DDM

Display Date 9-29-04
Publication Date 9-30-04
Certifier A. Corbin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. 2003P–0564]

Microbiology Devices; Reclassification of Hepatitis A Virus (HAV) Serological Assays (IgM Antibody, IgG Antibody and Total Antibodies (IgM and IgG))

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify hepatitis A virus (HAV) serological assays from Class III (premarket approval) to class II (special controls). These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis A or for determining if an individual has been previously infected with HAV. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by HAV in conjunction with other clinical laboratory findings. FDA is proposing this action after reviewing a reclassification petition submitted by Beckman Coulter, Inc. The agency is taking this action under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments), the Safe Medical Devices Act of 1990 (the SMDA), and the Food and Drug Administration Modernization Act of 1997 (FDAMA). Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a class II special controls draft guidance

entitled "Class II Special Controls Guidance Document: Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus."

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the* **Federal Register**]. See section VIII of this document for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http:// www.fda.gov/ dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Sally Hojvat, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–2096.

SUPPLEMENTARY INFORMATION:

I. Background (Regulatory Authorities)

The act, as amended by the 1976 amendments (Public Law 94–295), the SMDA (Public Law 101–629), and FDAMA (Public Law 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA

advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices generally remain in class III until the device is reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act, to a legally marketed device. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

Section 513(f)(3) allows FDA to initiate reclassification of a postamendments device classified into class III under section 513(f)(1) of the act, or the manufacturer or importer of a device to petition the Secretary of the Department of Health and Human Services for the issuance of an order classifying the device in class I or class II. FDA's regulations in § 860.134 (21 CFR 860.134) set forth the procedures for the filing and review of a petition for reclassification of such class III devices. To change the classification of the

device, it is necessary that the proposed new classification have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

II. Regulatory History of the Device

HAV serological assays are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis A or for determining if an individual has been previously infected with HAV. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by HAV in conjunction with other clinical laboratory findings. These devices are postamendments devices classified into class III under section 513(f)(1) of the act and must be the subject of an approved PMA under section 515 of the act before being placed into commercial distribution, unless they are reclassified under section 513(f)(3) of the act.

In accordance with section 513(f)(3) of the act and § 860.134, Beckman Coulter, Inc., submitted a petition on October 1, 2003, requesting reclassification of HAV antibody assays from class III to class II.

III. Device Description

Hepatitis A virus serological assays are devices that consist of antigens and antisera for the detection of hepatitis A virus-specific immunoglobulin M (IgM), immunoglobulin G (IgG), or total antibodies (IgM and IgG), in human serum or plasma (Refs. 1 and 2). 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 hepatitis A virus. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by the hepatitis A virus in conjunction with other clinical laboratory findings. The presence of IgM type antibodies

differentiates an acute infection from past infection. These devices are not intended for screening blood or solid or soft tissue donors.

Currently marketed HAV serological assays typically are used on automated laboratory analyzers, providing reportable results within 45 minutes. FDA has also approved assays based on manual enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay methods. Regardless of method, these assays typically rely on specific binding of antibodies to HAV and to fixed HAV antigen, which is then detected by a labeled secondary (anti-IgM or anti-IgG) antibody. HAV specific IgM may also be detected by the binding of human IgM to anti-human IgM bound to a solid matrix. Labeled HAV antigen is then added and if specific anti-HAV has been captured the antigen will bind. Serum and plasma are the common matrices for currently marketed assays for HAV antibodies, as antibodies reside physiologically in the liquid portion of the blood, and are therefore reliably detected there or in plasma. Currently, World Health Organization (WHO) material standards are available for standardization of anti-HAV assays (Refs. 3 and 4).

IV. Proposed Reclassification

The agency is proposing to reclassify HAV serological assays from class III to class II and has developed a guidance document which, when final, will serve as the special control. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of this draft guidance for comment in accordance with FDA's good guidance practices (GGPs) regulation (21 CFR 10.115). We have determined that there is adequate valid scientific evidence in the public domain to support this reclassification action and, therefore, it was unnecessary to refer the petition to a classification panel for its review and recommendation.

