BECKMAN COULTER

October 1, 2003

Regulations Staff (HFZ-215)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Dr.
Rockville, MD 20857

RE: Reclassification Petition
***In Vitro* Diagnostics for Anti-Hepatitis A Virus IgM and Total Anitbodies**

Dear Sir or Madam:

This submission is a reclassification petition for *In Vitro* Diagnostics for Anti-Hepatitis A Virus IgM and Total Anitbodies.

This submission contains:

- Reclassification Petition for *In Vitro* Diagnostics for Anti-Hepatitis A Virus IgM and Total Anitbodies
- Executive Summary
- FDA Form 3427 Supplemental Data Sheet
- FDA Form 3429 General Device Classification Questionnaire

If you have any questions or require further information regarding this submission, please contact me by telephone at 952-368-7629, via facsimile at 952-368-7610 or by e-mail at bachiponis@beckman.com.

Sincerely,

Barbara Chiponis
Group Manager Regulatory Affairs
Beckman Coulter, Inc.

Enclosures

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318-1084

Telephone: (952) 448-4848
Internet: www.beckmancoulter.com

2003P-0564

CCP1

REQUEST FOR RECLASSIFICATION OF *IN VITRO* DIAGNOSTICS FOR ANTI-HEPATITIS A VIRUS IGM AND TOTAL ANTIBODIES

Executive Summary

In accordance with Section 513(f)(3) of the Federal Food, Drug, and Cosmetic Act, we are requesting that *in vitro* diagnostics ("IVDs") for the detection of immunoglobulin M ("IgM") and total antibodies (IgM and immunoglobulin G ("IgG")) reactive to Hepatitis A Virus ("HAV"; Product Code LOL) be reclassified from Class III to Class II by the U.S. Food and Drug Administration ("FDA"). The detection of anti-HAV antibodies in human serum or plasma is an aid in the diagnosis of HAV infection, with the presence of IgM type antibodies differentiating an acute infection from past infection. IVDs intended for use in clinical laboratories for the detection of anti-HAV IgM and total antibodies have been marketed in the U.S. since 1979, which was only six years after HAV was first identified as an etiologic agent of infectious hepatitis. FDA reserves Class III for new technology and high risk devices, and, consistent with least burdensome principles, the goal of FDA's classification process is to seek the least restrictive level of regulatory control necessary to ensure the safety and effectiveness of the device. Given the important epidemiological and technological changes that have occurred in the past 24 years, Class III status is no longer appropriate and down-classification of IVDs for the detection of anti-HAV IgM and total antibodies is justified.

As discussed in detail in the request for reclassification, there have been significant changes in the public health considerations of the epidemiology, and in the understanding of the clinical consequences of HAV infections. Safe and effective vaccines for HAV have been available for the past eight years to target individuals at risk of infection, and only about 30,000 cases of HAV infection are reported annually in the United States. Additionally, improvements in sanitation and hygiene have made endemic transmission of HAV unlikely in the United States. It also has been established that HAV infection is an acute, self-limiting infection, with very low mortality. Because complete recovery without serious complications is generally the rule for HAV infections, when HAV infection is diagnosed, there is no therapy offered, other than supportive care. In contrast, other viral agents of hepatitis, for example, hepatitis B virus and hepatitis C virus, cause chronic infections that frequently result in cirrhosis of the liver, and liver cancer.

Further, FDA's classification of IVDs for the detection of IgM or total antibodies to viral agents is according to the specific virus, and the epidemiological and clinical features of HAV infection are consistent with other viruses where the IVDs are Class I or II devices. Examples of viruses that are diagnosed with the aid of Class I devices include: Epstein-Barr virus; influenza virus; Respiratory Syncytial Virus; and poliovirus. Examples of viruses that are diagnosed with the aid of Class II devices include Cytomegalovirus and Varicella-Zoster virus. The risks to public health and individuals infected with HAV are no greater than for these viruses, and, thus, down-classification would be consistent with the regulatory status of these other viral products.

Finally, the long history of safe and effective use of IVDs for the detection of anti-HAV IgM and total antibody supports their down-classification. The characteristics of tests for anti-HAV IgM and total antibodies that are necessary for their safe and effective performance are well-established. There is valid scientific evidence, including widespread laboratory experience, published literature, international standards, voluntary guidances from national and international

organizations, and lower classification by regulatory authorities in the European Union and Canada, that demonstrates that general and special controls would provide reasonable assurance of the safety and effectiveness of IVDs for the detection of anti-HAV IgM and total antibodies.

IVDs for detecting anti-HAV IgM and total antibodies, therefore, are no longer high risk or new technology devices warranting Class III status.

RECLASSIFICATION PETITION FOR *IN VITRO* DIAGNOSTICS FOR ANTI-HEPATITIS A VIRUS IGM AND TOTAL ANTIBODIES

BECKMAN COULTER, INC.

SEPTEMBER 25, 2003

TABLE OF CONTENTS

I. Introduction

In accordance with Section 513(f)(3) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"),[1/] Beckman Coulter, Inc. is requesting that *in vitro* diagnostics ("IVDs") for the detection of immunoglobulin M ("IgM") and total antibodies (IgM and immunoglobulin G ("IgG")) reactive to Hepatitis A Virus ("HAV") be reclassified from Class III to Class II by the U.S. Food and Drug Administration ("FDA"). The detection of anti-HAV antibodies in human serum or plasma is an aid in the diagnosis of HAV infection, with the presence of IgM type antibodies differentiating an acute infection from past infection.[2/] IVDs intended for use in clinical laboratories for the detection of anti-HAV IgM and total antibodies have been marketed in the U.S. since 1979.[3/]

Because FDA reserves Class III for new technology and high risk devices, the down-classification of these IVDs is justified based on important changes that have occurred in the past 24 years since these products were first marketed. As discussed in detail in this request, there have been significant changes in the public health considerations of the epidemiology, and in the understanding of the clinical consequences of HAV infections, primarily due to (1) the availability of safe and effective vaccines for HAV, and (2) improvements in hygiene that reduce transmission of HAV. In addition, there is valid scientific evidence, including widespread laboratory experience, published literature, voluntary guidances from national and international organizations, and lower classification by regulatory authorities in other jurisdictions, which demonstrates that general and special controls would provide reasonable assurance of the safety and effectiveness of IVDs for the detection of anti-HAV IgM and total antibodies. These IVDs, therefore, are no longer high risk or new technology devices warranting Class III status.

II. Request for Reclassification

The content and form of this petition for reclassification of IVDs for anti-HAV IgM and total antibodies is submitted in accordance with 21 C.F.R. § 860.123. Also included is a discussion of how general and special controls will provide reasonable assurance of safety and effectiveness in accordance with 21 C.F.R. § 860.7.

A. Specification of the device[4/]

The classification name for the *in vitro* diagnostic device requested to be down-classified to Class II is "Hepatitis A Virus Test (Antibody and IgM Antibody)." The product code is "LOL," and includes devices intended for use in clinical laboratories for the detection

---

1/ 21 U.S.C. § 360c(f)(3) (2003).

2/ S.M. Lemon and N. Binn, 1983. Serum neutralizing antibody response to Hepatitis A Virus. Journal of Infectious Diseases 14:1033-1039.

3/ The first approval was for Abbott Laboratories' HAVAB® (P780012).

4/ 21 C.F.R. § 860.123(a)(1) (2002).

of total antibodies to HAV or IgM class antibodies to HAV in human serum or plasma, as an aid in the diagnosis of individuals with HAV infection.

IVDs for anti-HAV IgM and total antibodies are currently classified as Class III devices. The Medical Device Amendments (May 28, 1976) to the FFDCA established a risk-based classification for all medical devices, and included "in vitro reagent" in the definition of device. The IVDs for anti-HAV IgM and total antibodies were classified as Class III devices based on a consideration of the public health risks, and because HAV infection was a notifiable disease in every state.[5/] Class III is reserved for new technology and high-risk devices, and requires submission of a premarket approval application ("PMA") to FDA prior to commercial distribution. The first IVD for anti-HAV antibodies was approved for marketing by FDA in 1979,[6/] which was only six years after HAV was first identified as an etiologic agent of infectious hepatitis.[7/] In the past 24 years, 8 PMAs, and 36 supplemental PMAs ("sPMAs") for product code LOL have been approved by FDA.[8/] As discussed below, the technological advances, and the reductions in the potential public health and clinical risks associated with the performance of these IVDs, provide the basis for their reclassification as Class II devices.

B. Action requested[9/]

It is requested that IVDs intended for use in clinical laboratories for the detection of total antibodies to HAV or IgM antibody to HAV in human serum or plasma, as an aid in diagnosis of individuals with HAV infection (product code LOL), be reclassified from a Class III device to Class II.

C. Supplemental data sheet[10/]

A completed supplemental data sheet (FDA Form 3427) is submitted as Attachment 1.

D. Classification questionnaire[11/]

A completed *in vitro* diagnostic product classification questionnaire (FDA Form 3429) is submitted as Attachment 2.

5/ This statement is based on informal discussions with staff in FDA's Office of *In Vitro* Diagnostic Device Evaluation and Safety.

6/ Abbott Laboratories HAVAB® (P780012).

7/ S.M. Feinstone et al., 1973. Hepatitis A: detection by immune electron microscopy of a virus-like antigen associated with acute illness. Science 182:1026-1028.

8/ See Center for Devices and Radiological Health ("CDRH") database for Product Code: LOL (available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm).

9/ 21 C.F.R. § 860.123(a)(2).

10/ 21 C.F.R. § 860.123(a)(3) (FDA Form 3427).

11/ 21 C.F.R. § 860.123(a)(4) (FDA Form 3429).

E. Statement of the basis for disagreement with the present classification status[12/]

The basis of this reclassification request is that the current classification of IVDs for detection of anti-HAV IgM and total antibody as Class III is no longer appropriate, given the reduction in the public health risks associated with performance of these devices, and the improvements in technical knowledge, standards and guidance documents that are currently available for the regulation of these IVDs. Specifically, the bases for disagreement are:

1. The classification of IVDs for the detection of IgM or total antibodies to viral agents is according to the specific virus,[13/] and the epidemiological and clinical features of HAV infection are consistent with other viruses where the IVDs are Class I or II devices.

2. The characteristics of anti-HAV antibody tests that are necessary for their safe and effective performance are well-established, and consistent with classification as Class II.

3. The long history of safe and effective use of IVDs for the detection of anti-HAV IgM and total antibody supports their down-classification.

4. The reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the regulatory status of IVDs for anti-HAV IgM and total antibodies in the European Union ("EU") and Canada.

5. The reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the "least burdensome" principles of the Food and Drug Administration Modernization Act of 1997 ("FDAMA").

F. Full statement of reasons and supporting data for reclassification[14/]

1. The classification of IVDs for the detection of IgM or total antibodies to viral agents is according to the specific virus, and the epidemiological and clinical features of HAV infection are consistent with other viruses where the IVDs are Class I or II devices.

FDA's classification of IVDs for the detection of IgM and total antibodies to HAV as a Class III device is not consistent with the classification of IVDs for the detection of antibodies to other viruses with similar epidemiological and clinical features. FDA guidance states that classification of IVDs for detection of antibodies to viral agents is

---

12/ 21 C.F.R. § 860.123(a)(5).

13/ FDA, Review Criteria for In Vitro Diagnostic Devices for Detection of IgM Antibodies to Viral Agents (Aug. 1992).

14/ 21 C.F.R. § 860.123(a)(6).

according to the specific virus.[15/] Consequently, the classification of IVDs for detection of antibodies to HAV should be consistent with the classification status of other viruses with comparable public health and clinical consequences. FDA also has stated that the review criteria for safety and effectiveness of IVDs for antibodies to viral agents are based on basic science and clinical experience, and that the review criteria will be re-evaluated and revised as advances in science and medicine are made.[16/] Therefore, it is appropriate to reclassify IVDs for the detection of antibodies to HAV because of the advances in science and medicine that have been made in regard to HAV infections.

a. Epidemiology of HAV Infections Supports Down-Classification

The epidemiology of HAV infections has changed significantly since the initial classification of IVDs for anti-HAV antibodies 24 years ago, primarily as a result of improvements in hygiene, and the introduction of safe and effective vaccines 8 years ago.[17/] The transmission of HAV is by a fecal-oral route, and the risk of infection world-wide is inversely proportional to the levels of sanitation and personal hygiene.[18/] In developing countries with poor hygienic conditions, nearly all children are infected with HAV before the age of 9, where infection is asymptomatic.[19/] For developed countries, like the U.S., WHO has stated that "[i]n most developed countries, endemic HAV transmission is unlikely."[20/]

The Centers for Disease Control and Prevention ("CDC") reports that, even in epidemic years in the U.S., the number of recorded cases of HAV infection reached only 35,000, with the last nationwide increase in incidence of HAV infections occurring in 1995, and an earlier peak in 1989-1990.[21/] In 1997, only 30,021 cases were reported to the Nationwide Notifiable Diseases Surveillance System ("NNDSS"), and after adjustment for under-reporting and asymptomatic infections, CDC estimates that there were only 180,000 persons with HAV infection.[22/] There also are estimates that about one-third of

---

15/ FDA, Review Criteria for In Vitro Diagnostic Devices for Detection of IgM Antibodies to Viral Agents (Aug. 1992).

