconomic demographic. This is clearly represented in a graphic of reported hepatitis A cases in the US (<http://www.cdc.gov/ncidod/diseases/hepatitis/a/vax/index.htm>). Would individuals without signs or symptoms collected in a high risk population, regardless of collection site location be representative of a “normal” population?

VI. Methods Comparison: Detectability and Comparative Performance

In the section on detectability and comparative performance on page 14, FDA states, “Prospective collection of specimens is recommended. However, repository banks may be used as the source for samples if . . . collected from one site over a contiguous time period.”

We note that prospective studies are recommended by the Agency. Such studies are very expensive and are not always necessary to assess an *in vitro* medical device. We support FDA’s recommendation allowing use of repository bank samples during studies that compare test

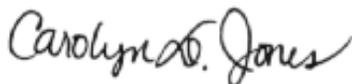
performance with a legally marketed device (predicate device). However, we ask that FDA provide a rationale for recommending that repository bank samples be collected from a single site over a contiguous time period. We believe that such a requirement will hinder manufacturers' efforts to design appropriate studies by unnecessarily restricting sample collection.

Allowing repository bank samples to be obtained from multiple geographic locations and tested at clinical sites, allows greater geographic diversity of samples included in the study population. Due to the low prevalence of acute HAV infection in the U.S. population, the use of repository bank samples collected from multiple geographic locations may also help to facilitate collection of the range of patient samples required to complete these studies.

CONCLUSION

We appreciate the opportunity to share our comments and look forward to working with the Agency to finalize the content of the Class II Special Controls Guidance document as a special control to support the down classification of hepatitis A serological assays into Class II.

Respectfully submitted,



Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs





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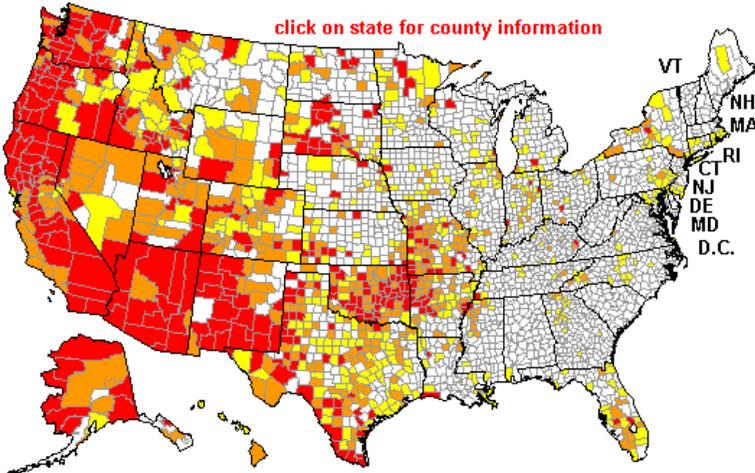
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Choose a state:

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Average reported cases of hepatitis A per 100,000 population*, 1987-1997

click on state for county information



<5 5 - <10 10 - <20 ≥20

*Approximately the national average during 1987-1997.
Source: National Notifiable Diseases Surveillance System.

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