V. Risks to Health

There are no known direct risks to an individual's health associated with the device. However, failure of HAV serological assays to perform as indicated or an error in interpretation of results may lead to improper patient management. There are no clinical features that distinguish HAV infection from infection by other etiologic agents of hepatitis such as the hepatitis B virus or hepatitis C virus. HAV serological assays are used to aid in this distinction. Therefore, false test results could contribute to misdiagnosis and improper patient management.

A false negative measurement with failure to detect HAV-specific IgM would misdiagnose an active HAV infection. False negative HAV serological assay results may place individuals infected with preexisting liver disease at risk for not receiving appropriate therapy. It has been shown that HAV infection in individuals with preexisting liver disease, e.g., HCV infection, has been associated with an increased rate of fulminant hepatitis and mortality (Refs. 5 to 7). The administration of HAV-specific hyperimmune globulin may help to prevent or improve the clinical manifestations of disease if given within 2 weeks of infection as prophylaxis, although it is generally not helpful in the acute phase of HAV infection (Ref. 8). In healthy individuals, HAV infections are generally self-limiting without serious consequences, with no chronic or persistent hepatitis (Ref. 9). The failure to detect HAV-specific total or IgG antibodies would result in misdiagnosis of past infection and may cause individuals to erroneously receive vaccination for HAV. It is believed that this would be of minimal risk because there is currently no contraindication for an individual immune to HAV receiving HAV vaccination.

A false positive measurement can result in incorrect diagnosis of active or past HAV infection. If HAV-specific total antibodies are detected erroneously, an individual may not receive the vaccine for HAV, and could continue to be at risk for HAV infection. A false positive anti-HAV IgM result also has public health considerations because the majority of state health departments are required to followup reported acute HAV infections. This would place an undue burden on state health department resources.

VI. Special Controls

In addition to general controls, FDA believes that the draft guidance entitled "Class II Special Controls Guidance Document: *Hepatitis A Serological Assays* for the Clinical Laboratory Diagnosis of Hepatitis A Virus" is an adequate special control to address the risk to health described above. Following the effective date of this final classification rule, any firm submitting a 510(k) premarket notification for Hepatitis A Virus (HAV) serological assays will need to address the issues covered in the special controls guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurance of safety and effectiveness.

The class II special controls guidance provides information on how to meet premarket (510(k)) submission requirements for the assays in sections that discuss performance characteristics and labeling. The performance characteristics section describes studies integral to demonstration of appropriate performance and control against assays that may fail to perform to current standards. The labeling section addresses factors such as directions for use, quality control and precautions for use and interpretation. FDA tentatively believes that complying with the act and regulations and following

the special controls guidance document will provide reasonable assurance of safety and effectiveness of these devices and adequately address the risk to health identified in section V of this document.

VII. FDA's Tentative Findings

The efficacy of diagnosis of HAV by HAV antibody detection has been well-established over the past 25 years. HAV antibody detection plays a key role in diagnosis of HAV infection, because there are no other approved clinical or laboratory methods that are specific for HAV infection. Technological improvements have increased the reliability and clinical sensitivity and specificity of performance of these devices. A technologically improved enzyme-linked immunosorbent assay (ELISA) format, new detection methodology, and the advent of monoclonal antibody technology have enhanced the sensitivity and specificity of the assays without introducing confounding issues (Ref. 10).

FDA has considered issues that could potentially complicate use or interpretation of HAV antibody assay results. There do not appear to be notable concerns for use and interpretation of HAV antibody assays because most assays are now automated, HAV infection is primarily self-limiting, and there are no specific treatment measures for HAV infection. In addition, a WHO material reference for HAV antibodies is available and assays from different manufacturers should be expected to report similarly due to standardization to this material (Refs. 3 and 4) . Because HAV antibody assays are currently the only approved specific diagnostic for HAV infection, the guidance recommends that assay results only be interpreted in the context of other laboratory findings and the total clinical status of the patient.