16/ Id.

17/ For reviews, F.B. Hollinger and S.U. Emerson, 2001. Hepatitis A Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 799-840; S.M. Lemon, 1997. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clinical Chemistry 43:8(B):1494-1499.

18/ World Health Organization, Department of Communicable Disease Surveillance and Response, Hepatitis A (WHO/CDS/CSR/EDC/2000.7), 5.

19/ Id.

20/ Id.

21/ CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Oct. 1, 1999), 5.

22/ Id.

the U.S. population has serologic evidence of prior HAV infection, with the highest prevalence of 75% among individuals greater than 70 years of age.[23/]

In addition, the U.S. is unlikely to be at risk from an increase in HAV infections because of the availability of safe and effective vaccines for HAV. In 1995, FDA licensed SmithKline Beecham's Havrix® (Hepatitis A vaccine, inactivated), which also was licensed in combination with recombinant Hepatitis B vaccine as Twinrix® in 2001. In 1996, FDA licensed Merck & Co.'s VAQTA® (Hepatitis A vaccine, inactivated). These formalin-killed whole-virus vaccines derived from attenuated HAV strains in culture have been shown to be highly effective in preventing HAV infection.[24/] Seroconversion rates of >99.4% have been reported when a single primary immunization is followed by a booster dose 6 to 12 months later.[25/] Additional vaccines are available commercially elsewhere in the world.[26/]

There is limited antigenic variability of HAV, which means that the whole virus vaccines should confer protection throughout different geographic regions. HAV strains recovered from humans in different regions of the world demonstrate negligible antigenic diversity.[27/] This has led to the conclusion that only a single serotype of HAV exists.[28/] HAV is neutralized by both IgM, which appears in serum about 2 weeks after exposure, and IgG, which appears in serum about 4 weeks after exposure.[29/] There is only 1 neutralization site on the virus, which is immunodominant, and antibody confers protective immunity that is life-long.[30/]

Vaccination in the U.S. is recommended for individuals at high risk of infection who are 2 years of age and older.[31/] The following groups are considered at risk for HAV infection, and are targeted for vaccination: persons with clotting-factor disorders; persons with chronic liver disease; injecting and non-injecting drug users; men who have

---

23/ Id. at 8.

24/ B.L. Innis et al., 1994. Protection against hepatitis A by an inactivated vaccine. JAMA 271(17):1328-1334; A. Werzberger et al., 2002. Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after Monroe field trial of VAQTA. Vaccine 20:1699-1701.

25/ World Health Organization, Department of Communicable Disease Surveillance and Response, Hepatitis A (WHO/CDS/CSR/EDC/2000.7).

26/ Id.

27/ S.M. Lemon, 1997. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clinical Chemistry 43:8(B):1494-1499.

28/ S.P. Day and S.M. Lemon, 1992. Hepatitis A virus. In S.L. Gorbach et al., eds. Infectious Diseases. WB Saunders Comp., Phila., 1787-1791.

29/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

30/ World Health Organization, Department of Communicable Disease Surveillance and Response, Hepatitis A (WHO/CDS/CSR/EDC/2000.7); S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

31/ CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Oct. 1, 1999).

sex with men; and travelers to endemic areas.[32/] Other groups targeted for vaccination include American Indians, Alaskan Natives, and populations in temporary camps after disasters.[33/] Therefore, the availability of safe and effective vaccines, and the improved targeting of at-risk groups, in combination with high levels of sanitation and personal hygiene, have changed the epidemiology of HAV infections in the U.S., and support a down-classification of IVDs for the detection of anti-HAV IgM and total antibodies.

b. Clinical Features of HAV Infection Support Down-Classification

The current clinical features of HAV infection also support a down-classification of IVDs for anti-HAV IgM and total antibodies. Since HAV was first identified as an etiologic agent of infectious hepatitis in 1973, and the subsequent development of IVDs for the detection of infection by HAV, additional hepatitis viruses have been identified. However, in contrast to hepatitis induced by other viruses, such as Hepatitis B Virus ("HBV") and Hepatitis C Virus ("HCV"), HAV infections are generally regarded as self-limiting.[34/]

The mean incubation period for HAV infection is about 28 days, with infectious virus shed in the stool prior to the onset of signs and symptoms of hepatitis.[35/] In primate models, virus shedding continues to increase in magnitude until just before the onset of biochemical evidence of liver disease, i.e., elevation of serum alanine aminotransaminase ("ALT"), which is indicative of liver damage.[36/] Fecal shedding of virus declines with increasing titer of neutralizing antibody.[37/] There are no clinical features that enable a diagnosis of HAV infection, and that rule out infection by HBV, HCV, or another etiologic agent of hepatitis, without recourse to specific laboratory tests. Consequently, diagnosis of HAV infection by altered liver function, symptoms of hepatitis (i.e., jaundice), and development of an antibody response is too late to prevent potential transmission of infectious virus through contaminated feces.

32/ CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Oct. 1, 1999); World Health Organization, Department of Communicable Disease Surveillance and Response, Hepatitis A (WHO/CDS/CSR/EDC/2000.7).

33/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

34/ D.M. Wolk et al., 2001. Laboratory diagnosis of viral hepatitis. Infectious Disease Clinics of North America 15(4):1109-1126; F.B. Hollinger and S.U. Emerson, 2001. Hepatitis A Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 799-840.

35/ F.B. Hollinger and S.U. Emerson, 2001. Hepatitis A Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 799-840; S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671; S.M. Lemon, 1997. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clinical Chemistry 43:8(B):1494-1499.

36/ S.M. Lemon, 1997. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clinical Chemistry 43:8(B):1494-1499.

37/ Id.

HAV infection is generally asymptomatic in children, and symptoms in older individuals generally are limited to jaundice, increasing fatigue, malaise, loss of appetite, nausea, and vomiting, which, although distressing, ordinarily are not distressing enough to cause the infected individual to stop work or consult a physician.[38/]

HAV infections are generally self-limiting, and complete recovery without therapy is generally the rule, with no chronic or persistent hepatitis.[39/] Therapy can only be supportive and aimed at maintaining comfort and adequate nutritional balance.[40/] The administration of anti-HAV IgG may help to prevent or improve the clinical manifestations of the disease if given within 2 weeks of infection as prophylaxis, but it is generally of no help in the acute phase of hepatitis A infection.[41/] Serious complications are rarely associated with HAV infection. HAV infection even during pregnancy is not associated with increased severity of hepatitis or fetal abnormalities.[42/] Death occurs in very few patients; the CDC estimates the death rate from HAV infection as 0.3%, with about 100 deaths in the U.S. per year.[43/] Therefore, when HAV infection is diagnosed, there is no therapy offered, other than supportive care.

c. HAV shares similarities with the epidemiological and clinical features of other viruses where the IVDs for serodiagnosis are Class II devices

The epidemiological and clinical features of HAV infection are consistent with other viruses where the IVDs to identify antibodies in serum are Class II devices, such as Cytomegalovirus ("CMV"),[44/] and Varicella-Zoster Virus ("VZV").[45/] Like HAV, CMV infection is more prevalent, and acquired at an earlier age in developing countries.[46/] Also similar to infection by HAV, infection by CMV is usually asymptomatic, or causes a mild mononucleosis.[47/] In contrast to HAV, however, CMV is considered a ubiquitous virus, and establishes a latent infection with reactivation believed to be more important

---

38/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

39/ F.B. Hollinger and S.U. Emerson, 2001. Hepatitis A Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 799-840.

40/ World Health Organization, Department of Communicable Disease Surveillance and Response, Hepatitis A (WHO/CDS/CSR/EDC/2000.7) (citing B.F. Hollinger et al., 1996. Hepatitis A virus. In: B.N. Fields et al., eds. Fields Virology, 3rd ed. Lippincott-Raven, Phila., 735-782.)

41/ J.T. Stapleton, 1995. Host immune response to hepatitis A virus. Journal of Infectious Diseases 171 (Suppl. 1):S24-28.

42/ R.S. Koff, 1982. Clinical manifestations and diagnosis of hepatitis A virus infection. Vaccine 10(S1):S15-S17.

43/ CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Oct. 1, 1999).

44/ 21 C.F.R. § 866.3175(b).

45/ 21 C.F.R. § 866.3900(b).

46/ R.F. Pass, 2001. Cytomegalovirus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2675-2705.

47/ Id.

for causing disease in an immunocompromised individual.[48/] CMV is a significant medical and public health problem, because it is the leading cause of congenital infection, and is associated with significant morbidity and mortality for immunocompromised individuals.[49/] Vertical transmission from mother to fetus is usually manifested at birth in the form of microcephaly, hepatosplenomegaly, and other abnormalities.[50/] CMV is the leading opportunistic infection in AIDS patients, and causes retinitis, esophagitis, and encephalitis.[51/] CMV disease in allograft recipients causes severe disease or death when seronegative recipients receive organs from seropositive donors.[52/]

Varicella-Zoster Virus also has similarities to HAV in its epidemiological and clinical features, but the IVDs for detecting antibodies to VZV are Class II devices. Infection with VZV usually occurs at a young age, and causes chicken-pox.[53/] VZV is a ubiquitous virus with a world-wide geographic distribution, and the annual incidence of infection in the U.S. is 4 million cases.[54/] Unlike HAV, VZV establishes a latent infection, and its reactivation produces herpes zoster, which is commonly referred to as shingles.[55/] Like HAV, morbidity and mortality associated with VZV is a nationally notifiable infectious disease with cases reported to the CDC Nationally Notifiable Infectious Disease Surveillance System, and, in 2003, VZV infection was added to the Nationally Notifiable Disease List. Therefore, the classification of IVDs for detection of anti-HAV antibodies should be consistent with the classification of IVDs for detection of antibodies to other viruses, such as CMV and VZV, which share epidemiological and clinical features with HAV.

d. HAV shares similarities with the epidemiological and clinical features of other viruses where the IVDs for serodiagnosis are Class I devices

HAV shares similarities with the epidemiological and clinical features of other viruses where the IVDs for serodiagnosis are Class I devices, e.g., Epstein-Barr virus ("EBV"),[56/]

48/ E.S. Mocarski and C.T. Courcelle, 2001. Cytomegaloviruses and Their Replication. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2629-2673.

49/ S.A. Plotkin, 1999. Cytomegalovirus Vaccines. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 903-908.

50/ Id.

51/ R.F. Pass, 2001. Cytomegalovirus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2675-2705; S.A. Plotkin, 1999. Cytomegalovirus Vaccines. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 903-908.

52/ Id.

53/ A.M. Arvin, 2001. Varicella-Zoster Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2731-2767.

54/ Id.

55/ Id.

56/ 21 C.F.R. § 866.3235(b).

and influenza virus.[57/] Like HAV, primary infection with EBV usually occurs in individuals in developing countries at a young age, and is asymptomatic.[58/] Seroepidemiologic surveys have shown that most children in the developing world become infected within the first 3 years of life, and that antibody prevalence reaches 100% by the age of 10.[59/] In contrast, but similar to HAV, infection with EBV in individuals in developed countries occurs later in life. Infection in older individuals is symptomatic in about 50% of the cases, with infection giving rise to mononucleosis.[60/]

However, unlike HAV, which is cleared from the human host after an acute infection,[61/] infection with EBV can result in persistent infection, or a latent infection, with latently infected B cells capable of producing infectious virus.[62/] These carrier states permit spread of infection by EBV to other susceptible individuals in the population, which increases the public health risks associated with EBV infection.

Infection with EBV also has an additional potential risk, relative to HAV, because EBV is an oncogenic virus that is associated with nasopharyngeal carcinoma, as well as B-cell lymphoproliferative disease in immunocompromised hosts, such as immunosuppressed transplant recipients.[63/] Despite the more significant clinical consequences of infection by EBV, and the absence of a vaccine to prevent infection, IVDs for the serodiagnosis of EBV are Class I devices, while IVDs for detection of anti-HAV IgM and total antibodies are Class III devices.

Influenza virus is another example of a virus that shares similarities in clinical and epidemiological features with HAV, but the IVD for serodiagnosis of influenza virus infection is a Class I device. Like HAV, infection by influenza virus is generally a mild, self-limiting acute infection, with no evidence of persistent or latent infection.[64/] However, primary viral pneumonia, and secondary bacterial pneumonia can occur in individuals at high risk for complications from infection by influenza virus, such as the

---

57/ 21 C.F.R. § 866.3330(b). Other Class I virus assays include: adenovirus (21 C.F.R. § 866.3020); lymphocytic choriomeningitis virus (21 C.F.R. § 866.3360); parainfluenzavirus (21 C.F.R. § 866.3400); and respiratory syncytial virus (21 C.F.R. § 866.3480).

58/ A.B. Rickinson and E. Kieff, 2001. Epstein-Barr Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2575-2627.

59/ IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 1997. Epstein-Barr Virus and Kaposi Sarcoma Herpesvirus/Human Herpesvirus 8. IARC Monograph (70). Lyon, France.

60/ A.B. Rickinson and E. Kieff, 2001. Epstein-Barr Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2575-2627.

61/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

62/ A.B. Rickinson and E. Kieff, 2001. Epstein-Barr Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2575-2627.

63/ Id.

64/ P.F. Wright and R.G. Webster, 2001. Orthomyxoviruses. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 1533-1579.

elderly or patients with cardiopulmonary disease, which are usually fatal.[65/] The CDC reports that millions of people in the U.S., approximately 10 - 20% of U.S. residents, will be infected with influenza virus each year.[66/] Moreover, the CDC estimates that 114,000 individuals in the U.S. are hospitalized annually because of influenza, and about 36,000 will die annually as a result of influenza virus infection.[67/] These numbers are orders of magnitude greater than the CDC's figures for HAV infection in the U.S., where there are approximately 100 deaths among the 30,000 reported cases of HAV infection.[68/]

In contrast to HAV, influenza virus is a significant public health problem. To help control infections by influenza virus, there are antivirals, such as amantadine and rimantadine, which are both approved by FDA for prophylactic and therapeutic use, and licensed vaccines.[69/] Despite the availability of vaccines and antivirals, influenza virus causes epidemics every winter. Continual genetic changes in influenza virus, manifested as antigenic drift and antigenic shift, result in lack of immune recognition and inactivation in individuals infected with previously circulating strains of influenza virus.[70/] New pandemic strains of influenza that are immunologically distinct, form as a result of a high degree of reassortment of segments of the influenza virus genome, which can occur in animal reservoirs.[71/] These continual genetic changes, and aerosolized spread of influenza virus create worldwide pandemics, which result in significant morbidity and mortality.

Reclassification of IVDs for detection of HAV IgM and total antibodies as Class II, therefore, would not be inconsistent with the classification of IVDs for serodiagnosis of other viruses, e.g., EBV and influenza virus, that have more serious clinical sequelae, and similar epidemiological features. Furthermore, HAV is a member of the picornavirus family,[72/] and devices that aid in the diagnosis of infections by other members of this

---

65/ E.D. Kilbourne and N.H. Arden, 1999. Inactivated Influenza Vaccines. In Vaccines 3rd ed. W.B. Saunders Comp., Phila., 531-551.

66/ CDC, Influenza: The Disease (available at: http://www.cdc.gov/ncidod/diseases/flu/fluinfo.htm).

67/ Id.

68/ CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Oct. 1, 1999).

69/ E.D. Kilbourne and N.H. Arden, 1999. Inactivated Influenza Vaccines. In Vaccines 3rd ed. W.B. Saunders Comp., Phila., 531-551.

70/ R.A. Lamb and R.M. Krug, 2001. Orthomyxoviridae: The viruses and their replication. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 1487-1531.

71/ Id.

72/ V.R. Racaniello, 2001. Picornaviridae: The viruses and their replication. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 685-722.

virus family, such as coxsackievirus,[73] echovirus,[74] rhinovirus,[75] and poliovirus,[76] are Class II.

e. Serological reagents for other viruses that are also etiological agents of nationally notifiable infectious diseases are Class I devices

FDA's current regulations also classify serological reagents for other viruses that are etiological agents of nationally notifiable infectious diseases, as Class I devices. For example, measles is included in the CDC's surveillance program, and devices that consist of antigens and antisera used in serological tests to identify antibodies to rubeola virus in serum to aid in the diagnosis of measles and provide epidemiological information on the disease are Class I devices.[77] Similarly, serological reagents for detection of antibodies to mumps virus to aid in the diagnosis of mumps and provide epidemiological information for mumps, a nationally notifiable infectious disease, are Class I devices.[78] Other examples of Class I devices for diagnostic aids for nationally notifiable infectious diseases are for poliomyelitis,[79] and Eastern equine encephalitis virus.[80] Classification of IVDs for the serological detection of anti-HAV IgM and total antibodies to aid in the diagnosis of HAV infection as Class II, therefore, would be consistent with the current classification of these devices for other nationally notifiable infectious diseases.

f. There are significant differences between HAV, and HBV, and HCV, where the IVDs for diagnosis are Class III devices

There are significant differences between the clinical features and epidemiology of infection by HAV, and infections by HBV, or by HCV, where the IVDs for diagnosis are Class III devices. Unlike HAV, which only causes an acute infection, and is associated with very low mortality rates, HBV and HCV establish chronic infections, and are associated with much higher morbidity and mortality. World-wide, most cases of hepatocellular carcinoma ("HCC") are associated with chronic infection by either HBV or HCV.[81] Approximately 25% of individuals infected by HBV will die of HCC or cirrhosis of the liver.[82] For HCV, approximately 3% of infected individuals die from

---

73/ 21 C.F.R. § 866.3145.

74/ 21 C.F.R. § 866.3205.

75/ 21 C.F.R. § 866.3490.

76/ 21 C.F.R. § 866.3405.

77/ 21 C.F.R. § 866.3520. Serological reagents for Rubella virus (German measles) is a Class II device (21 C.F.R. § 866.3510).

78/ 21 C.F.R. § 866.3380.

79/ 21 C.F.R. § 866.3405.

80/ 21 C.F.R. § 866.3240.

81/ M.E. Major et al., 2001. Hepatitis C Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 1127-1161.

82/ F.J. Mahoney and M. Kane, 1999. Hepatitis B Vaccine. In Vaccines 3rd ed. W.B. Saunders Comp., Phila., 158-182.

liver disease, and it is the leading indication for liver transplant.[83/] Although there is a vaccine available for HBV, infection frequently occurs by maternal transmission, and the CDC estimates that there are about 78,000 new infections each year in the U.S., with 1.25 million chronically infected.[84/] There is no vaccine for HCV, and the CDC estimates that there are 25,000 new infections each year in the U.S., with 2.7 million chronically infected.[85/] Unlike HAV, which has a very low risk of transmission via blood and blood products,[86/] HBV and HCV are readily transmitted by blood, and recognized as agents of post-transfusion hepatitis.[87/] Therefore, because HBV and HCV present significantly greater clinical and public health concerns than HAV, it is appropriate that the classification of IVDs to aid in diagnosis of HAV infection recognize the reduced concerns for HAV.

g. Support for down-classification of IVDs for detection of anti-HAV IgM and total antibodies has been expressed by several FDA officials

Several FDA officials have publicly expressed support for the down-classification of IVDs for detection of anti-HAV IgM and total antibodies. For example, in 1998, Dr. Steven Gutman, who is now Director of FDA's Office of *In Vitro* Diagnostic Device Evaluation and Safety, expressed support for the down-classification of IVDs for detection of anti-HAV antibodies. At a Microbiology Devices Panel Meeting discussing scientific criteria to be applied to the review of viral hepatitis IVDs, Dr. Gutman is quoted as saying with regard to HAV IVDs: "the assays have been around for so long, the disease is established so well, the conventional assays are well-established . . . maybe the assay should be down-classified from a Class III."[88/]

Similarly, officials in the Office of Blood Research and Review ("OBRR") in the Center for Biologics Evaluation and Research ("CBER") have expressed support for a lower classification than Class III for tests for the diagnosis of HAV in blood and blood products. In 2000, in discussing regulation of nucleic acid tests ("NAT") for HAV, none of which had been approved for marketing, officials in OBRR presented a mechanism for down-classification to the Blood Products Advisory Committee. Sheryl Kochman, Division of Blood Applications, Devices Review Branch, addressed the regulation of test kits for HAV NAT, for which there is no predicate, and, therefore, would be regulated as

---

83/ CDC, Hepatitis B Fact Sheet, available at http://www.cdc.gov/hepatitis.

84/ Id.

85/ Id.

86/ Dr. Robin Biswas (CBER) is quoted as saying "While transmission of HAV by plasma derivatives is not a major clinical problem, plasma derived volume expanders and immunoglobulins have been historically safe, rare transmissions by coagulation Factors VIII and IX have been reported." FDA, Blood Products Advisory Committee Sixty-Sixth Meeting (June 15, 2000).

87/ Blood Donor Suitability Workshop: Donor History of Hepatitis. FDA, Blood Products Advisory Committee (July 21, 1999).

88/ Transcript of Microbiology Devices Panel Meeting for developing guidance for characterizing performance tests of the diagnosis and monitoring of viral hepatitis (Feb. 12, 1998) (emphasis added).

Class III devices. The following is quoted from the Transcript of Blood Products Advisory Committee Meeting on June 15, 2000:

> Sheryl Kochman: "For the purposes of how CBER might choose to regulate HAV NAT tests, if for some reason we thought that we could review them by other than a PMA mechanism, we do have the opportunity to utilize Section 207 of FDAMA 1997. This is known as the evaluation of automatic Class III designation or also known as de novo classification. . . . if we follow current thinking it would make sense to review it as a 510(k)." (emphasis added).

Dr. Jay Epstein, Director of OBRR, added the following in response to a question from the Panel:

> Jay Epstein: "Well medical testing for hepatitis A has precedence in the agency. It is reviewed as a Class III PMA in CDRH. So, we wouldn't see a real difference between a NAT test versus an antibody test versus an antigen test. It should be treated as a medical diagnostic. So what we are trying to explain is that if we get the recommendation from the committee and concur, we wanted the committee to understand what was at stake with oversight of that test as a medical diagnostic, and what we are saying is that the current system would require that it be a Class III PMA but that there is a legal mechanism under the FDA Modernization Act for it to be, if you will, down-classified to a 510(k), which would then make the oversight more consistent with the way we deal with other non-required tests which are, nonetheless, sometimes reported as medical information to the donor, and that would include CMV, syphilis and ALT." (emphasis added).

Therefore, as expressed by Dr. Epstein, the classification of diagnostic IVDs for the detection of anti-HAV IgM or total antibodies as Class III that requires a PMA is inconsistent with the classification of IVDs for other viruses, such as CMV, where the IVDs are Class I or Class II devices. Indeed, each of the FDA officials quoted above acknowledged the significant changes in the epidemiology, and in the understanding of the clinical consequences of HAV infection that have occurred in the past 24 years, as developments supporting the reclassification of these IVDs to Class II.

2. Characteristics of IVDs for the detection of anti-HAV IgM and total antibodies that are necessary for their safe and effective performance are well-established

Characteristics of IVDs for the detection of anti-HAV IgM and total antibodies that are necessary for their safe and effective performance are well-established. Since the first product was approved in 1979, technological improvements have increased the reliability, and clinical sensitivity and specificity of performance of these IVDs. For example, IVDs

for the detection of anti-HAV IgM were initially available in a radioimmunoassay ("RIA") format, and, since 1982, in a technologically improved enzyme-linked immunosorbent assay ("ELISA") format. As discussed in the following, the state of the art of these devices has sufficiently advanced to address satisfactorily any safety or effectiveness concern.

a. Technological improvements have been made in the manufacture of components since 1979 when the first PMA was approved

There have been many important technological improvements in the manufacture of components of IVDs for anti-HAV IgM and total antibodies since 1979 when the first PMA was approved for Product Code LOL. These include the application of monoclonal antibodies as an alternative to polyclonal antibodies, improved reference standards, use of Receiver Operating Characteristic ("ROC") methodology, and automation.

One of the more significant improvements has been the application of monoclonal antibodies. In 1975, the generation of monoclonal antibodies was first described.[89/] Application of this technology to develop RIAs and ELISAs for hepatitis A virus and antibodies began several years later.[90/] For example, radiolabeled monoclonal and polyclonal antibodies were found to be equally effective in screening human sera for anti-HAV activity using a competitive RIA for total anti-HAV and an antibody capture format for IgM anti-HAV.[91/] By 1990, monoclonal antibodies had reached a 50% market share in diagnostics, and, by 2000, they had become the predominant immunoreagent.[92/] While stabilities of both monoclonal and polyclonal antibodies generally have been excellent, with numerous examples of shelf lives of several decades,[93/] the advent of monoclonal antibody technology enhanced manufacturing of IVD components by allowing immunoglobulins to be treated more as consistent, defined chemicals and less as variable, biological serum components, like polyclonal antibodies.

Antibody engineering also has significant potential to expand monoclonal antibody use in immunoassays by permitting enhancements to antibody affinity and specificity, and to the expression of antibody fragments as fusion proteins coupled to marker molecules.[94/]

89/ G. Kohler and C. Milstein, 1975. Continuous culture of fused cells secreting antibody of predefined specificity. Nature 256:495-497.

90/ A. MacGregor et al., 1983. Monoclonal antibodies against hepatitis A virus. Journal of Clinical Microbiology 18:1237-1243; G.J. Dawson et al., 1984. Monoclonal antibodies to hepatitis A virus. Journal of Medical Virology 14:1-8; A.G. Coulepis et al., 1985. Detection of hepatitis A virus and antibody by solid-phase radioimmunoassay and enzyme-linked immunosorbent assay with monoclonal antibodies. Journal of Clinical Microbiology 22:119-124.

91/ G.J. Dawson et al., 1984. Monoclonal antibodies to hepatitis A virus. Journal of Medical Virology 14:1-8.

92/ C.A. Borrebaeck, 2000. Antibodies in diagnostics - from immunoassays to protein chips. Immunology Today. 21:379-382.

93/ Id.

94/ Id.; J.P. Laurino et al., 1999. Monoclonal antibodies, antigens and molecular diagnostics: a practical overview. Annals of Clinical and Laboratory Science 29:158-166.

Shuffling gene segments encoding one or more complementarity determining regions or entire variable regions creates changes useful for affinity improvements. Thus, monoclonal antibody engineering technologies currently are useful for: (a) increased assay sensitivity; (b) decreased cross-reactivity; (c) standardized manufacturing; and (d) introduction of novel labeling agents.[95/]

Improvements in control of IVD safety and performance have been promoted for decades through readily available, continually improved, reference standards. Reference reagents are essential for the standardization, quality control, and safety of IVDs. The First International Reference for anti-Hepatitis A Immunoglobulin was established by the WHO in 1981,[96/] and it was subsequently discovered to be reactive for HCV RNA by polymerase chain reaction ("PCR").[97/] As a consequence, a Second International Standard for anti-Hepatitis A Immunoglobulin was established in 1998,[98/] and evaluated by an international collaboration.[99/] Such international reference reagents are essential for calibrating various national, regional, and manufacturer standards by comparative assay. Moreover, commercial assay enrollment in control surveys, such as United Kingdom National External Quality Assessment Service ("UKNEQAS"), Agence Francaise de Securite Sanitaire des Produits de Sante ("AFSSAPS"), and Laboratoire de Santé Publique du Québec ("LSPQ") facilitates continual improvements to IVD safety and efficacy. Manufacturers obtain samples from these surveys, and can compare assay results with those obtained by other participants throughout the world. The global visibility of discrepant results constitutes strong motivation for manufacturers to improve assays appropriately during subsequent assay development cycles.

Innovative improvements also have come from the use of ROC methodology to characterize diagnostic accuracy, or assay cut-off.[100/] It is widely known that sensitivity and specificity are inversely related assay parameters that together determine diagnostic accuracy. Each assay has a calculable, distinct cut-off value for optimum sensitivity and

---

95/ C.A. Borrebaeck, 2000. Antibodies in diagnostics - from immunoassays to protein chips. Immunology Today. 21:379-382.

96/ World Health Organization, 1981. WHO/BS/81.1339 (cited by M. Ferguson et al., 2000. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. Biologicals 28:239); World Health Organization, 1982. Hepatitis A Immunoglobulin Technical Report Series 673:21; R.J. Gerety et al., 1983. Standardization of the antibody to hepatitis A virus (anti-HAV) content of immunoglobulin. Development of Biological Standards 54: 411-416.

97/ M. Ferguson et al., 2000. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. Biologicals 28:233-240.

98/ World Health Organization, 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).

99/ M. Ferguson et al., 2000. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. Biologicals 28:233-240.

100/ National Committee for Clinical Laboratory Standards, 1995. Assessment of the clinical accuracy of laboratory tests using receiver operating characteristic (ROC) plots: approved guideline, GP10-A, Vol. 15, No. 19.

specificity, and ROC methodology has been increasingly used for the calculations. Between 1979 and 1989, ROC methodology development and usage escalated significantly,[101] and, since then, articles on both methodology[102] and ROC computer software[103] have been regularly published. Further, ROC analysis has been promoted by periodically updated, universally available guidelines that have been approved by the National Committee for Clinical Laboratory Standards ("NCCLS").[104] Availability of numerous ROC computer software applications[105] also has furthered the widespread use of this best practice approach to characterizing diagnostic accuracy. Additionally, because many quantitative tests do not discriminate perfectly between subjects with and without a given disease,[106] methodologies are available for use in conjunction with ROC analysis to calculate the equivocal, gray zones of such IVDs.[107]

Automation developed since FDA approval of the first HAV antibody test in 1979 has significantly enhanced assay reliability. Such safety and efficacy improvements are due in no small part to a reduction of imprecision attributable to inter-technician variability. Specifically, reproducibility enhancements due to automation have been attributed to precise control of parameters including volume, temperature, and assay timing,[108] and calibration curve stability.[109] For example, a study showed that an automated assay provided sensitivity, specificity, and detectability equivalent to commercially available

---

101/ J.A. Hanley, 1989. Receiver operating characteristic (ROC) methodology: the state of the art. Critical Reviews in Diagnostic Imaging. 29:307-335.

102/ Id.; A.R. Henderson, 1993. Assessing test accuracy and its clinical consequences: a primer for receiver operating characteristic curve analysis. Annals of Clinical Biochemistry 30:521-539; E.K. Shultz, 1995. Multivariate receiver-operating characteristic curve analysis: prostate cancer screening as an example. Clinical Chemistry 41:1248-1255; D.E. Shapiro, 1999. The interpretation of diagnostic tests. Statistical Methods in Medical Research 8:113-134; J.J. ten Bosch et al., 2000. Characterization and validation of diagnostic methods. Monographs Oral Science 17:174-189.

103/ H.S. Fraser et al., 2000. New approaches to measuring the performance of programs that generate differential diagnoses using ROC curves and other metrics. Proceedings of AMIA Symposium 255-259; P.S. Heckerling, 2002. Parametric receiver operating characteristic curve analysis using mathematica. Computer Methods and Programs in Biomedicine 69:65-73.

104/ National Committee for Clinical Laboratory Standards, 1995. Assessment of the clinical accuracy of laboratory tests using receiver operating characteristic (ROC) plots: approved guideline, GP10-A, Vol. 15, No. 19.

105/ Id.

106/ A.R. Feinstein, 1990. The inadequacy of binary models for the clinical reality of three-zone diagnostic decisions. Journal of Clinical Epidemiology 43:109-113.

107/ J. Coste and J. Pouchot, 2003. A grey zone for quantitative diagnostic and screening tests. International Journal of Epidemiology 32:304-313.

108/ D.J. Robbins et al., 1991. Detection of total antibody against hepatitis A virus by an automated microparticle enzyme immunoassay. Journal of Virological Methods 32:255-263.

109/ V. Fayol and G. Ville, 1991. Evaluation of automated enzyme immunoassays for several markers for hepatitis A and B using the Abbott IMx® Analyser. European Journal of Clinical Chemistry and Clinical Biochemistry 29:67-70.

manual assays for anti-HAV IgM.[110/] An excellent correlation of 99.8% was observed in comparison to both commercial EIA and RIA manual methods. Moreover, the automated assay provided better reproducibility. The ranges in the coefficient of variation ("CV"), expressed as a percentage, for within-runs was 2.5 - 3.4%; for between-runs was 4.0 - 5.4%; and for the total range was 4.9 - 6.2%.

In sum, there have been many advances in technology for IVDs, which have been applied to assays for the detection of anti-HAV IgM and total antibodies to ensure the continued safety and effectiveness of these devices.

c. Reliability of IVDs for anti-HAV IgM and total antibodies

In determining the safety and effectiveness of devices for classification, the reliability of the device is to be considered.[111/] To establish reliability, FDA's regulations require that there be valid scientific evidence that provides reasonable assurance that the device is safe and effective.[112/] In determining the safety and effectiveness of IVDs for anti-HAV IgM and total antibodies, the analytical sensitivity, analytical specificity, specimen handling, precision (reproducibility), and clinical sensitivity and specificity of these assays are considered in the following.

Analytical sensitivity

The IVDs for the detection of IgM and total antibodies to HAV that have been marketed for the past 24 years have demonstrated adequate analytical sensitivity or detection limits to aid in the diagnosis of HAV infection. IgM appears in serum about 2 weeks after exposure, and IgG appears in serum about 4 weeks after exposure.[113/] Fecal shedding of virus declines with increasing antibody titer, and biochemical evidence of infection, e.g., elevation of ALT, occurs after the peak of virus shedding.[114/] Consequently, significant levels of anti-HAV antibodies are likely to be present when symptoms occur, e.g., jaundice, and medical care is sought. Indeed, studies using commercially available IVDs have shown that anti-HAV antibody titers rise during the first 20 weeks after presentation of symptoms, and then decline with time.[115/]

Comparative studies also have demonstrated that the commercially available IVDs have sufficient analytical sensitivity to detect the levels of antibodies present during HAV

110/ K. Eble et al., 1991. Differential diagnosis of acute viral hepatitis using rapid, fully automated immunoassays. Journal of Medical Virology 33:139-150.

111/ 21 C.F.R. § 860.7(b)(4).

112/ 21 C.F.R. § 860.7(c)(1).

113/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

114/ S.M. Lemon, 1997. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clinical Chemistry 43:8(B):1494-1499.

115/ D.J. Robbins et al., 1991. Detection of total antibody against hepatitis A virus by an automated microparticle enzyme immunoassay. Journal of Virological Methods 32:255-263.

infection. For example, typical analytical sensitivities for IMx HAVAB, HAVAB RIA, and HAVAB EIA have been determined using a sensitivity panel calibrated against the WHO standard, and were 20, 150, and 150 U/l, respectively.[116/] The sensitivity of IMx was reported as 100% in a study using 211 sera submitted to the Regional Virology Laboratory, Hamilton, Canada for investigations for viral hepatitis.[117/] Blinded comparisons were made using HAVAB-M, an ELISA from Abbott Laboratories, and IMx HAVAB-M, a microparticle ELISA, for detection of anti-HAV IgM. There were no discordant results in the HAV tests. Forty-six of the sera were scored as positive by both IVDs, and 165 were scored as negative by both IVDs. Other studies comparing the sensitivity of commercially available anti-HAV antibody tests by end-point dilution have also demonstrated sufficient analytical sensitivity.[118/]

Analytical specificity

The commercially available IVDs to detect anti-HAV IgM and total antibodies have demonstrated adequate analytical specificity, or the ability to identify the target, rather than a similar, but different substance. For example, several studies have demonstrated that the commercially available IVDs consistently score serum samples from patients as positive or negative for anti-HAV antibodies. One study reported on comparative analyses of 659 sera submitted to the Regional Virology Laboratory, Hamilton, Canada for investigations for viral hepatitis.[119/] The specificity of IMx for anti-HAV IgM was reported as 100%, based on the correlation of comparative test results. In another study, 5 different commercially available tests were used for the testing of 1835 sera collected from 7 laboratories involved in serodiagnosis of hepatitis. The evaluation revealed only 59 (3.2%) discrepant sera (54 positive, 5 negative), with 770 sera uniformly positive, and 1003 sera uniformly negative. In addition, "tricky panels" consisting of sera from patients with HBV, HCV, EBV, CMV, HSV, toxoplasmosis, rubella, or autoantibodies, as well as pregnant women and dialysis patients, were evaluated to assess specificity. Of 345 sera from the "tricky panels" analyzed, only 16 sera (4.6%) gave discrepant results.

Such "tricky panels" are used to evaluate analytical specificity because it has long been recognized that interfering substances may perturb analytical tests[120/] by mechanisms including chemical effects, physical effects, matrix effects, enzyme inhibition, non-specificity, and cross-reactivity.[121/] Concomitantly, control of IVD safety and efficacy

---

116/ Id.

117/ M.A. Chernesky et al., 1991. The diagnosis of acute viral hepatitis A or B by microparticle enzyme immunoassay. Journal of Virological Methods 34:291-296.

118/ For example, G. Hess et al., 1995. Analysis of immunoassays to detect antibodies to hepatitis A virus (anti-HAV) and anti-HAV immunoglobulin M. Journal of Virological Methods 51:221-228.

119/ M.A. Chernesky et al., 1991. The diagnosis of acute viral hepatitis A or B by microparticle enzyme immunoassay. Journal of Virological Methods 34:291-296.

120/ C. Selby, 1999. Review Article: Interference in immunoassay. Annals of Clinical Biochemistry 36:704-721.

121/ National Committee for Clinical Laboratory Standards, 2002. Interference Testing in Clinical Chemistry: approved guideline, EP7-A, Vol. 22, No. 27, p. 4.

has been promoted for decades through a widely reviewed, continually improved, readily available, interference testing guideline. The most recent version of this NCCLS guideline was approved in late 2002 and "offers an effective interference testing strategy for manufacturers that can be used to characterize new methods."[122/] Moreover, for ease of use, this guideline has been organized into laboratory- and manufacturer-oriented sections and includes a guideline for investigating discrepant results.

Manufacturers are responsible for characterizing the analytical performance of their assays and for analyzing hazards to patients caused by interfering substances. Furthermore, manufacturers are required to provide information regarding interference susceptibility to those who use their systems.[123/] Thus, clinical chemists who develop and manufacture IVDs are mindful of these requirements as they select the active reagents, buffer additives, and format for each assay. Numerous strategies are widely known by, and readily available to, assay developers for eliminating or minimizing the vulnerabilities of a given IVD to assay interference. These strategies include using: a two-step rather than a one-step format; monoclonal rather than polyclonal antibodies; Fab rather than whole, inactivated immunoglobulin (Ig) in the reporter molecule conjugate; isotype (and, ideally, allotype) matching of blocker Ig with each active reagent Ig (e.g., mouse IgG)[124/]; inactivated alkaline phosphatase blocker; and/or commercially available defined blocking agents (e.g., MAK33 and Poly MAK, Roche Applied Science). Such strategies have been discussed in several recent reviews of assay interference and its mechanisms.[125/]

For anti-HAV antibody tests, certain endogenous blood components, namely, albumin, bilirubin, hemoglobin, and triglycerides, are recognized as potential interfering substances. The NCCLS recommends comprehensive interference screening conducted at the highest concentrations that a laboratory expects to observe among patient specimens submitted for analysis, because such screening reveals if substances can interfere under "worst case" conditions.[126/] Normal concentrations of serum albumin are 3.2 - 5.6 g/dl.[127/] Albumin is synthesized in the liver, but is decreased during disease

---

122/ Id.

123/ Id.

124/ Human anti-mouse antibodies, or other heterophile antibodies, such as human anti-goat antibodies, may be present in samples from some patients, and, although the assays are formulated to minimize the effects of these antibodies, product labeling recommends that results from patients known to have such antibodies should be evaluated carefully.

125/ S.S. Levinson and J.J. Miller, 2002. Review Article: Towards a better understanding of heterophile (and the like) antibody interference with modern immunoassays. Clinica Chimica Acta 325:1-15; C. Selby, 1999. Review Article: Interference in immunoassay. Annals of Clinical Biochemistry 36:704-721; R.S. Schrijver and J.A. Kramps, 1998. Critical factors affecting the diagnostic reliability of enzyme-linked immunosorbent assay formats. Reviews Science Technology 17:550-561.

126/ National Committee for Clinical Laboratory Standards, 2002. Interference Testing in Clinical Chemistry: approved guideline, EP7-A, Vol. 22, No. 27, p. 10.

127/ J.B. Henry, 1996. Clinical Diagnosis and Management By Laboratory Methods (18th ed.), 1367.

states affecting liver function, such as HAV infection.[128/] Total serum protein (albumin) concentrations up to about 20 g/dl are typically tested for any effect on assay results for anti-HAV antibody tests. Whereas the normal reference range for total serum bilirubin in adults is 0.1 - 1.2 mg/dl,[129/] expected peak total bilirubin in patients with HAV infection ranges from 7.7 - 12.4 mg/dl.[130/] Similarly, total serum bilirubin concentrations up to about 20 mg/dl are typically tested for any effect on assay results. The normal reference range for plasma hemoglobin is 0.5 - 5 mg/dl, reflecting minimal red blood cell lysis in non-diseased states.[131/] Hemolytic states of varying degrees are a common complication of acute HAV infections.[132/] The etiology of hemolysis in HAV infection is thought to be immune-mediated.[133/] Levels up to 25 - 30 mg/dl are commonly reported in hemolytic anemia, a disorder that can be immune-mediated.[134/] Higher levels are associated with intravascular hemolysis.[135/] Thus, plasma hemoglobin concentrations up to about 500 - 1,000 mg/dl are typically tested for any effect on assay results. The normal reference range for serum triglycerides (as triolein) is 35 - 160 mg/dl, and patients with hepatitis have mean serum triglycerides in the range of 171 - 360 mg/dl.[136/] Accordingly, triglyceride (triolein) concentrations up to 3,000 - 3,600 mg/dl are typically tested for any effect on assay results.

Therefore, assay interference has been widely recognized for decades both by the NCCLS and by clinical chemists as an important IVD performance parameter. A continually increasing number of strategies and reagents are available to prevent or minimize the vulnerabilities of IVDs to such interference, so that its frequency in modern assays containing blocking agents is very low.[137/]

128/ S. Bakerman, 1994. Bakerman's ABC's of Interpretive Laboratory Data (3rd ed.), 23.

129/ J.B. Henry, 1996. Clinical Diagnosis and Management By Laboratory Methods (18th ed.), 1367.

130/ G.R. Brown and K. Persley, 2002. Hepatitis A epidemic in the elderly. South Medical Journal 95:826-833.

131/ J.B. Henry, 1996. Clinical Diagnosis and Management By Laboratory Methods (18th ed.), 1369.

132/ S. Ritter et al., 1996. Haemolysis in Hepatitis A Virus infections coinciding with the occurrence of autoantibodies against triosephosphate isomerase and the reactivation of latent persistent Epstein-Barr Virus infection. Journal of Medical Virology 50:272-275; T. Chau et al., 1997. Haemolysis complicating acute viral hepatitis in patients with normal or deficient glucose-6-phosphate dehydrogenase activity. Scandinavian Journal of Infectious Diseases 29:551-553; D.J. Lyons et al., 1990. Severe haemolysis associated with Hepatitis A and normal glucose-6-phosphate dehydrogenase status. Gut 31:838-839.

133/ S. Ritter et al., 1996. Haemolysis in Hepatitis A Virus infections coinciding with the occurrence of autoantibodies against triosephosphate isomerase and the reactivation of latent persistent Epstein-Barr Virus infection. Journal of Medical Virology 50:272-275.

134/ J.B. Henry, 1996. Clinical Diagnosis and Management By Laboratory Methods (18th ed.), 643.

135/ Id.

136/ J. I. Gallin et al., 1969. Serum lipids in infection. New England Journal of Medicine 281:1081-1086; W.V.R. Vieweg, 1973. Viral hepatitis: Metabolic studies during acute and convalescent phase. Medical Society Of The District Of Columbia 42:480-485.

137/ S.S. Levinson and J.J. Miller, 2002. Review article: Towards a better understanding of heterophile (and the like) antibody interference with modern immunoassays. Clinica Chimica Acta 325:1-15.

Specimen handling

Reliability of IVDs is consistently promoted by regularly updated, universally available guidelines and standards that have been approved by NCCLS, and include specimen handling. IVD safety and efficacy are encouraged by a standard that describes a stepwise procedure for collection of diagnostic blood specimens by venipuncture.[138/] This document includes special considerations for venipuncture in children, line draws, blood culture collection, and venipuncture in isolation situations. IVD reliability also is advanced by guidelines that consider the multiple variables involved in handling and processing blood specimens.[139/] Compliance with these guidelines enables users to recognize and control accuracy and precision factors that occur between the time of blood collection and the time of testing. These guidelines establish criteria for optimal serum, plasma, or whole blood samples, together with criteria for performance of *in vitro* devices used to process blood specimens. Compliance with these recommendations "should assist laboratories in the pursuit of excellent performance, with useful, accurate patient test results as the ultimate goal."[140/]

Precision (reproducibility)

The precision or reproducibility of IVDs for detection of anti-HAV IgM and total antibodies, in particular, the intra-assay variability, the inter-assay variability, the inter-laboratory variability, and the lot-to-lot variability, have been adequately demonstrated to ensure safety and effectiveness. Precision of diagnostic tests also has been continually promoted by a universally available, regularly updated, NCCLS guideline.[141/] Section 4.9 of this most recent version describes approaches for user comparison with manufacturer's precision claims. Section 5 recommends the best approach for manufacturers to establish precision performance. The manufacturer's goal is to establish precision performance claims "with sufficient rigor so that they will be valid over a wide variety of operating environments that individual users may encounter in the routine use of the method, device, or instrument."[142/]

Whereas the intra-assay and total imprecision are highlighted to be of more general interest, this NCCLS guideline describes various contributors to total reproducibility,

---

138/ National Committee for Clinical Laboratory Standards, 1998. Procedures for the collection of diagnostic blood specimens by venipuncture: Approved standard – 4th ed., H3-A4, Vol. 18, No. 7.

139/ Id.

140/ Id.

141/ National Committee for Clinical Laboratory Standards, 1999. Evaluation of precision performance of clinical chemistry devices: Approved guideline, EP5-A, Vol. 19, No. 2.

142/ Id.

including inter-assay variability, inter-laboratory variability, and lot-to-lot variability. Assay imprecision is described in some HAV antibody assay product inserts.[143/]

Intra-assay reproducibility has been reported to be low for IVDs for the detection of anti-HAV IgM and total antibodies. For example, the CV for anti-HAV IgM assays has been reported to be ≤5%,[144/] 2.5 - 4.5%,[145/] and 2.1 - 8.1%.[146/] Similarly, intra-assay reproducibility of anti-HAV total antibody assays has been reported as: ≤4.2%,[147/] and 4.6 - 10.5%.[148/]

Inter-assay reproducibility (CV) of anti-HAV IgM assays has been reported to be 4.5 - 13.4%,[149/] 1.7 - 4.4%,[150/] and 4.3 - 13.3%.[151/] Inter-assay reproducibility (CV) of anti-HAV total antibody assays has been reported as: <10%,[152/] ≤7.0%,[153/] and 5.3 - 17.5%.[154/]

The preceding data represent the state of the art in assay precision, and adequate reproducibility has been shown over the long history of safe and effective use of these assays.

Clinical sensitivity and specificity

Technological advances since the first HAV-specific antibody test was approved in 1979 have sustained the robust clinical accuracy of anti-HAV IgM and total antibody tests. Early manual assays required significant sample dilution, multiple assay steps, and about 2 days for a reportable result. The advent of the Abbott IMx assays introduced speed in

---

143/ For examples, HAVAB®-M EIA, Abbott Laboratories, 1992, #83-7219/R9, and HAVAB®EIA, Abbott Laboratories, 1991, #83-7196/R8.

144/ Access® HAV IgM, Beckman Coulter, 1998, #104951C HAV IgM, p. 3 (authorized for marketing outside of the U.S.).

145/ IMx HAVAB®-M, Abbott Laboratories, 1990, #83-5742/R2, p. 8.

146/ ETI-HA-IGMK PLUS, DiaSorin Inc., 2002, Catalog No. P001925, p. 13.

147/ IMx HAVAB®, Abbott Laboratories, 1997, #68-1597/R6, p. 10.

148/ ETI-AB-HAVK PLUS, DiaSorin Inc., 2002, Catalog No. P001926, p. 13. Intra-assay reproducibility of 38.6%, which is reported for the high positive sample tested with this competitive assay, corresponds to a response that is both remote from the decision point of the test, and based on a mean absorbance value of 0.004 that is very near the detection limit of the microwell plate reader.

149/ Access® HAV IgM, Beckman Coulter, 1998, #104951C HAV IgM, p. 3.

150/ IMx HAVAB®-M, Abbott Laboratories, 1990, #83-5742/R2, p. 8.

151/ ETI-HA-IGMK PLUS, DiaSorin Inc., 2002, Catalog No. P001925, p. 13.

152/ Access® HAV Ab, Beckman Coulter, 1999, #105223A HAV Ab, p. 3.

153/ IMx HAVAB®, Abbott Laboratories, 1997, #68-1597/R6, p. 10.

154/ ETI-AB-HAVK PLUS, DiaSorin Inc., 2002, Catalog No. P001926, p. 13. Inter-assay reproducibility of 42%, which is reported for the high positive sample tested with this competitive assay, corresponds to a response that is both remote from the decision point of the test, and based on a mean absorbance value of 0.004 that is very near the detection limit of the microwell plate reader.

obtaining reportable results (24 tests in less than 45 minutes), full automation that included specimen dilution, and enhanced reproducibility, while preserving clinical accuracy. Reports in the scientific literature have demonstrated the clinical sensitivity (how often the test is correct in diseased patients), and clinical specificity (how often the test is correct in non-diseased patients) for these IVDs by analyses of performance with clinical specimens.

For example, in 1991, a fully automated EIA for detecting HAV-specific IgM, IMx HAVAB-M, yielded equivalent clinical accuracy to commercial EIA and RIA methods. In clinical studies, 983 specimens were tested by IMx HAVAB-M and EIA and another 490 specimens were tested by IMx HAVAB-M and RIA. Agreement between IMx and EIA was 99.8% (981/983); and agreement between IMx and RIA also was 99.8% (489/490). These data demonstrated the equivalent clinical accuracy of IMx HAVAB-M and commercial EIA and RIA assays.[155/] Another similar IMx HAVAB-M comparison yielded equivalent results.[156/]

Additionally, tests for measuring total HAV-specific antibody have been used to assess immune status in naturally infected and experimentally vaccinated individuals, as well as in epidemiological studies. In 1991, IMx HAVAB, which is a fully automated EIA for detecting anti-HAV antibodies (both IgM and IgG subclasses), yielded equivalent clinical accuracy to commercial EIA and RIA tests. Three clinical laboratories tested 1377 specimens in parallel with IMx HAVAB and EIA or with IMx HAVAB and RIA. Intra-laboratory studies yielded 99.7% (742/744) agreement between IMx and RIA or EIA methods. Overall agreement between the IMx and commercial assays was 99.9% (1376/1377). Thus, technological advances since the first HAV-specific antibody test was approved in 1979 have sustained the robust clinical accuracy of anti-HAV IgM and total antibody tests.

Additional evidence of safety and effectiveness in approved PMAs

Finally, additional evidence on the safety and effectiveness of IVDs for anti-HAV IgM and total antibodies is available in the PMAs that have been submitted to FDA for marketing approval of theses products. Pursuant to Section 520(h)(4)(A)(iv) of the FFDCA,[157/] information contained in an application filed with FDA for premarket approval for a Class III device, including information from clinical and pre-clinical tests or studies that demonstrate the safety and effectiveness of the device, but excluding descriptions of methods of manufacture and product composition and other trade secrets, is available, 6 years after an application has been approved by FDA, for use in reclassifying another device. FDA, therefore, can use the evidence in the 8 approved

---

155/ K. Eble et al., 1991. Differential diagnosis of acute viral hepatitis using rapid, fully automated immunoassays. Journal of Medical Virology 33:139-150.

156/ M.A. Chernesky et al., 1991. The diagnosis of acute viral hepatitis A or B by microparticle enzyme immunoassay. Journal of Virological Methods 34:291-296.

157/ 21 U.S.C. 360j(h)(4)(A)(iv).

PMAs, plus many supplements, for these IVDs as further support of the safety and effectiveness of these devices.

3. A long history of 24 years of safe and effective use of IVDs for anti-HAV IgM and total antibodies in the U.S. supports reclassification

The long history of safe and effective use of IVDs for anti-HAV IgM and total antibodies further supports the reclassification of the devices from Class III to Class II. IVDs intended for use in clinical laboratories for the detection of anti-HAV IgM and total antibodies, Product Code LOL, were first approved by FDA in 1979.[158/] Commercial assays for anti-HAV IgM have been available in an RIA format since 1980, and in an EIA format since 1982.[159/] Abbott Laboratories adopted the test to run on its IMx automated clinical laboratory instrument, using a microparticle enzyme immunoassay technology.[160/] Indeed, because of the reliability of these tests, detection of IgM anti-HAV antibodies is considered to be the gold standard for HAV diagnosis.[161/]

Further, there have been very few reports of adverse events involving these medical devices. A search of FDA's Medical Device Reporting ("MDR")[162/] and Manufacturer and User Facility Device Experience ("MAUDE")[163/] databases reveal only 18 reports of adverse events or product malfunctions, with 17 occurring between 1994 and 1996, and only one occurring between 1997 and 2003. Importantly, none of the 18 reports was for patient injury resulting from the product malfunction. The content of these reports is as follows: 1 report of malfunction of data analysis program in 2002; 2 reports of no "alert" issued for an empty sample well; 1 report of the positive control out of range; 1 report of poor precision associated with certain tray positions; and 13 reports of discrepant results. Furthermore, search of FDA and public databases revealed only one relevant product recall, for the software used with the ETI-HA-IGMK Plus Enzyme Immunoassay for anti-HAV IgM antibody.[164/]

158/ Abbott Laboratories' HAVAB, P780012, Decision Date 01/19/1979.

159/ D.J. Robbins et al., 1991. Detection of total antibody against hepatitis A virus by an automated microparticle enzyme immunoassay. Journal of Virological Methods 32: 255-263; K. Eble et al., 1991. Differential diagnosis of acute viral hepatitis using rapid, fully automated immunoassays. Journal of Medical Virology 33:139-150.

160/ K. Eble et al., 1991. Differential diagnosis of acute viral hepatitis using rapid, fully automated immunoassays. Journal of Medical Virology 33:139-150.

161/ S.R. Weston and P. Martin, 2001. Serological and molecular testing in viral hepatitis: An update. Canadian Journal of Gastroenterology 15:177-184.

162/ The MDR database contains information on medical devices that may have malfunctioned or caused a death or serious injury during the years 1992 through 1996. Since 1996, all reportable events are included in the MAUDE database.

163/ The MAUDE database consists of all voluntary reports of adverse events involving medical devices since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996.

164/ F-D-C Reports ("The Gray Sheet"). FDA Recalls & Court Actions: Medusa Software (Sept. 2, 2002).

The number of reported adverse events and safety recalls is extraordinarily low, especially considering the large number of people that have been tested with HAV diagnostics. The CDC states that during epidemic years, the number of reported HAV cases reached 35,000.[165/] However, the number of reported HAV cases underestimates the number of HAV diagnostic tests performed, because it does not account for those who are tested, but are negative for the virus. Moreover, symptoms of HAV infection are indistinguishable from those resulting from other types of hepatitis viruses,[166/] and patients with suspected acute hepatitis are tested to confirm and categorize the viral etiology.[167/] Thus, the number of patients tested for HAV significantly exceeds the number of reported, and suspected cases of HAV, likely in excess of 50,000 every year.

Searches of similar databases of Health Canada and United Kingdom's Medicines and Healthcare Products Regulatory Agency ("MHRA") failed to reveal any adverse events or safety recalls associated with HAV diagnostic devices. Thus, the worldwide marketing history of the HAV diagnostic testifies to its safety. Although Abbott Laboratories, a manufacturer of an IVD for detection of anti-HAV IgM and total antibodies, entered into a consent decree with FDA due to Agency concerns with that company's good manufacturing practices for its IVD products,[168/] no serious adverse events were reported with use of the HAV IVD diagnostic, despite these manufacturing concerns.[169/]

Further evidence that the safety and effectiveness of IVDs for anti-HAV IgM and total antibodies is well established can be derived from comments of experts in the field. The recognized importance of these IVDs in the diagnosis of HAV is illustrated by references to them as "the gold standard."[170/] Well regarded experts on HAV infection have stated that "highly sensitive immunoassays have been developed for detecting antibodies for HAV."[171/] An expert has been quoted as saying, in reference to the commercial assays for detecting anti-HAV antibodies, that there are "no concerns at all about the current

---

165/ See http://www.cdc.gov/ncidod/diseases/hepatitis/a/fact.htm.

166/ D.M. Wolk et al., 2001 Laboratory diagnosis of viral hepatitis. In Infectious Disease Clinics of North America. The Role of the Clinical Microbiology Laboratory in the Diagnosis and Therapy of Infectious Disease. Cockerill, ed. 15: 1109-1126.

167/ Y.K. Chitkara and M.D. Fontes, 1999. Guidelines for serological testing in the diagnosis of acute hepatitis A and B. Diagnosis and Microbiology of Infectious Diseases 33: 241-245.

168/ "Abbott Labs Signs Consent Decree with FDA; Agrees to Correct Manufacturing Deficiencies" (Nov. 2, 1999), online at http://www.fda.gov/bbs/topics/NEWS/NEW00697.html.

169/ "Devices Which Can Be Sold or Distributed in the United States and Internationally after December 6, 1999" online at http://www.fda.gov/cdrh/ocd/ForSale12-6.pdf; see also "Dear Colleague Letter: Abbott Labs Consent Decree" (Nov. 3, 1999) online at http://www.fda.gov/cdrh/ocd/abbottletter.html.

170/ S.R. Weston and P. Martin, 2001. Canadian Journal of Gastroenterology 15(3):177-184.

171/ F.B. Hollinger et al., 1991. Hepatitis viruses. In: A. Balows et al., eds. Manual of Clinical Microbiology. 5th ed. American Society for Microbiology, Wash. DC, 959-983.

assays for detecting immunity, nor do I have any concerns at all about acute infection. I think the IgM assay is an excellent assay and the total antibody is also."[172/]

Indeed, these assays for detecting anti-HAV IgM and total antibodies are so highly regarded, that experts have not perceived a need to develop more sensitive assays. For example, in a review on HAV vaccine, it was stated that the "ease, accuracy, and sensitivity of the serological tests preclude the necessity of specialized assays," such as polymerase chain reaction, to detect virus in clinical samples.[173/] This well-established history of safe and effective use, therefore, provides strong support for the reclassification of these IVDs to Class II.

4. Reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the regulatory status of IVDs for HAV IgM and antibodies in the EU and Canada

Reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the regulatory status for these IVDs in the EU and Canada. In the EU, classification is based on risk, and the 1998 Directive on In Vitro Diagnostics Medical Devices ("IVDD") states that HAV is not one of the "certain types of hepatitis [that] require a conformity assessment guaranteeing, with a view to their design and manufacture, an optimum level of safety and reliability." Moreover, the Commission Decision of 7 May 2002 on common technical specifications for *in vitro* diagnostic medical devices (2002/364/EC) explicitly includes HBV, HCV, and HDV, and not HAV, as higher risk devices. Importantly, this lower level of regulatory control in the EU has not resulted in reports of adverse events associated with these IVDs, which demonstrates that Class II status in the U.S. would provide an adequate level of control.

Similarly, in Canada, a risk-based classification system is used,[174/] and IVDDs for HAV antibodies are Class II.[175/] In Canada, IVDDs are classified as Class II if they present a low community risk, because they detect infectious agents that are not known to be easily propagated in the Canadian population, or the infectious agents normally cause self-limiting diseases. Because HAV is recognized as presenting a low risk to community, and causing an acute, not chronic, self-limiting infection, Health Canada has classified IVDs to aid in the diagnosis of HAV infection as Class II. Importantly, adverse events or safety recalls have not resulted from this less stringent classification in Canada.

172/ Comments of Dr. F.B. Hollinger at the Microbiology Devices Panel Meeting on Feb. 12, 1998 in discussions of performance tests for the diagnosis and monitoring of viral hepatitis.

173/ S.M. Feinstone and I.D. Gust, 1999. Hepatitis A Vaccine. In: S.A. Plotkin and W.A. Orenstein, eds. Vaccines 3rd ed. W.B. Saunders Comp., Phila., 650-671.

174/ Medical Devices Regulations, Schedule 1, Part 2, *In Vitro* Diagnostic Devices, *Use with Respect to Transmissible Agents.*

175/ Health Canada, Guidance for the Risk Based Classification System of *In Vitro* Diagnostic Devices (Draft #2, March 17, 1998).

Therefore, reclassification by FDA would provide consistency with the regulatory status of these IVDs in the EU and Canada.

5. Reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the "least burdensome" principles of FDAMA

Reclassification of IVDs for anti-HAV IgM and total antibodies to Class II is consistent with the "least burdensome" principles of FDAMA. FDAMA requires consideration of the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in marketing approval. Given the long history of safe and effective use of these IVDs, a determination of substantial equivalence to marketed products via a 510(k) premarket notification should be sufficient to clear these well-established diagnostic devices.

Given the changes that have occurred in the epidemiology of HAV infections, it is now unduly burdensome to undertake Class III testing to support refinements to these products. While HAV diagnostics are considered the "gold standard," manufacturers nevertheless continually seek to improve these products, but must weigh the potential benefits against the cost and burden of conducting product testing. Such testing has become more difficult to undertake, because the incidence of HAV infections in the U.S. has declined as a result of continuing improvements in sanitation, and the availability of safe and effective vaccines to prevent naturally occurring infections. Because individuals at risk of infection with HAV are targeted for vaccination, it is difficult to obtain seroconversion panels consisting of pre- and post-HAV infection samples from the same individual. Obtaining these panels, however, would not be necessary under a substantial equivalence standard. The Agency's longstanding review policy in making the substantial equivalence determination for IVDs involves "comparative device descriptions, including performance characteristics; and . . . performance testing . . . [involving] analytical testing (i.e., precision, accuracy, limit of detection, cross-reactivity, and effects of interfering substances, and clinical sensitivity/specificity)."[176/]

Comparison of new IVDs for anti-HAV IgM and total antibodies to reliable, established products has been supported by several government experts. For example, the comments of Dr. Jay Hoofnagle (National Institutes of Health, National Institute of Diabetes, and Digestive and Kidney Diseases, Director, Division of Digestive Diseases and Nutrition) and Dr. Gutman at a Microbiology Devices Panel Meeting[177/] are supportive of clearance of a 510(k). Dr. Hoofnagel is quoted as saying:

176/ CDRH, Office of Device Evaluation, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, 5 (Oct. 4, 2002).

177/ Microbiology Devices Panel Meeting, Medical Advisory Committee Meeting to discuss characterizing performance of tests for the diagnosis and monitoring of viral hepatitis (Feb. 12, 1998).

> "It seems that for anti-HAV tests that reliance on comparison to previous assays would be of great value in evaluating new tests, because as you say, when you have a natural infection with HAV, you make high levels of antibody. . . . So, it seems to me it would be very valuable to compare your new test to the established tests that have been around a while and are pretty reliable."

Dr. Gutman was quoted as saying for a new HAV antibody test:

> "maybe we could in fact, take the predicate and take some modest clinical data, in fact, develop a mechanism for bringing it to market. . . . maybe the assay should be down-classified from a Class III."

Consistent with least burdensome principles, the goal of FDA's classification process is to seek the least restrictive level of regulatory control necessary to ensure the safety and effectiveness of the device. FDA's "least burdensome" guidance acknowledges that reclassification should be used to ensure that the proper level of regulatory control is applied to a device type, and reinforces "the Medical Device Amendments of 1976 directive to continue to consider the lowest appropriate level of regulatory control sufficient to provide reasonable assurance of the safety and effectiveness of the device."[178/]

G. Reasons with supporting data on how the proposed classification will provide reasonable assurance of the safety and effectiveness of the device[179/]

1. General and Special Controls

General controls and special controls provide reasonable assurance of safety and effectiveness of IVDs for anti-HAV IgM and total antibodies.[180/] The general controls provisions of the FFDCA include: prohibitions against adulteration and misbranding; device registration and listing requirements; premarket notification; good manufacturing practices ("GMP") (i.e., Quality Systems Regulation, "QSR"); records and reports; and restricted devices. Those provisions that specifically address the assurance of safety and effectiveness of IVDs for anti-HAV IgM and total antibodies when down-classified are: premarket notification (510(k)) review, QSR, and postmarket controls.

Premarket notifications (510(k)s) for IVDs for anti-HAV IgM and total antibodies will provide data and information establishing the substantial equivalence of the IVDs to legally marketed HAV antibody tests.[181/] A demonstration of substantial equivalence

---

178/ CDRH, Office of Device Evaluation, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, 17 (Oct. 4, 2002).

179/ 21 C.F.R. § 860.123(a)(6).

180/ 21 C.F.R. § 860.7.

181/ According to FDA's on-line PMA database, 8 PMAs have been approved for product code LOL.

means that the device has the same intended use, and the same or different technological characteristics. If technological characteristics differ, then it must be demonstrated that the new device does not raise different questions of safety and effectiveness.[182/] Moreover, there must be accepted scientific methods for assessing the effects of the new characteristics, and data to demonstrate that the device is not less safe or effective than the predicate device.

The current GMP requirements, as set forth in the QSR,[183/] describe the components of a quality system (i.e., design, manufacture, packaging, labeling, storage, installation, and servicing) that must be in place for all finished devices, regardless of device classification, that are intended for human use via commercial distribution in the U.S. Thus, QSR requirements are not driven by device classification, and apply to Class I, II, and III devices. All IVDs must be manufactured in compliance with GMP requirements,[184/] including requirements on complaint files,[185/] and records.[186/] Any device that fails to meet specifications and/or has caused an adverse event will be investigated, and corrective actions will be taken.

In addition, postmarket controls provide for the continued safe use of IVDs. MDR requirements help to ensure the continued safe use of a device once it is on the market.[187/] Pursuant to MDR requirements, a manufacturer must notify FDA whenever it receives complaints that a device it markets may have caused or contributed to a death or serious injury, or reports of device malfunctions that, if they were to recur, would be likely to cause or contribute to a death or serious injury. Therefore, MDRs provide both the manufacturer and FDA with a means to identify and monitor significant adverse events associated with medical devices, enabling manufacturers to detect and correct problems with devices in a timely manner, which further ensures the safety and effectiveness of IVDs irrespective of classification.

In the event that device problems require correction in, or removal from, the field, FDA correction and removal regulations, also applicable to all classes of devices, require that certain reports be made to FDA and/or records be created and maintained. These regulations provide FDA with another mechanism to ensure the safety and effectiveness of devices in the field.

Currently available special controls, i.e., existing performance standards, and FDA guidance documents, also will provide reasonable assurance of safety and effectiveness of IVDs for anti-HAV IgM and total antibodies. Among the existing performance standards that can be used as special controls are NCCLS guidelines, the

---

182/ 21 C.F.R. § 807.100(b)(2)(ii)(C).

183/ 21 C.F.R. Part 820.

184/ 21 C.F.R. § 809.20.

185/ 21 C.F.R. § 820.198.

186/ 21 C.F.R. § 820.180.

187/ 21 C.F.R. Part 803.

European/British Standard for the performance evaluation of *in vitro* diagnostic medical devices, and international standards for anti-HAV immunoglobulin. One of the NCCLS guidelines that is available as a special control is entitled "Specifications for Immunological Testing for Infectious Diseases" (I/LA18-A2). This document sets forth guidelines for the performance of immunodiagnostic tests for antibody responses to infectious agents, and focuses on improving the negative and positive predictive values in diagnosis of disease, and on enhancing interlaboratory comparability and performance. Indeed, FDA has included this NCCLS document as special controls for IVDs for other viruses, e.g., Rubella virus,[188/] that are Class II devices.

Another existing performance standard that would serve as an appropriate special control for these IVDs is the European/British Standard for the performance evaluation of *in vitro* diagnostic medical devices (EN 13612:2002). This standard describes how a manufacturer can fulfill its obligation to conduct a scientifically sound performance evaluation study for IVDs, if a performance evaluation study is necessary to support performance claims. It specifies the responsibilities and general requirements for the planning, conduct, assessment, and documentation of a performance evaluation study by the manufacturer.

In addition to guidelines, FDA has used reference standards as special controls.[189/] A reference standard for anti-HAV immunoglobulin was first established by WHO in 1981,[190/] and the Second International Standard for HAV immunoglobulin was established in 1998 from immunoglobulin supplied by the Central Laboratory of the Netherlands Red Cross, Amsterdam.[191/] This WHO reference standard was calibrated in an international collaborative study, which consisted of 16 laboratories from 11 countries contributing data derived from 64 assays that were performed using 6 commercial assay kits and 4 in-house methods.[192/] It was adopted as a standard by the WHO Expert Committee on Biological Standardisation, and is available to manufacturers as a reference standard.

In addition, there are several existing FDA guidance documents that would serve as appropriate special controls. These are: (1) Review Criteria For In Vitro Diagnostic Devices For Detection of IgM Antibodies To Viral Agents (Aug. 1992); (2) Guideline for the Manufacture of In Vitro Diagnostic Products (Jan. 10, 1994); and (3) Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Draft

---

188/ 21 C.F.R. § 866.3510.

189/ For example, WHO's International Rubella Standard. 21 C.F.R. § 866.3510.

190/ R.J. Gerety et al., 1982. Standardization of the antibody to hepatitis A virus (anti-HAV) content of immunoglobulin. Development of Biological Standards 54:411-416.

191/ 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).

192/ M. Ferguson et al., 2000. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. Biologicals 28:233-240.

Guidance for Industry and FDA Reviewers (March 12, 2003). These guidances, together with the performance standards described above, would provide appropriate special controls for regulating IVDs for detection of anti-HAV IgM and total antibodies as Class II devices.

2. Additional factors to be considered in determining the safety and effectiveness of a device for purposes of classification[193/]

There are additional factors to be considered in determining the safety and effectiveness of a device for purposes of classification, including: a) skilled intended user[194/]; b) conditions of use in the labeling[195/]; c) interpretation of results by a physician; and d) additional aids in diagnosing HAV infection.

a. Skilled intended user

IVDs for detection of anti-HAV IgM and total antibodies are used by skilled technicians, who generally are functioning in clinical laboratories with extensive experience and expertise in running laboratory tests. This knowledge base and skill provide an added level of protection to ensure the safe and effective use of these devices.

b. Conditions of use in the labeling and advertising

The conditions of use of the IVDs for the detection of anti-HAV IgM and total antibodies are explicitly addressed in the labeling of the devices. Advertising is directed towards skilled users, usually clinical laboratories that specialize in running many IVDs. Because these IVDs have been commercially available for 24 years, there is extensive knowledge on the information required for their safe and effective use, which is communicated in labeling and advertising.

c. Interpretation of results by a physician

The results of tests for the detection of anti-HAV IgM and total antibodies are interpreted by a physician, who is aware of the potential problems with these and other IVDs, and can request a repeat of the test, or additional testing if erroneous results are suspected.

d. Additional aids in diagnosing HAV infection

There are additional aids in the diagnosis of HAV infection. The diagnosis of viral hepatitis involves clinical, laboratory, and epidemiological findings.[196/] Hepatitis is

---

193/ 21 C.F.R. § 860.7(b).

194/ 21 C.F.R. § 860.7(b)(1).

195/ 21 C.F.R. § 860.7(b)(2).

196/ D.M. Wolk et al., 2001. Laboratory diagnosis of viral hepatitis. In Infectious Disease Clinics of North America. The Role of the Clinical Microbiology Laboratory in the Diagnosis and Therapy of Infectious Disease. Cockerill, ed. 15: 1109-1126.

generally suspected based on presenting symptoms, although the symptoms do not allow identification of the etiologic agent of viral hepatitis, and by the time symptoms develop (mean of 30 days after infection, range of 15 to 50 days), anti-HAV IgM is usually detectable.[197] Serum ALT[198] and bilirubin usually rise concomitantly with dark urine and jaundice,[199] and serum transaminase level has been reported as a reliable screen for acute infection by hepatitis virus.[200] Rapid laboratory diagnosis of acute viral hepatitis usually involves analyses for HBV and HCV as well, including HBV surface antigen, IgM to HBV core antigens, and IgM to HCV.[201] Consequently, multiple laboratory tests are used to identify the correct viral pathogen.

In addition to the clinical and laboratory findings, epidemiological information, such as travel to endemic areas or disruptions in hygiene due to natural disasters, may suggest increased potential for infection by pathogens that are transmitted by the fecal-oral route, such as HAV. Therefore, the IVDs for detection of anti-HAV IgM and total antibodies are used in conjunction with these other sources of information to aid in the diagnosis of HAV infection.

3. Probable benefit to health from the use of the device weighed against any probable injury from such use[202]

In weighing the probable benefit to health from use of the device against any probable injury from use, the impact of an erroneous result, i.e., false positive and false negative results, needs to be considered from the patient and public health perspectives. First, a false positive result, that is erroneously determining that anti-HAV antibodies are present, would probably not cause any significant injury. If anti-HAV IgM is detected erroneously, an acute HAV infection could be diagnosed in the patient. No injury to the patient would occur because no therapy is available to treat HAV infection, and the patient would not be administered any therapy, other than supportive care. If anti-HAV total antibodies are detected erroneously, the patient may not receive a vaccine for HAV, and could be at risk for a naturally occurring infection. However, HAV infections are generally self-limiting without serious consequences.

The public health consequences of a false positive are also minimal. HAV infection is a nationally notifiable disease, and reporting a false positive would impose a small administrative burden as a result of the notification procedures.

197/ Id.

198/ 21 C.F.R. § 862.1030 (Class I).

199/ R.S. Koff, 1982. Clinical manifestations and diagnosis of hepatitis A virus infection. Vaccine 10:S15-S17.

200/ Y.K. Chitkara and M.D. Fontes, 1999. Guidelines for serological testing in the diagnosis of acute hepatitis A and B. Diagn. Microbiol. Infect. Dis. 33:241-245.

201/ F.B. Hollinger and T.J. Liang, 2001. Hepatitis B Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 2971-3036.

202/ 21 C.F.R. § 860.7(b)(3).

Secondly, a false negative result, that is failure to detect anti-HAV antibodies, is not likely to cause a significant injury. The impact on the patient is minimal; therapy is not being withheld because no therapy is available. Public health consequences also are minimal because virus shedding already has occurred before symptoms appear,[203/] and with adequate hygiene there is minimal transmission to other individuals. Therefore, the probable benefit from the device far outweighs any probable injury from use of IVDs to detect anti-HAV IgM and total antibodies.

H. Representative data and information unfavorable to reclassification as Class II[204/]

We are unaware of any data and information that is unfavorable to reclassification of IVDs for the detection of anti-HAV IgM and total antibodies as Class II devices.

III. Financial Certification[205/]

Financial certification and disclosure by clinical investigators, consistent with 21 C.F.R. Part 54, are required for clinical studies submitted in support of reclassification petitions for medical devices.[206/] Because no clinical studies are included in this request for reclassification, financial certification and disclosure forms are not being submitted.

IV. Conclusions

In conclusion, Beckman Coulter, Inc. is requesting that IVDs for the detection of IgM and total antibodies reactive to HAV (Product Code LOL) be reclassified from Class III to Class II by FDA. In the 24 years since these IVDs were first approved for marketing, there have been significant changes in the public health considerations of the epidemiology, and in the understanding of the clinical consequences of HAV infections. Safe and effective vaccines for HAV have been available for the past eight years to target individuals at risk of infection, and improvements in sanitation and hygiene have made endemic transmission in the U.S. unlikely. It has also been established that HAV infection is an acute, self-limiting infection, with very low mortality.

Furthermore, the long history of safe and effective use of IVDs for the detection of anti-HAV IgM and total antibody supports their down-classification. The characteristics of these IVDs that are necessary for their safe and effective performance are well-established. There is valid scientific evidence, including widespread laboratory experience, published literature, international standards, voluntary guidances from national and international organizations, and lower classification by regulatory authorities

---

203/ F.B. Hollinger and S.U. Emerson, 2001. Hepatitis A Virus. In Fields Virology 4th ed. D.M. Knipe et al., eds. Lippincott Williams & Wilkins, Phila., 799-840.

204/ 21 C.F.R. § 860.123(a)(7).

205/ 21 C.F.R. § 860.123(a)(10).

206/ 21 C.F.R. § 54.1(a).

in the EU and Canada, that demonstrates that general and specific controls would provide reasonable assurance of the safety and effectiveness of IVDs for the detection of anti-HAV IgM and total antibodies.

FDA reserves Class III for new technology and high risk devices, and, consistent with least burdensome principles, the goal of FDA's classification process is to seek the least restrictive level of regulatory control necessary to ensure the safety and effectiveness of the device. IVDs for detecting anti-HAV IgM and total antibodies are no longer high risk or new technology devices warranting Class III status, and down-classification is justified.

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE --- FOOD AND DRUG ADMINISTRATION

GENERAL DEVICE CLASSIFICATION QUESTIONNAIRE

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 31, 2006
(See OMB Statement on Page 2)

PANEL MEMBER / PETITIONER
Beckman Coulter, Inc.

DATE
October 1, 2003

GENERIC TYPE OF DEVICE
In vitro diagnostic device for the detection of anti-Hepatitis A virus IgM and total antibodies to aid in the diagnosis of infection with Hepatitis A virus (product code LOL)

CLASSIFICATION RECOMMENDATION
Class II

1. IS THE DEVICE LIFE-SUSTAINING OR LIFE-SUPPORTING ?	☐ YES	X NO	Go to Item 2.
2. IS THE DEVICE FOR A USE WHICH IS OF SUBSTANTIAL IMPORTANCE IN PREVENTING IMPAIRMENT OF HUMAN HEALTH ?	☐ YES	X NO	Go to Item 3.
3. DOES THE DEVICE PRESENT A POTENTIAL UNREASONABLE RISK OF ILLNESS OR INJURY ?	☐ YES	X NO	Go to Item 4.
4. DID YOU ANSWER "YES" TO ANY OF THE ABOVE 3 QUESTIONS ?	☐ YES	X NO	If "Yes," go to Item 6. If "No," go to Item 5.
5. IS THERE SUFFICIENT INFORMATION TO DETERMINE THAT GENERAL CONTROLS ARE SUFFICIENT TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	☐ YES	X NO	If "Yes," Classify in Class I. If "No," go to Item 6.
6. IS THERE SUFFICIENT INFORMATION TO ESTABLISH *SPECIAL CONTROLS* IN ADDITION TO *GENERAL CONTROLS* TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	X YES	☐ NO	If "Yes," Classify in Class II and go to Item 7. If "No," Classify in Class III.
7. IF THERE IS SUFFICIENT INFORMATION TO ESTABLISH *SPECIAL CONTROLS* TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS IDENTIFY BELOW THE SPECIAL CONTROL(S) NEEDED TO PROVIDE SUCH REASONABLE ASSURANCE. FOR CLASS II. X Guidance Document: Existing guidances: NCCLS Specifications for Immunological Testing for Infectious Diseases (I/LA 18-A2); FDA, Guideline for the Manufacture of In Vitro Diagnostic Products (Jan. 10, 1994); FDA, Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (March 12, 2003); FDA, Review Criteria for In Vitro Diagnostic Devices for Detection of IgM Antibodies to Viral Agents (Aug. 1992); European/British Standard for the Performance Evaluation of *In Vitro* Diagnostic Medical Devices (EN 13612:2002). X Performance Standard(s): Existing WHO International Standard for Anti-Hepatitis A Immunoglobulin ☐ Device Tracking ☐ Testing Guidelines ☐ Other *(Specify)*			
8. IF A REGULATORY PERFORMANCE STANDARD IS NEEDED TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY ANDEFFECTIVENESS OF A CLASS II OR III DEVICE, IDENTIFY THE PRIORITY FOR ESTABLISHING SUCH A STANDARD. ☐ Low Priority _____ ☐ Medium Priority _____ ☐ High Priority _____ X Not Applicable Standard established: existing WHO International Standard for Anti-Hepatitis A Immunoglobulin			

9. FOR A DEVICE RECOMMENDED FOR RECLASSIFICATION INTO CLASS II, SHOULD THE RECOMMENDED REGULATORY PERFORMANCE STANDARD BE IN PLACE BEFORE THE RECLASSIFICATION TAKES EFFECT ?	X YES ☐ NO ☐ NOT Applicable	
10. FOR A DEVICE RECOMMENDED FOR CLASSIFICATION / RECLASSIFICATION INTO CLASS III, IDENTIFY THE PRIORITY FOR REQUIRING PREMARKET APPROVAL APPLICATION (PMA) SUBMISSIONS. ☐ Low Priority _____ ☐ Medium Priority _____ ☐ High Priority _____ X Not Applicable _____		

11. IDENTIFY THE NEEDED RESTRICTION(S)

☐ Only upon the written or oral authorization of a practitioner licensed by law to administer or use the device

X Use only by persons with specific training or experience in its use

☐ Use only in certain facilities

☐ Other *(Specify)*

13. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Health and Industry Programs (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration, (HFZ-215)
2094 Gaither Road
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

SUPPLEMENTAL DATA SHEET

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 31, 2003
(See OMB Statement on Page 2)

Panel Recommendation

1. GENERIC TYPE OF DEVICE
In vitro diagnostic device for the detection of anti-Hepatitis A virus IgM and total antibodies to aid in the diagnosis of infection with Hepatitis A virus (product code LOL)

2. ADVISORY PANEL
Microbiology Devices

3. IS DEVICE AN IMPLANT (21 CFR 860.3)?
☐ Yes X No

4. INDICATIONS FOR USE IN THE DEVICE'S LABELING
Indicated as an aid in the diagnosis of Hepatitis A virus infection, with detection of anti-Hepatitis A virus IgM differentiating an acute infection.

5. IDENTIFICATION OF ANY RISKS TO HEALTH PRESENTED BY DEVICE
General No risks to health presented by performance of the device

6. RECOMMENDED ADVISORY PANEL CLASSIFICATION ANDPRIORITY

Classification Class II Priority (Class II or III Only) High

7. IF DEVICE IS AN IMPLANT, OR IS LIFE-SUSTAINING OR LIFE-SUPPORTING AND HAS BEEN CLASSIFIED INA CATEGORY OTHER THAN CLASS III, EXPLAIN FULLY, THE REASONS FOR THE LOWER CLASSIFICATION WITH SUPPORTING DOCUMENTATION AND DATA
Device is not an implant or life-supporting.

8. SUMMARY OF INFORMATION, INCLUDING CLINICAL EXPERIENCE OR JUDGMENT, UPON WHICH CLASSIFICATION RECOMMENDATION IS BASED
In vitro diagnostic devices ("IVDs") for detecting anti-Hepatitis A virus IgM and total antibodies were first approved 24 years ago, and are no longer high risk or new technology devices warranting Class III status. There have been significant changes in the public health considerations of the epidemiology, and in the understanding of the clinical consequences of hepatitis A virus infections. Safe and effective vaccines for this virus have been available for the past 8 years to target individuals at risk of infection, and improvements in sanitation and hygiene have made endemic transmission in the U.S. unlikely. It has also been established that hepatitis A virus infection is an acute, self-limiting infection, with very low mortality.

The long history of safe and effective use of IVDs for the detection of anti-Hepatitis A virus IgM and total antibodies supports their down-classification. The characteristics of these IVDs that are necessary for their safe and effective performance are well-established. There is valid scientific evidence, including widespread laboratory experience, published literature, international standards, voluntary guidances from national and international organizations, and lower risk classification by regulatory authorities in Canada and the European Union that demonstrates that general and specific controls would provide reasonable assurance of the safety and effectiveness of IVDs for the detection of anti-Hepatitis A virus IgM and total antibodies. Therefore, down-classification to Class II is appropriate.

9. IDENTIFICATION OF ANY NEEDED RESTRICTIONS ON THE USE OF THE DEVICE *(e.g., special labeling, banning, or prescription use)*

Use only by persons with specific training or experience in its use.

10. IF DEVICE IS RECOMMENEDED FOR CLASS I, RECOMMEND WHETHER FDA SHOULD EXEMPT IT FROM

Justification / Comments

☐ a. Registration / Device Listing _____

☐ b. Premarket Notification _____

☐ c. Records and Reports _____

☐ d. Good Manufacturing Practice _____

11. IF DEVICE IS RECOMMENDED FOR CLASS II, RECOMMEND WHETHER FDA SHOULD EXEMPT IT FROM PREMARKET NOTIFICATION

☐ a. Exempt

X b. Not Exempt

Justifications/Comments

12. EXISTING STANDARDS APPLICABLE TO THE DEVICE, DEVICE SUBASSEMBLIES *(Components)* OR DEVICE MATERIALS *(Parts and Accessories)*

Existing standard: WHO International Standard for Anti-Hepatitis A Immunoglobulin

Existing guidances: NCCLS Specifications for Immunological Testing for Infectious Diseases (I/LA 18-A2); FDA, Guideline for the Manufacture of In Vitro Diagnostic Products (Jan. 10, 1994); FDA, Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (March 12, 2003); FDA, Review Criteria for In Vitro Diagnostic Devices for Detection of IgM Antibodies to Viral Agents (Aug. 1992); European/British Standard for the Performance Evaluation of *In Vitro* Diagnostic Medical Devices (EN 13612:2002).

13. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Health and Industry Programs (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration, (HFZ-215)
2094 Gaither Road
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR SUPPLEMENTAL DATA SHEET

1. The Supplemental Data Sheet should be prepared in conjunction with the General Device Questionnaire. The preparer should refer to Title 21 Part 860 of the Code of Federal Regulations for classification / reclassification definitions and procedures.

2. The Supplemental Data Sheet is designed to provide the device description, intended use, the risks of the device, the recommended class and the scientific support for the class and proposed level of controls.

3. The information requested by questions 1 through 8 must be provided for all devices.
4. Question 9 can be answered by referring to question 11 of the General Device Questionnaire.

5. Question 10 refers only to devices recommended for class I, and is a recommendation for exemptions form the General Controls listed.

6. Question 11 refers only to devices recommended for Class II.

7. Question 12 requests the listing of any existing standards for the device being classified. The standards to be listed could be standards drafted by professional groups, standards groups or manufacturers.

8. Send this completed form and the appropriate questionnaire to the address indicated in item 13.