

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: IgM Antibody to Hepatitis A Virus (Anti-HAV IgM Assay)

Device Trade Name: ADVIA Centaur[®] HAV IgM ReadyPack Reagents
ADVIA Centaur[®] HAV IgM Quality Control Materials

Applicant's Name and Address: Bayer HealthCare, LLC
511 Benedict Avenue
Tarrytown, NY 10591-5097

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P040018

Date of Notice of Approval to Applicant: December 22, 2004

II. INDICATIONS FOR USE

The ADVIA Centaur HAV IgM assay is an *in vitro* diagnostic immunoassay for the qualitative determination of IgM response to the hepatitis A virus (HAV) in human serum or plasma (EDTA, lithium heparinized, or sodium heparinized) using the ADVIA Centaur[®] System. This assay is intended for use as an aid in the diagnosis of acute or recent infection (usually 6 months or less) with hepatitis A virus.

III. CONTRAINDICATIONS

None known

IV. WARNINGS AND PRECAUTIONS

For in vitro diagnostic use only.

Warnings and precautions for ADVIA Centaur[®] HAV IgM ReadyPack Reagents and ADVIA Centaur[®] HAV IgM Quality Control Materials are stated in the respective product labeling.

V. DEVICE DESCRIPTION

Kit Configuration and Components

For detection of anti-HAV IgM, the ADVIA Centaur® HAV IgM Assay is comprised of the following:

- ADVIA Centaur HAV IgM ReadyPack primary reagent pack

The ADVIA Centaur HAV IgM Ready Pack primary reagent pack is composed of three components:

- Lite Reagent
Mouse anti-HAV human IgM monoclonal antibody labeled with acridinium ester in buffer with bovine serum albumin and preservatives.
- Solid Phase
Streptavidin coated paramagnetic microparticles with bovine serum albumin and preservatives
- Ancillary Well Reagent
Inactivated purified hepatitis A virus (<0.1 ug/ml) in buffer with bovine serum albumin and preservatives
- ADVIA Centaur HAV IgM ReadyPack ancillary reagent pack

ADVIA Centaur HAV IgM Ancillary Reagent is composed of biotinylated mouse monoclonal to anti-human IgM in buffer with bovine serum albumin and preservatives

In addition, the following components are required:

- ADVIA Centaur System is a dedicated random access instrumentation, which provides automated analysis of the Centaur assays.
- ADVIA Centaur HAV IgM quality control material which consist of a negative and positive control and an expected Value card.
- ADVIA Centaur Multi-Diluent 2 is goat serum with preservatives.
- ADVIA Centaur Wash 1 is PBS with preservatives.

A Principle of Device Methodology

The ADVIA Centaur HAV IgM assay is an IgM capture immunoassay uses a 2-pass format. It is designed for the qualitative detection of HAV IgM in human serum or plasma. The Assay reagent kit consists of an Ancillary Reagent containing biotinylated anti-human IgM monoclonal antibody, a Solid Phase containing streptavidin-coated paramagnetic microparticles, an ancillary well reagent containing inactivated HAV antigen and a Lite Reagent containing anti-HAV monoclonal antibody labeled with acridinium ester (AE).

Sample is diluted in a cuvette using on-board diluent. An aliquot of diluted sample is then transferred to a 2nd cuvette and incubated with the Ancillary Reagent for 6 minutes at 37°C. During this incubation biotinylated anti-human IgM monoclonal antibody binds to IgM present in the sample. The Solid Phase is added next, and the streptavidin-coated microparticles in the Solid Phase bind the biotin of the sample IgM / Ancillary Reagent complex during an 18 minute incubation at 37°C. The microparticles are then held fast by a magnet and washed multiple times to remove unbound sample. The Ancillary Well Reagent and Lite Reagent are next added and the reaction mix incubated for 18 minutes at 37°C. HAV antigen in the Ancillary Well Reagent binds to any HAV IgM present in the sample and the acridinium conjugated HAV antibody in the Lite Reagent binds to the HAV IgM/HAV antigen complex. The microparticles are then held fast by a magnet and washed multiple times to remove unbound Lite Reagent. The reaction mix is next reacted with acid and base to initiate a chemiluminescent reaction of the bound acridinium ester. The chemiluminescent signal is detected and quantified as relative light units (RLUs) by the photomultiplier tube (PMT) of the ADVIA Centaur Instrument. The RLUs detected by the ADVIA Centaur system are used to calculate the Signal-to-Cutoff (S/CO) value from the master curve. The RLU value is compared to a stored calibration curve to generate a patient result. A result of reactive, equivocal or nonreactive is determined according to the S/CO Value established with the calibrators.

Calibration

The ADVIA Centaur Anti-HAV IgM assay utilizes a factory set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The master curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The 2 calibrators in the kit are run when the lot is first used or after expiration of the calibrator interval (28 days). If the calibration run is valid as determined by prearranged parameters, the values are stored and used to “normalize” test values to the Master Curve.

The system reports HAV IgM results in S/CO Values and as reactive, equivocal, or nonreactive. Samples with a calculated value greater than or equal to 1.20 S/CO Value are considered reactive for IgM antibodies to hepatitis A virus.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Determination of the presence of anti-HAV IgM in patients may be achieved by using a number of commercially available, FDA licensed/approved, serological tests. When the results of such tests are evaluated in conjunction with a physician's assessment, other biochemical test results, susceptibility to HAV can be excluded.

VII. MARKETING HISTORY

The following is a list of countries where the ADVIA Centaur® HAV IgM Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act.

The Americas:	Colombia
Europe:	Sweden, Norway, Finland, France, Germany, Italy, Spain, Portugal, UK, Belgium, Austria
Africa:	South Africa
Asia:	China, Hong Kong, Singapore, Malaysia, Korea, Australia, New Zealand

The ADVIA Centaur® HAV IgM Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act.

This product has not been withdrawn from any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ADVIA Centaur® HAV IgM ReadyPack Reagents and ADVIA Centaur® HAV IgM ReadyPack Calibrators are for *in vitro* diagnostic use, thus there is no direct adverse effect on the patient. Failure of the product to perform as intended, or errors in the use of the product, may lead to a false result. A false non-reactive result does not exclude the possibility of exposure to hepatitis A virus. A non-reactive result may be due to IgM antibody levels below the detection limits of this assay. This assay is used in combination with other hepatitis assays to define the clinical status of known HAV infected patients or it can be combined with other HBV (hepatitis B virus), and HCV (hepatitis C virus) assays for the diagnosis of patients presenting symptoms of acute viral hepatitis. Since this assay is used in combination with other HAV assays, a non-reactive result cannot be considered a public health risk, as the individual would be tested with other methodologies if signs and symptoms are indicative of an acute HAV infection. A false reactive result would not be considered a public health risk due to the fact that an individual would be tested with other hepatitis A virus marker assays to define the clinical status of the patient.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

The following laboratory studies were conducted to determine the performance characteristics of the ADVIA Centaur HAV IgM assay. These laboratory studies included HAV performance panels, HAV seroconversion panels, potential cross reactive specimens, endogenous interferences, HAV IgG interference, DTT treatment of HAV IgM positive specimens, precision, matrix and collection tube type effects, sample handling, stability, microbial studies and instrument studies

HAV Performance Panels

Two commercially available performance panels comprised of anti-HAV IgM positive serum and/or plasma samples in a range of titers were tested with ADVIA Centaur HAV IgM reagents. One panel was from Cypress Diagnostics (CD) (Langdrop, Belgium) and the other from Boston Biomedica Inc. (BBI) (West Bridgewater, MA). For the CD panel the ADVIA Centaur HAV IgM results agree with the reference assay's results for 19 of 20 panel members. For one panel member the ADVIA Centaur HAV IgM assay gave an equivocal result whereas the competitor assay's result was positive. For all samples in the BBI panel the ADVIA Centaur HAV IgM result agrees with at least two of the three reference assay's results.

HAV Seroconversion Panels

Four commercially available HAV patient seroconversion panels from three vendors were tested with the ADVIA Centaur HAV IgM assay. Samples in the panels represent the patients' HAV seroconversion through early infection, acute phase, and recovery. The ADVIA Centaur HAV IgM assay results are compared to the results from another commercially available HAV IgM assay. In summary, the ADVIA Centaur assay detects all seroconversion panels as being reactive on the same day (same bleed number) as the reference's assays.

Potential Cross Reactive Specimens

A study was performed to evaluate the Centaur HAV IgM assay for potential cross-reactivity to other disease states, viruses, microorganisms or historically problematic specimens. One hundred fifty-seven distinct serums and plasma specimens from twenty groups of potential cross-reactants were assayed. The vendor used FDA approved methods to confirm the disease state of each specimen. ADVIA Centaur HAV IgM testing was done in singleton. One sample in the EBV IgG group was ADVIA Centaur equivocal & Abbott IMx HAVAB-M negative.

Table 1: Cross-Reactivity Study

Clinical Category	Number Tested	ADVIA Centaur HAV IgM Results		
		Nonreactive	Equivocal	Reactive
Hepatitis B Infection (HBV)	2	2	0	0
Hepatitis C Infection (HCV)	10	10	0	0
Epstein-Barr Virus (EBV) IgG	10	9	1	0
Epstein-Barr Virus (EBV) IgM	10	10	0	0
Herpes Simplex Virus (HSV) IgG	10	10	0	0
Herpes Simplex Virus (HSV) IgM	10	10	0	0
Syphilis IgG	10	10	0	0
Human Immunodeficiency Virus (HIV 1/2)	10	10	0	0
Varicella Zoster (VZV) IgG	10	10	0	0
Cytomegalovirus (CMV) IgG	2	2	0	0
Cytomegalovirus (CMV) IgM	3	3	0	0
Toxoplasma IgG	10	10	0	0
Toxoplasma IgM	9	9	0	0
Rubella IgG	10	10	0	0
Multiparity	10	10	0	0
Flu Vaccine Recipient	6	6	0	0
Rheumatoid Arthritis (RF)	9	9	0	0
Anti-Nuclear Antibody (ANA)	5	5	0	0
Systemic Lupus Erythematosus (SLE)	2	2	0	0
Human Anti-Mouse Antibodies (HAMA)	9	9	0	0
Total Samples Tested	157	156	1	0

Endogenous Interferents

The ADVIA Centaur HAV IgM assay was tested following the guidelines described by NCCLS EP7-P for interference due to high levels of endogenous substances. The effects of conjugated bilirubin @ 60 mg/dL, unconjugated bilirubin @ 40 mg/dL, hemoglobin @ 500 mg/dL, triglycerides @ 3000 mg/dL, and human serum albumin @ 12 g/dL (i.e. high total protein.) were evaluated in serum and plasma samples. No interference was found.

Interfering Substance-HAV IgG

Analysis of HAV seroconversion panel PHT902 (Boston Biomedica Inc.) demonstrates that HAV specific IgG in samples does not interfere with the ability of the ADVIA Centaur HAV IgM assay to detect HAV specific IgM. Sample obtained 163 days from 1st bleed was negative on Centaur HAV IgM assay and positive on a competitor HAV Total assay. In addition, ten anti-HAV IgM reactive samples (free of HAV IgG) were spiked with HAV IgG at levels from 27 – 405 mIU/mL. In all cases, no interference was observed.

DTT Treatment of HAV IgM Positive Specimens

Further support that the Centaur HAV IgM assay is specific for IgM antibody was demonstrated by testing HAV IgM specimens that had been treated with the reducing

agent, DTT. Incubation with the reducing agent causes the IgM within the samples to break apart, making it impossible for the Centaur HAV IgM assay format to detect. Twenty samples, covering the S/CO range of 0.71 – 4.81, (either native or spiked with HAV IgM positive pool) were used in the study. The samples were made 5mM in DTT and incubated for 1 hour at 37°C. Next, the samples were tested in the Centaur HAV IgM assay vs a control sample. The percent reduction of the signal upon treatment with DTT was calculated. Of the 15 positive, 4 equivocal and 1 high negative specimens tested, none return a positive result when reduced by DTT treatment. This indicates that the HAV IgM assay is specific for IgM class antibody.

Precision Studies

A twenty-day NCCLS precision study was performed. Frozen (-20°C) single donor units were obtained of each of the following anti-coagulants; Serum, K₂EDTA Plasma, Lithium Heparin Plasma, and Sodium Heparin. Each unit was used to prepare a five-member panel targeting the low to mid range of the assay. The same high titer anti-HAV IgM positive pool was used to prepare the spiked positive panel members. These samples were assayed in triplicates in each run along with calibrators and controls. Two runs were performed per day over 20 days on one instrument. All data were analyzed using a 2-point stored (day 0) calibration. Sample panel within run %CVs ranged from 2.8% to 9.4 %. Sample panel total %CVs ranged from 3.7% to 11%.

Matrix, Collection Tube Type, Effects

Blood was collected during in-house blood draws from 50 healthy, normal donors in glass and plastic serum tubes (red top), serum-SST, heparin (Na and Li) plasma (green top) and EDTA plasma tubes (purple top). The samples were tested on the Centaur as a negative donor population, then spiked with high titer HAV IgM positive pool plasma to form specimens that was also tested on the Centaur. Spiking volume was varied among samples in order to create a population in which the low to mid range of the assay was represented. Performance of samples collected in the various blood collection tubes were assessed by percent recovery vs the control condition (glass red top). Tube type compatibility is defined as 100± 20% overall recovery of the “test” tube type vs. the control red top and no change in the clinical status of the individual samples from the same donor.

Serum (red top; plastic), serum-SST (glass+ plastic) plasma/EDTA (glass+plastic) and plasma/heparin (Na+Li) (glass+plastic) provide S/CO % recoveries within 100±20% of the control condition. In addition, there is no change in the clinical status of the individual samples from the same donor. All the test tube types tested are recommended sample types for use in the ADVIA Centaur anti-HAV IgM assay. Heparin has been shown to increase the S/CO values in some HAV IgM reactive samples by up to 14% relative to serum. Equivocal and reactive heparin plasma samples near the cutoff should be interpreted accordingly.

Sample Handling Studies

The sample handling studies are a series of experiments in which specimens collected in all of the sample matrices claimed as suitable for use with the Centaur HAV IgM assay are subjected to potential stresses and tested to determine the impact of the stress on assay accuracy. The sample handling studies described here evaluate the effect of the following patient sample handling conditions on ADVIA Centaur HAV IgM S/CO value:

1. Extended time on-board the ADVIA Centaur Instrument
2. Extended time in refrigerated (2-8°C) storage.
3. Extended time at room temperature (25°C) storage.
4. Extended time in freezer (-20°C) storage.
5. Multiple freeze/ thaw (-20°C/2-8°C) cycles.

Samples were collected during in-house blood draws from healthy donors in serum and plasma with a variety of anti-coagulants. Samples were aliquotted and placed in appropriate storage/stress conditions on the day of collection. A baseline S/CO value for each sample was established by testing with the ADVIA Centaur HAV IgM assay on the day of collection. All % recoveries are calculated against the baseline (day 0) value. Results from the ADVIA Centaur HAV IgM sample handling studies indicate that samples can be subjected to the following conditions and still generate accurate results when tested in the ADVIA Centaur HAV IgM assay:

1. Samples can be kept on-board the Centaur instrument for up to 24 hours. to
2. Samples can be stored at room temperature for up to 8 hours.
3. Samples can be stored refrigerated (2-8°C) for up to 2 days.
4. Samples can be stored frozen (-20°C) for up to 180 days.
5. Samples can be frozen and thawed up to 4 times.

On-The-Clot Specimen Storage

Samples can be stored in the primary collection tubes at 4°C up to 2 days.

Sample Processing – Time to Centrifugation

A study was done to determine the effect of fresh sample time to centrifugation on the HAV IgM S/CO value. The recommendation in the package insert is to centrifuge samples within 2 hours post draw.

Sample Handling – Inversion of Gel barrier Collection tubes

A study was done to determine if inversion of barrier gel blood collection tubes interferes with ADVIA Centaur HAV IgM assay results. Blood was drawn from ten healthy volunteers in-house in the following tube types: Serum SST (plastic) and Plasma SST Lithium Heparin (plastic). Each donor tube was spiked with HAV IgM positive plasma.

Spiking levels varied from donor to donor in order to create spiked specimens in the low to mid range of the assay. After centrifugation an aliquot was taken and used as control. The tubes were then inverted five times and a 2nd aliquot was taken. Finally, the tubes were again inverted five times and a 3rd aliquot was taken. The 2nd and 3rd aliquots were compared to the control in order to determine if inversion altered sample S/CO value. Inversion of the barrier gel collection tube, 5 times, had no effect on the assay results for both positive and negative samples. The average % recovery is 100.1% for PST and 99.3% for SST.

Stability Studies

Real Time Stability Studies for Centaur ReadyPack reagents, calibrators and controls were conducted. All kits and reagents are stored at the recommended storage temperature of 2-8°C. Reagents, calibrators and controls are monitored at several checkpoints post manufacturing date. The Shelf-life studies presented support a claim of a 16 month expiration dating for the HAV IgM ReadyPack reagents. The Shelf-life studies presented support a claim of a 16 month expiration dating for the HAV IgM calibrators and controls.

Reagent On-Board Stability (OBS) Studies: Two lots of reagents have undergone reagent OBS studies on two Centaur instruments. OBS testing on the instruments occurs at several checkpoints after the reagent is placed on-board. A fresh pack serves as the control for each time-point. Dose recovery within 10% or 2SD of the fresh pack serves to define acceptable performance.

A calibration interval of 28 days was also evaluated using these results. The on-board studies for the reagents support 41 days OBS for the Centaur HAV IgM reagents. The OBS studies also support a re-calibration interval of 28 days.

The Shipping study of the reagents provides insight into the likelihood of aggregation and clumps occurring when the material is shipped to or handled by the customer. The recommended shipping conditions are to ship the ReadyPack reagents upright at 2-8°C and store at 2-8°C immediately after receiving.

The calibrator and control open bottle use study examine the length of time the calibrator or control is stable once the vial is opened. Open vials are stored at the recommended storage conditions of 2-8°C. The open bottles are sampled periodically up to 62 days post initial opening. Fresh (unopened) bottles are evaluated at each time point to serve as controls. The acceptance criteria for this study is dose recovery within 10% (or 2SD) of the fresh bottle dose. The study supports an open bottle use lifetime of up to 62 days.

A calibrator and control shipping study has also been performed. The HAV IgM calibrators and controls underwent 3x freeze/thaw cycles with no adverse effects.

Microbiology Studies

The ADVIA Centaur HAV IgM reagents contain 0.09% sodium azide, 0.002% Amphotericin B and 0.005% Gentamicin sulfate and the ADVIA Centaur HAV IgM calibrators and controls contain 0.2% Proclin 300 as a preservative to protect against adventitious contamination by microorganisms. Reagents, calibrators and controls were challenged in a study conducted according to USP requirements for Antimicrobial Effectiveness testing to assess the ability to withstand or control microbial contamination. The test involved testing seven microorganisms. The preservative showed bactericidal activity for all of the bacteria except *C. piscicola* where it was bacteriostatic. Results indicated that the preservative systems for reagents, calibrators and controls met the USP requirements for antimicrobial effectiveness testing.

A performance microbial challenge was performed using one lot of HAV IgM reagents, calibrators and controls. Reagents, calibrators and controls were inoculated with two pools of microbes at 10^3 and 10^6 CFU/mL then run on the Centaur instrument. Controls and QC panel all were within release ranges when tested using inoculated reagents at all time points. Inoculated Calibrator and Control S/CO values were consistent with the non-inoculated material, providing a dose recovery of 100+/-10% at day 65. No clinically significant changes in S/CO values were observed after using inoculated reagents versus control reagents.

Additionally, Bayer routinely performs microbial load testing during the manufacturing of ADVIA Centaur HAV IgM reagents, calibrators and controls. The microbial load for any batch must be < 50 CFU/ml.

Environmental Testing

The purpose of environmental testing is to assess ADVIA Centaur HAV IgM assay control recovery at the mean and extreme environmental conditions as specified. Each assay is calibrated and run on a single unit in an environmental chamber set at temperatures above and below room temperature. These studies demonstrated acceptable performance of the HAV IgM assay when performed on instruments operating at the extremes of the temperature range for the ADVIA Centaur instrument (18°C to 30°C).

Reagent Compatibility Testing

The purpose of this study was to confirm there are no primary reagent interactions for assays that share the same reagent probe, and might therefore be susceptible to reagent carryover affects. Mitigation of any interference identified is accomplished through Test Definition scheduling options, using multiple water washes, or, in rare occasions, a Wash Pack with a solution other than water may be required.

The ADVIA Centaur HAV IgM assay was evaluated for its potential affect on all other assays using the same reagent probes and for the affect of all the other assay reagents on the HAV IgM assay. To be accepted there must be <5% difference in dose between test

and control, or no statistically significant change in dose, or no more than 1SD difference in dose as appropriate for the assay and the control being tested.

There were no compatibility issues between this assay and any of the assays sharing the same reagent probe.

Conclusions Drawn from the Non Clinical Studies

The ADVIA Centaur® HAV IgM assay was evaluated to demonstrate performance claims for cross-reactivity, interference, precision, matrix type, specimen handling, and reagent stability. The results of the non-clinical studies will be used in conjunction with results of the clinical trial studies to support the intended use statements of the ADVIA Centaur® HAV IgM assay.

X. SUMMARY OF CLINICAL STUDIES

The objective of this clinical study was to assess the efficacy of ADVIA Centaur HAV IgM for the qualitative determination of IgM response to hepatitis A virus in human serum or plasma as presumptive evidence of an acute or recent infection with hepatitis A virus.

Study Design

The safety and effectiveness of the ADVIA Centaur® HAV IgM assay was determined by a clinical trial consisting of the following studies:

The prospective study consisted of patient samples from high risk for HAV population, signs and/or symptoms of HAV infection population, acute HAV infected population, HAV infected/HAV recovered population and hospitalized patient population. These samples were tested with both the ADVIA Centaur® HAV IgM assay and a reference HAV IgM assay at the clinical trial sites.

A study of retrospectively obtained samples from HAV acutely infected patients. These samples were tested with both the ADVIA Centaur® HAV IgM assay and a reference HAV IgM assay at the clinical trial sites.

A study of retrospectively (commercial vendor) obtained HAV seroconversion panels. These samples were tested with both the ADVIA Centaur® HAV IgM assay and a reference HAV IgM assay at the clinical trial sites.

A precision and reproducibility study in which a specimen panel was assayed over several days, at multiple clinical trial sites, and using multiple ADVIA Centaur® HAV IgM assay reagent lots. The results were analyzed to derive precision estimates.

A paired matrix study in which a subset of the prospective study samples was collected in serum, EDTA plasma, and lithium heparin plasma collection tubes. The samples from all collection tube types were then compared by testing in the ADVIA Centaur® HAV IgM assay.

These studies are described in detail below.

Gender Bias

- a. There was no selection bias on the basis of gender identified during the review. In a population of 949 patients which included both prospectively and retrospectively obtained specimens 42.26% (n=401) were women and 57.74% (n=548) were men.
- b. No difference in the safety and effectiveness of the Centaur HAV IgM assay based on gender was identified. The distribution of reactive and non reactive results were similar for both genders.

Expected Results

The ADVIA Centaur HAV IgM results for the prospective population for all sites combined by age group and gender are summarized in the following table:

ADVIA Centaur HAV IgM Assay
 Distribution of Prospective Population by Age Group and Gender; All Testing Sites

Age (years)	Gender	Reactive ^a		Equivocal ^b		Non-reactive ^c		Total	
		N	%	N	%	N	%	N	%
10-19	Female	0		0		2	100.00	2	40.00
	Male	0		0		3	100.00	3	60.00
	Overall	0		0		5	100.00	5	100.00
20-29	Female	0		0		36	100.00	36	59.02
	Male	0		0		25	100.00	25	40.98
	Overall	0		0		61	100.00	61	100.00
30-39	Female	0		0		71	100.00	71	47.02
	Male	0		0		80	100.00	80	52.98
	Overall	0		0		151	100.00	151	100.00
40-49	Female	0		0		93	100.00	93	35.63
	Male	0		1	0.60	167	99.40	168	64.37
	Overall	0		1	0.38	260	99.62	261	100.00
50-59	Female	0		0		75	100.00	75	36.76
	Male	0		1	0.78	128	99.22	129	63.24
	Overall	0		1	0.49	203	99.51	204	100.00
60-69	Female	0		0		45	100.00	45	45.92
	Male	0		0		53	100.00	53	54.08
	Overall	0		0		98	100.00	98	100.00
70+	Female	1	3.13	0		31	96.88	32	48.48
	Male	0		0		34	100.00	34	51.52
	Overall	1	1.52	0		65	98.48	66	100.00
Total	Female	1	0.28	0		353	99.72	354	41.84
	Male	0		2	3.44	490	99.59	492	58.16
	Overall	1	0.12	2	0.24	843	99.65	846	100.00

^a Sample with ≥ 1.2 S/CO. ^b Sample with $\geq 0.8 < 1.2$ S/CO. ^c Sample with < 0.8 S/CO

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Clinical Study Results

The prospective study population for the ADVIA Centaur HAV IgM assay consisted of 846 patients. Of these 846 patients, 249 patients (29.43%) were from the high risk population, 178 patients (21.04%) were from the signs and symptoms population, 2 patients (0.24%) were from the acute HAV infected patient population, 215 patients (25.41%) were from the HAV infected/HAV recovered patient population and 202 patients (23.88%) were from the hospitalized patient population. The prospective study population was 29.20% Caucasian, 37.59% Hispanic, 28.37% Black, 1.65% Asian, and 3.2% from unknown or other ethnicity. The majority of patients were male (58.16% male and 41.84% female). The mean age was 48.42 years (range of 18 to 101 years). Patients in the prospective study population were from the following geographic regions: Florida (58.39%), Texas (29.67%), and New York (11.94%).

The ADVIA Centaur HAV IgM assay results were compared to the reference HAV IgM assay results. The population evaluated consisted of 846 prospective subjects and 103 HAV acute samples obtained retrospectively. The method comparison for all subject categories across all testing sites is presented in the following table:

ADVIA Centaur HAV IgM
Method Comparison in all Subject Categories
ADVIA Centaur HAV IgM Assay vs. Reference HAV IgM Assay

All Testing Sites

Subject Category	Reference HAV IgM Assay									Total										
	Negative ADVIA Centaur HAV IgM Assay			Equivocal ADVIA Centaur HAV IgM Assay			Positive ADVIA Centaur HAV IgM Assay													
	Reactive N (%)	Nonreactive N (%)	Equivocal N (%)	Reactive N (%)	Nonreactive N (%)	Equivocal N (%)	Reactive N (%)	Nonreactive N (%)	Equivocal N (%)	N	(%)									
Acute HAV	0	0.00	1	0.95	0	0.00	0	0.00	2	1.90	0	0.00	99	94.29	1	0.95	2	1.90	105	11.06
Clinic or Hospitalized Patient	0	0.00	200	99.00	1	0.50	0	0.00	0	0.00	0	0.00	1	0.50	0	0.00	0	0.00	202	21.29
High Risk for Hepatitis A	0	0.00	248	99.60	0	0.00	0	0.00	1	0.40	0	0.00	0	0.00	0	0.00	0	0.00	249	26.24
Infected/Recovered HAV	0	0.00	214	99.53	0	0.00	0	0.00	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00	215	22.66
Signs and Symptoms of Hepatitis	0	0.00	176	98.88	1	0.56	0	0.00	1	0.56	0	0.00	0	0.00	0	0.00	0	0.00	178	18.76
Total	0	0.00	839	88.41	2	0.21	0	0.00	5	0.53	0	0.00	100	10.54	1	0.11	2	0.21	949	100.00

The percent agreement between the ADVIA Centaur HAV IgM assay and the reference assay for each specimen, including the upper and lower 95% confidence intervals, was presented in a table format. The positive, negative, and overall percent agreements were also calculated. The formulas used for these calculations are presented below.

Positive percent agreement =

$$\frac{\text{Number of ADVIA Centaur HAV IgM reactive results in agreement with reference HAV IgM}}{\text{Total number of reference HAV IgM reactive results}} \times 100$$

Negative percent agreement =

$$\frac{\text{Number of ADVIA Centaur HAV IgM nonreactive results in agreement with reference HAV IgM}}{\text{Total number of reference HAV IgM nonreactive results}} \times 100$$

Overall percent agreement =

$$\frac{\text{Number of ADVIA Centaur HAV IgM results in agreement with reference HAV IgM}}{\text{Total number of reference HAV IgM reactive and nonreactive results}} \times 100$$

For purposes of percent agreement calculations, the ADVIA Centaur equivocal results (n = 4) were assigned the opposite clinical interpretation than that of the comparative assay result and analysis performed. Comparative assay equivocals (n = 5) were removed from the analysis.

The percent agreement between the ADVIA Centaur HAV IgM assay and the comparative HAV IgM assay by subject category across all testing sites is summarized in the following table.

ADVIA Centaur HAV IgM Assay Percent Agreement and Confidence Intervals in All Subject Categories ADVIA Centaur HAV IgM Assay vs. HAV IgM Comparative assay All Testing Sites^a				
Subject Category	Positive Percent Agreement % (x/n) ^b	95% Exact Confidence Interval	Negative Percent Agreement % (x/n) ^c	95% Exact Confidence Interval
Acute HAV	97.06 (99/102)	91.64 to 99.39	100.00 (1/1)	2.50 to 100.00
Clinic / Hospitalized Patient	100.00 (1/1)	2.50 to 100.00	99.50 (200/201)	97.26 to 99.99
High Risk for HAV	0.00 (0/0)	NA	100.00 (248/248)	98.52 to 100.00
Infected / Recovered HAV	0.00 (0/0)	NA	100.00 (214/214)	98.29 to 100.00
Signs / Symptoms of HAV	0.00 (0/0)	NA	87.37 (176/177)	96.89 to 99.99
Total	97.09 (100/103)	91.72 to 99.40	99.76 (839/841)	99.14 to 99.97

a Five samples were excluded from the percent agreement analysis. All five samples were Comparative assay equivocal and ADVIA Centaur HAV IgM negative

b x = the number of ADVIA Centaur HAV IgM results that are reactive in agreement with the comparative HAV IgM; n = the total number of comparative HAV IgM results that are reactive

c x = the number of ADVIA Centaur HAV IgM results that are nonreactive in agreement with the comparative HAV IgM; n = the total number of comparative HAV IgM results that are nonreactive

Seroconversion Study

Four commercially available seroconversion panels were tested with the ADVIA Centaur HAV IgM assay and a reference HAV IgM assay. A summary of seroconversion results is presented in the following table:

Panel ID	Anti-HAV IgM Positive Result From Initial Draw Date		Comparative assay vs ADVIA Centaur Assay Difference (Bleeds)*
	Comparative assay (Days)	ADVIA Centaur Assay (Days)	
RP004	7	7	0
RP013	9	9	0
PHT902	16	16	0
ProMedx 1	1	1	0

* The difference in bleed numbers is relative to the comparative assay. In all seroconversion panels both the ADVIA Centaur assay and the comparative assay detected the first reactive sample at the same day.

Compared to the reference assay results, the first reactive time-point for the ADVIA Centaur HAV IgM assay occurred at the same time-point as the

Reference assay in all 4 panels.

Reproducibility

The ADVIA Centaur HAV IgM reproducibility study was performed at 3 testing sites utilizing 3 reagent lots per site. A 20-member panel (consisting of 5 samples in 4 matrices) and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The data from all 3 sites and from all 3 reagent lots were combined to achieve SD and percent CV for within-run, between-day, between-site, between-lot, and total. The precision estimates were derived from variance component analysis. The reproducibility results are presented in the following table:

Bayer ADVIA Centaur HAV IgM Assay
Reproducibility
Between Testing Sites and Between Reagent Lots Estimates
(Across All Reagent Lots and All Testing Sites)

Panel Member	Matrix or Control Lot	Mean ADVIA Centaur HAV IgM S/CO Value	Within Run ^a		Between Run ^b		Between Testing Site ^c		Between Lot ^d		T
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	
1	EDTA	0.09	0.01	N/A	0.00	N/A	0.01	N/A	0.04	N/A	0.04
1	Li Heparin	0.10	0.01	N/A	0.00	N/A	0.02	N/A	0.03	N/A	0.04
1	Na Heparin	0.11	0.01	N/A	0.00	N/A	0.02	N/A	0.03	N/A	0.03
1	Serum	0.09	0.01	N/A	0.00	N/A	0.02	N/A	0.04	N/A	0.04
2	EDTA	2.77	0.17	6.0	0.10	3.5	0.36	13.1	0.00	0.0	0.41
2	Li Heparin	2.85	0.19	6.7	0.14	5.0	0.39	13.6	0.00	0.0	0.46
2	Na Heparin	2.86	0.20	7.1	0.19	6.7	0.47	16.5	0.00	0.0	0.55
2	Serum	2.60	0.15	5.9	0.14	5.3	0.28	10.8	0.00	0.0	0.35
3	EDTA	1.08	0.05	4.7	0.02	2.0	0.09	8.6	0.00	0.0	0.11
3	Li Heparin	1.16	0.07	6.0	0.04	3.4	0.12	10.6	0.00	0.0	0.15
3	Na Heparin	1.16	0.08	6.6	0.05	4.7	0.13	10.8	0.00	0.0	0.16
3	Serum	1.01	0.06	5.5	0.04	3.7	0.08	8.1	0.00	0.0	0.11
4	EDTA	1.69	0.09	5.1	0.04	2.2	0.16	9.6	0.00	0.0	0.19
4	Li Heparin	1.84	0.09	4.7	0.08	4.5	0.23	12.5	0.00	0.0	0.26
4	Na Heparin	1.84	0.10	5.3	0.09	4.7	0.22	11.8	0.00	0.0	0.25
4	Serum	1.59	0.08	5.2	0.05	3.4	0.15	9.3	0.00	0.0	0.18
5	EDTA	0.54	0.03	5.8	0.02	3.7	0.06	12.0	0.00	0.0	0.07
5	Li Heparin	0.63	0.05	7.5	0.03	5.4	0.08	12.8	0.00	0.0	0.10
5	Na Heparin	0.62	0.04	6.5	0.04	6.8	0.08	12.1	0.00	0.0	0.10
5	Serum	0.53	0.03	5.1	0.02	3.8	0.06	11.9	0.00	0.0	0.07
Low Control	702034	0.08	0.00	N/A	0.00	N/A	0.02	N/A	0.03	N/A	0.03
High Control	702034	1.2	0.09	4.9	0.09	4.9	0.22	12.0	0.00	0.0	0.25

a Variability of the assay performance within day (all testing sites and reagent lots).

b Variability of the assay performance between days (all testing sites and reagent lots).

c Variability of the assay performance between testing sites (from testing site to testing site).

d Variability of the assay performance between reagent lots (from reagent lot to reagent lot, across all testing sites).

e Variability of the assay performance incorporating all testing sites, all reagent lots, and all days. Values < 0.02 (below the reportable range).

f The number of observations used to perform the mean value calculation. Values

CV = coefficient of variation

NA = Not applicable (Replicates of negative samples Panel member 1 and Low Control reported as below the reportable range were non-numeric and excluded from the analyses.)

Note: 5 replicates per panel in 1 run per day for 6 days

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multi-centered clinical studies were conducted in the US. The ADVIA Centaur HAV IgM assay performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

- The overall positive percent agreement between the ADVIA Centaur HAV IgM method and the reference assay was 97.09% (100/103) in the combined population (acute HAV, clinic/hospitalized patients, high risk for HAV, infected/recovered HAV patients, and signs/symptoms populations). The overall negative percent agreement between the ADVIA Centaur HAV IgM method and the reference assay was 99.76% (839/841) in the same combined population.
- The ability of the ADVIA Centaur HAV IgM assay to detect HAV infections was demonstrated with the seroconversion panel evaluation. When the ADVIA Centaur HAV IgM result was compared to the reference assay results, the first reactive time point for the ADVIA Centaur HAV IgG assay occurred at the same time as the Reference assay in all 4 panels.
- Precision and reproducibility of the ADVIA Centaur HAV IgM assay was good with minor variability from run to run, day to day, site to site and reagent lot to reagent lot.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur HAV IgM assay can be used safely and effectively for the qualitative in vitro determination of anti-HAV IgM in human serum and plasma. The ADVIA Centaur HAV IgM assay may be used with other HAV serological markers to define the clinical status of patients known to be infected with HAV or may be used with other HBV, HAV, and HCV assays

Risk Benefit Analysis

As a diagnostic test, the ADVIA Centaur HAV IgM Assay involves removal of blood from an individual for testing purposes. This test presents no more of a safety hazard to an individual than is presented to an individual who is having their blood drawn for any other diagnostic evaluation. The benefits to HAV-infected individuals tested by these assays outweigh any potential adverse event or risk to the patient or user due to assay malfunction or operator error.

The potential risks encountered with *in vitro* diagnostic tests are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for these devices. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user.

Safety

Based on the results of the preclinical and clinical laboratory studies, the ADVIA Centaur® HAV IgM assay, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and effective and pose minimal risk to the patient due to false test results.

Effectiveness

The effectiveness of the ADVIA Centaur® HAV IgM assay has been demonstrated for use in determining if HAV IgM is present in an individual's serum or plasma. A reasonable determination of effectiveness of the ADVIA Centaur® HAV IgM assay for aiding in the diagnosis of acute and recent HAV infection has been demonstrated.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on December 22, 2004.

The applicant's manufacturing facilities were inspected on May 11, 2004 and April 28, 2004 and found to be in compliance with the Quality Systems Regulation (21 CFR 820)

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.