The FDAMA added section 510(m) to the act (21 U.S.C. 360(m)). Section 510(m) of the act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the act (21 U.S.C. 360(k)), if the agency determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness and, therefore, the device is not exempt from the premarket notification requirements. FDA review of performance characteristics will provide reasonable assurance that acceptable levels of performance for both safety and effectiveness are addressed before marketing clearance. Thus, persons who intend to market this device must submit to FDA a premarket notification submission containing information on HAV antibody detection assays before marketing the device.

VIII. Effective Date

FDA proposes that any final regulation that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

IX. Environmental Impact

The agency has determined that under 21 CFR 25.34(b) that this reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order

12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because reclassification of the device from class III to class II will relieve manufacturers of the cost of complying with the premarket approval requirements of section 515 of the act and may permit small potential competitors to enter the marketplace by lowering their costs, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $110 million. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

XI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XII. Request for Comments and Proposed Dates

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, 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. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XIII. References

The following references have been placed on display in the Division of Dockets Management (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Lemon, S.M., and N. Binn, "Serum Neutralizing Antibody Response to Hepatitis A Virus," *Journal of Infectious Diseases*, 14:1033–1039, 1983.

2. Lemon, S.M., "Type A Viral Hepatitis: Epidemiology, Diagnosis, and Prevention," *Clinical Chemistry*, 43:1494–1499, 1997.

3. WHO International Standard for anti-HAV Immunoglobulin; 2nd International Standard 1998, WHO/BS/98.1878, 98.1878. Add. 1 (Cited in WHO International Biological Reference Preparations (Version 2001 Catalog, page 3 of 34 at: *http://www9.who.int/vaccines/Biologicals/KAlph.pdf*)).

4. Ferguson, M., et al., "Hepatitis A Immunoglobulin: an International Collaborative Study to Establish the Second International Standard," *Biologicals*, 28:233–240, 2000.

5. Devalle, S., V.S. de Paula, J.M. de Oliveira, et. al., "Hepatitis A virus infection in hepatitis C Brazilian patients," *Journal of Infectious Diseases*, August, 47(2):125–128, 2003.

6. Koff, R.S., "Risks associated with hepatitis A and hepatitis B in patients with hepatitis C," *Journal of Clinical Gastroenerology,* July, 33(1):20–26, 2001.

7. Vento, S., "Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C," *Journal of Viral Hepatitis,* May; 7 Suppl 1:7–8, 2000.

8. Stapleton, J.T., "Host immune response to hepatitis A virus," *Journal of Infectious Diseases,* 171(S1):S9–S14, 1995.

9. Hollinger, F.B. and S.U. Emerson, "Hepatitis A Virus," in D.M. Knipe et al., eds. *Fields Virology,* 4th ed. Lippincott Williams and Wilkins, Philadelphia, 799–840, 2001.

10. Brown, E.A., and J.T. Stapleton, "Hepatitis A Virus" in P.R. Murray et al., eds., Manual of Clinical Microbiology, 8th ed., ASM Press, Washington, DC, 1452–1463, 2003.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is proposed to be amended as follows:

per OFR Deidre Gabbe 9-28-04

PART 866–IMMUNOLOGY AND MICROBIOLOGY DEVICES

■ 1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

■ 2. Section 866.3310 is added to subpart D to read as follows:

§ 866.3310 Hepatitis A Virus (HAV) serological assays.

(a) *Identification.* 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 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. These devices are not intended for screening blood or solid or soft tissue donors.

(b) *Classification.* Class II (special controls). The special control is "Class II Special Controls Guidance Document: Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus." See § 866.1(e) for the availability of this guidance document.

Dated: 9/21/04
September 21, 2004.

Linda S. Kahan

Linda S. Kahan,
Deputy Director,
Center for Devices and Radiological Health.

[FR Doc. 04–????? Filed ??–??–04; 8:45 am]

BILLING CODE 4160–01–S

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL