Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION:

Device Generic Name: IgM Antibody to Hepatitis B Virus Core Antigen (IgM anti-HBc)

Device Trade Name: AxSYM CORE-M™ 2.0
AxSYM CORE-M 2.0 Controls

Name and Address of Applicant: Abbott Laboratories
Abbott Diagnostics Division
100 Abbott Park Road
Abbott Park, IL 60064-3500

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P060009

Date of Notice of Approval to the Applicant: August 25, 2006

II. INDICATIONS FOR USE:

AxSYM CORE-M 2.0 Reagent Kit

AxSYM CORE-M 2.0 is a microparticle enzyme immunoassay (MEIA) intended for the qualitative detection of IgM antibody to hepatitis B virus core antigen (IgM anti-HBc) in adult and pediatric serum (including serum collected in serum separator tubes) or plasma (collected in potassium EDTA, sodium citrate, sodium heparin, lithium heparin, or plasma separator tubes). The assay is used as an aid in the diagnosis of acute or recent hepatitis B virus (HBV) infection in conjunction with other laboratory results and clinical information.

AxSYM CORE-M 2.0 Controls

The AxSYM CORE-M 2.0 Controls are used for monitoring the performance of the AxSYM System (reagent and instrument) when used for the qualitative detection of IgM antibody to hepatitis B virus core antigen (IgM anti-HBc) when using the AxSYM CORE-M 2.0 Reagent Pack. The performance of the AxSYM CORE-M 2.0 Controls has not been established with any other IgM anti-HBc assays.

III. CONTRAINDICATIONS: None known.

IV. WARNINGS AND PRECAUTIONS: For *in vitro* diagnostic use only.

Warnings and precautions for the AxSYM CORE-M™ 2.0 Reagent Kit and AxSYM CORE-M 2.0 Controls are stated in the respective product labeling.

V. DEVICE DESCRIPTION:

Kit Configurations and Components

The AxSYM CORE-M 2.0 Reagent Kit contains one AxSYM CORE-M 2.0 Reagent Pack and one bottle of Index Calibrator. The AxSYM CORE-M 2.0 Reagent Pack holds the following four reagents:

- 1 Bottle (17.6 mL) Hepatitis B Virus Core Antigen (*E. coli*, Recombinant) in TRIS buffer with protein (10% bovine) stabilizer. Minimum concentration: 0.175 µg/mL. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents. (Reagent Bottle 1)

- 1 Bottle (12.2 mL) Antibody to Hepatitis B Virus Core Antigen (Human):Alkaline Phosphatase Conjugate in TRIS buffer with protein (1% bovine) stabilizer. Minimum concentration: 0.1 µg/mL. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents. (Reagent Bottle 2)

- 1 Bottle (10.5 mL) Antibody to Human IgM (Goat) Coated Microparticles in TRIS buffer with protein (0.05% porcine) stabilizer. Minimum concentration: 0.06% solids. Preservative: 0.1% Sodium Azide. (Reagent Bottle 3)

- 1 Bottle (50.2 mL) Specimen Diluent containing 0.3 M Sodium Chloride in TRIS buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents.
(Reagent Bottle 4)

The Index Calibrator is used to determine the cutoff rate of the AxSYM CORE-M 2.0 assay and contains the following:

- 1 Bottle (5.5 mL) AxSYM CORE-M 2.0 Index Calibrator. Recalcified human plasma reactive for IgM anti-HBc and nonreactive for HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV. Plasma is also tested for HBsAg and may be either nonreactive or reactive. Minimum titer = 1:1. Preservative: 0.1% Sodium Azide. Dye: Green (Acid Yellow No. 23 and Acid Blue No. 9).

The AxSYM CORE-M 2.0 Controls are packaged and sold separately and contain the following:

- 1 Bottle (7.4 mL) Negative Control. Recalcified human plasma nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, anti-HCV, anti-HBc, and anti-HBs. Preservative: 0.1% Sodium Azide.
- 1 Bottle (7.4 mL) Positive Control. Recalcified human plasma reactive for IgM anti-HBc and nonreactive for HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV. Plasma is also tested for HBsAg and may be either nonreactive or reactive. Preservative: 0.1% Sodium Azide.

In addition, the following components are required:

- The AxSYM System is an automated immunoassay analyzer designed for the performance of routine immunoassays and analyte determinations via random access, continuous access, and STAT test processing. The analyzer performs sample and reagent transfers, incubations, optical readings, data processing, and printing of assay reports and screen displays.
- AxSYM Probe Cleaning Solution containing 2% Tetraethylammonium Hydroxide (TEAH).
- Solution 1 (MUP) containing 4-Methylumbelliferyl Phosphate, 1.2 mM, in AMP buffer. Preservative: 0.1% Sodium Azide.
- Solution 3 (Matrix Cell Wash) containing 0.3 M Sodium Chloride in TRIS buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents.
- Solution 4 (Line Diluent) containing 0.1 M Phosphate buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agent.

Assay Principle and Format

AxSYM CORE-M 2.0 is based on MEIA technology and utilizes the principle of direct binding of the IgM anti-HBc in the sample to anti-human IgM coated microparticles, and detection of the IgM anti-HBc by rHBcAg, followed by anti-HBc (human):alkaline phosphatase conjugate. The Matrix Cell is washed with Matrix Cell Wash to remove materials not bound to the microparticles. The substrate (MUP), is added and the fluorescent product is measured by the MEIA optical assembly on the AxSYM System.

The presence or absence of IgM anti-HBc in the sample is determined by comparing the rate of formation of fluorescent product to the mean Index Calibrator rate, which is calculated from a previous AxSYM CORE-M 2.0 Index Calibration, to determine an Index Value. Samples with Index Values greater than 1.20 are considered reactive by AxSYM CORE-M 2.0. Samples with Index Values from 0.80 to 1.20 are considered gray zone reactive by AxSYM CORE-M 2.0. Samples with Index Values less than 0.80 are considered nonreactive by AxSYM CORE-M 2.0.

Results

The AxSYM System calculates the mean rate of the Index Calibrator replicates and stores the result. The AxSYM CORE M 2.0 assay protocol calculates a result based on the ratio of the sample rate to the stored Index Calibrator mean rate for each sample and control.

Index Value = Sample Rate / Index Calibrator Mean Rate

Interpretation of Results

AxSYM CORE-M 2.0		
Index Value	**Instrument Interpretation**	**Interpretation**
> 1.20	REACTIVE	Presumptive evidence of IgM anti-HBc.
0.80 to 1.20	GRAYZONE REACTIVE[a]	Presumptive evidence of IgM anti-HBc. Patients with specimens exhibiting gray zone reactive test results should be retested at approximately one-week intervals.
< 0.80	NONREACTIVE	IgM anti-HBc not detected. Does not exclude the possibility of exposure to or infection with HBV.

[a] The word "GRAYZONE" will appear in the interpretation field on the printout.

- Monitoring the level of IgM anti-HBc by retesting at approximately one-week intervals will distinguish rapidly rising IgM anti-HBc levels associated with early acute hepatitis B infection from gradually decreasing or unchanging IgM anti-HBc levels often associated with late acute stage of HBV infection, 6 to 9 months from the appearance of HBsAg.

- Immunosuppressed or immunocompromised individuals may not produce IgM anti-HBc above the detection limit of the AxSYM CORE-M 2.0 assay.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The patient's medical history and thorough physical examination, including hepatitis serology, determination of liver enzyme levels, and biopsy of the liver, will provide further information on the status of a hepatitis B viral infection. Alternative procedures for the detection of HBV in human serum and plasma depend on the detection of HBV deoxyribonucleic acid (DNA) by research polymerase chain reaction (PCR) assays or nucleic acid testing (NAT), or the detection of HBV antigens and antibodies by commercially-available assays that are licensed or approved in the United States.

VII. MARKETING HISTORY

AxSYM CORE-M 2.0 (List No. 8B89), has not been marketed in any other country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The main risk involved in the use of the AxSYM CORE-M 2.0 assay is one associated with any available IgM anti-HBc immunoassay: A nonreactive test result does not exclude the possibility of exposure to or infection with HBV. Levels of IgM anti-HBc may be undetectable in both the early and late stages of infection. For diagnostic purposes, IgM anti-HBc reactivity should be correlated with the overall clinical picture, including the presence or absence of other hepatitis markers.
Other than the circumstances mentioned above, there is no known potential adverse effect on the health of the patient or user if this in vitro device is used according to the AxSYM CORE-M 2.0 package insert instructions.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical laboratory studies were performed at Abbott Laboratories to evaluate the performance characteristics of the AxSYM CORE-M 2.0 assay. The studies are summarized below.

Cutoff Rationale

The AxSYM CORE-M 2.0 assay results are expressed as an Index Value, which is calculated by dividing the sample rate by the mean rate of two replicates of the AxSYM CORE-M 2.0 Index Calibrator. The Index Calibrator contains recalcified human plasma positive for IgM anti-HBc. Because the assay cutoff is determined by the mean rate of the Index Calibrator, the concentration of IgM anti-HBc in the Index Calibrator will affect the ability of the assay to detect the early acute and late acute/early recovery stages of HBV infection. Therefore, a study was conducted to select an appropriate IgM anti-HBc concentration range for the Index Calibrator.

Index Calibrator was prepared at various IgM anti-HBc concentrations ranging from 45 to 138 Abbott Units per mL (AU/mL) by adding recalcified human plasma positive for IgM anti-HBc to recalcified nonreactive human plasma. The Index Calibrators and three HBV seroconversion panels from three HBV-infected individuals were tested using AxSYM CORE-M 2.0. The ability of the assay to detect the early acute and late acute/early recovery stages of HBV infection was evaluated at each Index Calibrator concentration level.

The results of this study demonstrated that setting the Index Calibrator concentration range from 45 to 138 AU/mL and using an assay cutoff of 0.80 Index Value allowed appropriate detection of the early acute and late acute/early recovery stages of HBV infection by the AxSYM CORE-M 2.0 assay.

Sample Handling and Collection

Sample Types (Serum and Plasma)

A study was conducted to evaluate which specimen collection tube types are acceptable for use with the AxSYM CORE-M 2.0 assay. Sets of specimens assumed to be nonreactive for IgM anti-HBc were collected in the control specimen collection tube type (serum in glass) and the specimen collection tube types selected for evaluation. The specimens were spiked with human plasma positive for IgM anti-HBc to prepare high nonreactive samples (0.6 Index Value target) and low reactive samples (1.0 Index Value target), and all samples were tested.

On average, the tube types evaluated showed less than a 10% difference when compared to the control tube type (serum in glass), with the exception of sodium citrate, which showed a 12% difference when compared to the control tube type. The distribution of the %difference values for each tube type are summarized in Table 1.

The data support the use of the AxSYM CORE-M 2.0 assay with serum specimens, specimens collected in serum separator tubes (SST®) or plasma separator tubes (PST), and specimens collected in tubes containing the following anticoagulants:

- potassium ethylenediaminetetraacetic acid (EDTA)
- sodium citrate
- sodium heparin
- lithium heparin

Table 1
AxSYM CORE-M 2.0
Sample Types (Serum and Plasma) Study
Summary of Results

Evaluation Tube Type	Distribution of %Differences		
	0% to ≤ 10%	> 10% to ≤ 20%	> 20%
Serum in plastic	83.3% (35/42)	9.5% (4/42)	7.1% (3/42)
SST in glass	88.1% (37/42)	7.1% (3/42)	4.8% (2/42)
SST in plastic	88.1% (37/42)	4.8% (2/42)	7.1% (3/42)
PST	90.5% (38/42)	4.8% (2/42)	4.8% (2/42)

Evaluation Tube Type	Distribution of %Differences		
	0% to ≤ 10%	> 10% to ≤ 20%	> 20%
Potassium EDTA	85.7% (36/42)	7.1% (3/42)	7.1% (3/42)
Sodium Citrate[a]	61.9% (26/42)	26.2% (11/42)	11.9% (5/42)
Sodium Heparin	90.5% (38/42)	4.8% (2/42)	4.8% (2/42)
Lithium Heparin	88.1% (37/42)	7.1% (3/42)	4.8% (2/42)

[a] Sodium citrate tubes have been shown to increase the Index Values in specimens near the assay cutoff in a positive direction. Low positive results (0.80 to 0.90 Index Value) obtained on samples collected with this anticoagulant should be interpreted accordingly.

Sample Storage Conditions

The Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) document H18-A3[3] guidelines provides the following recommendations for storing blood specimens:

- Store samples at 22°C (72°F) for no longer than 8 hours.
- If the assay will not be completed within 8 hours, refrigerate the sample at 2 to 8°C (36 to 46°F).
- If the assay will not be completed within 48 hours, freeze at or below –20°C (-4°F).

Sample Freeze/Thaw

Sets of specimens from individuals assumed to be nonreactive for IgM anti-HBc were collected in all recommended specimen collection tube types (serum, and potassium EDTA, sodium citrate, sodium heparin, or lithium heparin plasma). Tubes from each set were spiked with human plasma positive for IgM anti-HBc to prepare high nonreactive samples (0.6 Index Value target) and low reactive samples (1.2 Index Value target). The samples were tested on Day 0 (within eight hours of draw) and after being subjected to one and two freeze/thaw cycles.

The data support the use of the AxSYM CORE-M 2.0 assay with specimens collected in all recommended collection tubes that have undergone up to two freeze/thaw cycles.

Analytical Specificity

A study was conducted to characterize the performance of the AxSYM CORE-M 2.0 assay when used to test specimens from individuals with medical conditions unrelated to HBV infection.

All 185 specimens (100.0%) were nonreactive by AxSYM CORE-M 2.0. The results are summarized in Table 2.

Table 2
AxSYM CORE-M 2.0
Analytical Specificity Study: Specimens from Individuals with Medical Conditions Unrelated to HBV Infection
Summary of Results

Category[a]	Number of Specimens Tested	AxSYM CORE-M 2.0 Nonreactive	AxSYM CORE-M 2.0 Gray Zone Reactive	AxSYM CORE-M 2.0 Reactive
Hepatitis A Virus[b]	12	12	0	0
Hepatitis C Virus[b]	10	10	0	0
Human Immunodeficiency Virus	10	10	0	0
Human T-Lymphotropic Virus[b]	9	9	0	0
Cytomegalovirus[b]	10	10	0	0
Epstein-Barr Virus[b]	10	10	0	0
Herpes Simplex Virus[b]	10	10	0	0
Rubella[b]	10	10	0	0
Systemic Lupus Erythematosus	10	10	0	0
Rheumatoid Arthritis Disease[c]	10	10	0	0
Elevated IgG	10	10	0	0
Elevated IgM	10	10	0	0
Influenza Vaccine Recipients	10	10	0	0
HBV Vaccine Recipients	5	5	0	0
Toxoplasmosis[b]	4	4	0	0
Alcoholic Liver Disease	10	10	0	0
Fatty Liver Disease	15	15	0	0
Obstructive Jaundice	15	15	0	0
Hepatocellular Carcinoma	5	5	0	0
Total (%)	**185**	**185/185 (100.0%)**	**0/185 (0.0%)**	**0/185 (0.0%)**

[a] Information about age and gender of the individuals is not available.
[b] Only IgG antibodies are present
[c] Both IgG and IgM antibodies are present for eight out of ten specimens. The remaining two specimens were categorized based on clinical diagnosis.

Potentially Interfering Substances – Triglycerides, Total Protein, Bilirubin, and Hemoglobin

Human serum nonreactive for IgM anti-HBc was spiked with human plasma positive for IgM anti-HBc to prepare high nonreactive samples (0.6 Index Value target) and low reactive samples (1.0 Index Value target). A triglyceride test sample was prepared by supplementing the high nonreactive and low reactive samples with LIPOSYN® II to a minimum triglyceride concentration of 3,000 mg/dL. A total protein test sample was prepared by supplementing the high nonreactive and low reactive samples with human albumin powder to a minimum concentration of 12 g/dL. A bilirubin (unconjugated) test sample was prepared by supplementing the high nonreactive and low reactive samples with unconjugated bilirubin stock prepared in 0.1 N sodium hydroxide to a minimum concentration of 20 mg/dL. A hemoglobin test sample was prepared by supplementing the high nonreactive and low reactive samples with hemoglobin stock solution to a minimum concentration of 500 mg/dL. Control samples were prepared for each interferent. The controls and samples were tested.

The data support the use of the AxSYM CORE-M 2.0 assay with specimens that contain up to 3,000 mg/dL of triglycerides, up to 12 g/dL of total protein, up to 20 mg/dL of bilirubin (unconjugated), and up to 500 mg/dL of hemoglobin.

At the concentrations listed below, total bilirubin (unconjugated), hemoglobin, total protein, and triglycerides showed less than 0.08 index value interference in the AxSYM CORE-M 2.0 assay for high negative (0.6 Index Value target) serum samples and less than or equal to 10% interference in the AxSYM CORE-M 2.0 assay for low positive (1.0 Index Value target) serum samples:

- Total Bilirubin ($\leq$ 20 mg/dL)
- Hemoglobin ($\leq$ 500 mg/dL)
- Total Protein ($\leq$ 12 g/dL)
- Triglycerides ($\leq$ 3000 mg/dL)

Within-Laboratory (20-day) Precision

A 20-day precision study was conducted based on guidance from Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) document EP5-A2[1] to evaluate the precision performance of the AxSYM CORE-M 2.0 assay.

Testing was performed using two AxSYM CORE-M 2.0 Reagent Kit lots and one AxSYM CORE-M 2.0 Control lot on each of two AxSYM instruments. Testing included two precision runs per day for each reagent kit lot, on each instrument, on each of 20 days. Each precision run included two replicates of the AxSYM CORE-M 2.0 Index Calibrator, Negative Control, and Positive Control, and each of two members of a precision panel with Index Values of 0.6 and 1.0. Panel members were prepared by adding recalcified human plasma reactive for IgM anti-HBc to nonreactive human serum.

The data demonstrated the acceptable precision of the AxSYM CORE-M 2.0 assay. The results are summarized in Tables 3 and 4.

Table 3
AxSYM CORE-M 2.0
Within-Laboratory (20 Day) Precision Study
Overall Precision—Two Instruments, Two Reagent Lots

Panel Members/ Controls	Total No. Reps	Grand Mean Index Value	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision With Additional Component of Between-Lot		Precision With Additional Component of Between-Instrument	
			SD	%CV	SD	%CV	SD	%CV	%CV CL	SD	%CV	SD	%CV
Panel 1	320	0.62	0.019	3.1	0.022	3.5	0.028	4.6	5.0	0.035	5.6	0.029	4.7
Panel 2	320	0.99	0.026	2.6	0.030	3.0	0.041	4.1	4.5	0.051	5.2	0.043	4.3
NC	320	0.03	0.003	10.2	0.003	10.8	0.004	11.2	12.0	0.004	13.7	0.004	11.2
PC	320	1.55	0.043	2.8	0.047	3.1	0.062	4.0	4.4	0.081	5.2	0.062	4.0

Index Calibrator	Total No. Reps	Grand Mean Rate	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision With Additional Component of Between-Lot		Precision With Additional Component of Between-Instrument	
			SD	%CV	SD	%CV	SD	%CV	%CV CL	SD	%CV	SD	%CV
IC	320	272.22	7.426	2.7	7.967	2.9	10.632	3.9	4.3	10.632	3.9	10.950	4.0

Reps = Replicates, SD = Standard Deviation, CV = Coefficient of Variation, CL = Upper One-sided 95% Confidence Limit

Table 4
AxSYM CORE-M 2.0
Within-Laboratory (20-day) Precision Study
Individual Component Analysis—Two Instruments, Two Reagent Lots

Panel Members/ Controls	Total No. Reps	Grand Mean Index Value	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Instrument		Total[a]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Panel 1	320	0.62	0.019	3.1	0.010	1.7	0.018	3.0	0.020	3.3	0.006	0.9	0.028	4.6
Panel 2	320	0.99	0.026	2.6	0.016	1.6	0.027	2.8	0.031	3.1	0.013	1.3	0.041	4.1
NC	320	0.03	0.003	10.2	0.001	3.5	0.001	3.0	0.003	7.9	0.000	0.0	0.004	11.2
PC	320	1.55	0.043	2.8	0.019	1.2	0.041	2.6	0.052	3.4	0.004	0.3	0.062	4.0

Index Calibrator	Total No. Reps	Grand Mean Index Value	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Instrument		Total[a]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
IC	320	272.22	7.426	2.7	2.886	1.1	7.040	2.6	0.000	0.0	2.620	1.0	10.632	3.9

[a] Total variability contains within-run, between-run, and between-day variance components.

Seroconversion Detectability

A study was conducted to demonstrate the ability of the AxSYM CORE-M 2.0 assay to detect the early acute and late acute/early recovery stages of HBV infection when used to test serial bleed specimens from HBV-infected individuals.

Seven seroconversion panels (a total of 181 serial bleed specimens) from seven HBV-infected individuals were obtained from two commercial vendors and tested. The AxSYM CORE-M 2.0 results were compared to the historical results from FDA-approved or FDA-licensed assays for HBsAg, IgM anti-HBc, anti-HBc, and anti-HBs.

IgM anti-HBc was detected by AxSYM CORE-M 2.0 coincident with the reference IgM anti-HBc assay in six panels, and two days later than the reference IgM
anti-HBc assay in one panel. In this panel, the initial IgM anti-HBc reactive specimen was also reactive for HBsAg.

One seroconversion panel showed sustained HBsAg reactivity for longer than six months without detectable anti-HBs, which is indicative of an acute HBV infection progressing to a potential chronic HBV infection. The profiles of the remaining six seroconversion panels were characteristic of an acute HBV infection progressing to eventual recovery and immunity to HBV. AxSYM CORE-M 2.0 detected IgM anti-HBc following detection of HBsAg in all panels during the acute stage of disease. IgM anti-HBc remained detectable over a period of seven months after the appearance of HBsAg in the single panel from an acute HBV infection progressing to a potential chronic infection, and over a range of two to eleven months in the other six panels. The overall AxSYM CORE-M 2.0 results were consistent with the known serological profile of each panel.

These data demonstrate the ability of the AxSYM CORE-M 2.0 assay to detect the early acute and late acute/early recovery stages HBV infection when used to test serial bleed specimens from HBV-infected individuals.

High Dose Hook Effect

A study was conducted to characterize the performance of the AxSYM CORE-M 2.0 assay when used to test a high-titer IgM anti-HBc specimen that has the potential to cause a high dose hook effect.

High-titer IgM anti-HBc reactive human plasma (titer > 1:256) was serially diluted and tested. The mean Index Value of the neat sample was greater than the mean Index Value of the diluted samples, indicating that no high dose hook effect was observed in the AxSYM CORE-M 2.0 assay.

Within- and Between-assay Sample Carryover

Studies were conducted to evaluate the susceptibility of the AxSYM CORE-M 2.0 assay to sample carryover within the assay or from other AxSYM assays when processing samples containing high concentrations of IgM anti-HBc.

Carryover events were modeled by testing human plasma nonreactive for IgM anti-HBc to mimic a sample that was not exposed to potential sample carryover (protected negative), followed by a human plasma sample containing a high concentration of IgM anti-HBc (2.50 Index Value), followed again by human plasma nonreactive for IgM anti-HBc to mimic a sample exposed to potential sample carryover (unprotected negative).

For the within-assay carryover study, the difference between the protected negative and unprotected negative mean or median Index Values was 0.00, indicating that no within-assay sample carryover was present within the AxSYM CORE-M 2.0 assay.

For the between-assay carryover study, the difference between the protected negative and unprotected negative mean or median Index Values ranged from 0.00 to 0.02 in the Sampling Center, and the difference between the protected negative and unprotected negative mean or median Index Values ranged from 0.00 to 0.02 in the Processing Center. These results indicate that no between-assay sample carryover was present between the AxSYM CORE-M 2.0 assay and any of the potential contaminator assays evaluated.

Microbial Challenge Studies

Studies were conducted to establish the level of antimicrobial protection provided by the preservative system used in the components of the AxSYM CORE-M 2.0 Reagent Kit and Controls, and to determine the effect of bioburden and/or its by-products on assay performance.

Components of the AxSYM CORE-M 2.0 Reagent Kit and Controls were inoculated with the following groups of microorganisms at concentrations between 10^5 to 10^6 colony forming units/mL (CFU/mL): Spore (*Baccillus subtilis*, *Candida albicans*), Mold (*Aspergillus niger*), vegetative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*), and environmental (*Psuedomonas* [fluorescent group]). The inoculated materials were evaluated for microbial growth over a period of 15 months.

Components of the AxSYM CORE-M 2.0 Reagent Kit and Controls were inoculated with the following microorganisms at concentrations between 10^2 to 10^3 CFU/mL and at concentrations between 10^3 to 10^4 CFU/mL: *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and

Psuedomonas (fluorescent group). The inoculated materials were evaluated for assay performance after a period of 35 days.

No growth of the challenge organisms was observed during the study, with the exception of the rHBcAg reagent inoculated with the spore group, which demonstrated growth between Month 12 and Month 15. However, the bioburden count at Month 15 was below the bioburden count observed at Day 0 by more than one log and was within one log of the bioburden count observed for all other time points. Assay performance of the inoculated components was acceptable. The data demonstrate that the AxSYM CORE-M 2.0 Reagent Kit and Controls are adequately protected by the preservative system used.

Recommended Storage Stability - Reagent Kit and Controls

Real-time stability studies are being conducted to demonstrate the shelf-life integrity of the AxSYM CORE-M 2.0 Reagent Kit and Controls at the recommended storage condition (2 to 8°C).

Three lots of AxSYM CORE-M 2.0 Reagent Kits and Controls were stored at the recommended storage condition of 2 to 8°C. The AxSYM CORE-M 2.0 Reagent Kits and Controls were tested at Month 0 and monthly thereafter. The stability studies are ongoing and are scheduled to continue for a maximum of 20 months (minimum of seven months). At this time, the data for the first eight months of testing is complete.

The data presented demonstrate that the evaluation criteria were met for both the AxSYM CORE-M 2.0 Reagent Kits and Controls at the recommended storage condition (2 to 8°C) for eight months. Additional data will be submitted at a later date.

Transport Stability

A study was conducted to evaluate the performance of the AxSYM CORE-M 2.0 Reagent Kit and Controls following a simulation of ambient shipping conditions (transport simulation).

One lot each of the AxSYM CORE-M 2.0 Reagent Kit and Controls was tested after being subjected to a series of storage temperatures simulating transport stress.

The data support ambient shipment of the AxSYM CORE-M 2.0 Reagent Kit and Controls.

Onboard Reagent Pack Stability

Testing was performed using three lots of AxSYM CORE-M 2.0 Reagent Packs that were stored continuously at 2 to 8°C (recommended storage) and at 31°C (simulated onboard storage) for 24, 48, 72, 96, 120, 144, 192, 240, 288, or 336 hours. The AxSYM CORE-M 2.0 Index Calibrator was not evaluated for onboard stability because this reagent is not left on board the AxSYM System.

The AxSYM CORE-M 2.0 Reagent Pack may be on board the AxSYM System for a maximum of 112 cumulative hours; for example, 14 eight-hour shifts.

Calibration Stability and Control Frequency

An analysis was performed to determine if an AxSYM CORE-M 2.0 calibration that is stored on the AxSYM System for a minimum of 14 days can be used to generate valid results (calibration stability), and to support a minimum control requirement to test controls once every 24 hours (control frequency).

The validity data generated in the Within-Laboratory (20-day) Precision Study were used for this analysis. The study was conducted using two AxSYM instruments and two AxSYM CORE-M 2.0 Reagent Kit lots for 20 days. A calibration was performed on the first day of testing for each instrument and reagent kit lot combination. The AxSYM CORE-M 2.0 Negative Control and Positive Control were each tested for validity purposes, once per run, twice daily, on each of 20 days, using each instrument and reagent kit lot combination.

X. SUMMARY OF CLINICAL STUDIES

A multi-center study was conducted to demonstrate that the AxSYM CORE-M 2.0 assay performs as intended in a diagnostic population. The study was designed to measure the precision of the AxSYM CORE-M 2.0 assay and determine the percent agreement between AxSYM CORE-M 2.0 and an FDA-approved IgM anti-HBc reference method.

System Reproducibility (5-day Precision)

The precision of the AxSYM CORE-M 2.0 assay was evaluated by testing three AxSYM CORE-M 2.0 Reagent Kit and Control master lots at three clinical testing sites for five days. Testing included two precision runs per day (a minimum of two hours apart) for each of three reagent master lots, on each of five days. Each precision run included four replicates of each precision panel member and four replicates each of AxSYM CORE-M 2.0 Index Calibrator, Negative Control, and Positive Control. Panel members were prepared by adding recalcified human plasma reactive for IgM anti-HBc to nonreactive human serum. The analysis method was based on National Committee for Clinical Laboratory Standards (formerly NCCLS) document EP15-A2[2]. The results are presented in Tables 5 through 7.

Table 5
AxSYM CORE-M 2.0 System Reproducibility: Overall Precision
Three Reagent Master Lots, Three Clinical Testing Sites

Panel Members/ Controls	Total No. Reps	Grand Mean Index Value	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision With Additional Component of Between-Lot		Precision With Additional Component of Between-Site		Precision with Additional Components of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV	SD	%CV
Panel 1	360	0.65	0.030	4.6	0.052	8.1	0.053	8.1	9.1	0.075	11.6	0.072	11.1	0.084	13.0
Panel 2	360	1.03	0.028	2.8	0.038	3.7	0.042	4.0	4.4	0.082	8.0	0.091	8.8	0.107	10.4
NC	360	0.03	0.003	9.9	0.003	9.9	0.003	10.5	11.3	0.005	18.2	0.003	12.1	0.005	18.6
PC	360	1.58	0.037	2.4	0.049	3.1	0.052	3.3	3.6	0.083	5.2	0.126	8.0	0.126	8.0

Index Calibrator	Total No. Reps	Grand Mean Rate	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision With Additional Component of Between-Lot		Precision With Additional Component of Between-Site		Precision with Additional Components of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV	SD	%CV
IC	360	293.84	8.414	2.9	10.891	3.7	12.334	4.2	4.6	20.841	7.1	25.368	8.6	29.436	10.0

Reps = Replicates; SD = Standard Deviation; CV = Coefficient of Variation, CL = Upper One-sided 95% Confidence Limit

Table 6
AxSYM CORE-M 2.0 System Reproducibility: Individual Component Analysis
Three Reagent Master Lots, Three Clinical Testing Sites

Panel Members/ Controls	Total No. Reps	Grand Mean Index Value	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Site		Total[a]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Panel 1	360	0.65	0.030	4.6	0.043	6.7	0.005	0.8	0.053	8.2	0.049	7.5	0.084	13.0
Panel 2	360	1.03	0.028	2.8	0.025	2.5	0.017	1.6	0.071	6.9	0.081	7.8	0.107	10.4
NC	360	0.03	0.003	9.9	0.000	0.0	0.001	3.6	0.004	14.9	0.002	5.9	0.005	18.6
PC	360	1.58	0.037	2.4	0.032	2.0	0.018	1.1	0.064	4.1	0.114	7.2	0.126	8.0

Index Calibrator	Total No. Reps	Grand Mean Index Value	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Instrument		Total[a]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
IC	360	293.84	8.414	2.9	6.915	2.4	5.789	2.0	16.799	5.7	22.168	7.5	29.436	10.0

[a] Total variability contains within-run, between-run, between-day, between-lot, between-site, and lot-site interaction variance components.

Table 7
AxSYM CORE-M 2.0 System Reproducibility: By-site Precision
Clinical Testing Sites 1, 2, and 3, Three Reagent Master Lots

Clinical Testing Site	Panel Members/ Controls/ Calibrator	Total No. Reps	Grand Mean Index Value / Rate[a]	Within-Run		Within-Day		Within-Laboratory Precision (Total)		Precision With Additional Component of Between-Lot	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	Panel 1	120	0.60	0.015	2.4	0.022	3.7	0.024	4.0	0.039	6.4
	Panel 2	120	0.95	0.023	2.5	0.031	3.3	0.034	3.5	0.052	5.5
	NC	120	0.03	0.002	6.7	0.002	6.7	0.002	6.9	0.006	21.9
	PC	120	1.46	0.032	2.2	0.037	2.5	0.045	3.1	0.087	6.0
	IC	120	275.72	7.002	2.5	9.134	3.3	9.383	3.4	13.148	4.8
2	Panel 1	120	0.67	0.046	6.8	0.085	12.7	0.085	12.7	0.115	17.1
	Panel 2	120	1.08	0.036	3.3	0.049	4.6	0.049	4.6	0.114	10.6
	NC	120	0.03	0.003	11.5	0.003	11.5	0.003	11.7	0.004	15.0
	PC	120	1.65	0.044	2.7	0.060	3.6	0.060	3.6	0.102	6.2
	IC	120	288.41	9.990	3.5	12.339	4.3	15.075	5.2	28.821	10.0
3	Panel 1	120	0.67	0.018	2.7	0.020	3.0	0.022	3.3	0.046	6.8
	Panel 2	120	1.07	0.025	2.3	0.031	2.9	0.040	3.8	0.068	6.3
	NC	120	0.03	0.003	10.4	0.003	10.4	0.003	11.7	0.005	17.7
	PC	120	1.63	0.034	2.1	0.044	2.7	0.051	3.1	0.051	3.2
	IC	120	317.40	7.973	2.5	10.962	3.5	11.878	3.7	17.307	5.5

[a] Panel 1, Panel 2, NC, and PC are reported in Grand Mean Index Value. The IC is reported in Grand Mean Rate.

Method Comparison

Clinical Performance

The clinical specimens used in the study were obtained from six specimen collection sites and three specimen vendors. A total of 2,352 linked serum specimens were prospectively collected and tested. In addition, 100 specimens from a surplus pediatric population were obtained.

The specimens included the following categories:

Specimens Collected From Individuals Living in the United States (US) (Population 1)

- 1,313 specimens from individuals at increased risk of hepatitis B virus (HBV) infection
- 703 specimens from individuals with signs and symptoms of hepatitis infection
- 11 specimens from individuals diagnosed with acute HBV infection

- 25 preselected IgM anti-HBc positive specimens
- 100 specimens from a pediatric population (This population included specimens from children > 2 to 12 years of age and adolescents > 12 to 19 years of age.)

Specimens Collected From Individuals Living in Vietnam (Population 2)

- 100 specimens from individuals at increased risk of HBV infection
- 200 specimens from individuals with signs and symptoms of hepatitis infection

Three AxSYM CORE-M 2.0 Reagent Kit and Control master lots were used in the percent agreement evaluation. Three clinical testing sites performed AxSYM CORE-M 2.0 testing. Specimens were sent to an external reference laboratory for reference IgM anti-HBc assay testing. A summary of the percent agreement results for all specimen categories is presented in Table 8.

Table 8
Summary of Percent Agreement Between
AxSYM CORE-M 2.0 and the Reference IgM Anti-HBc Assay

Specimen Category	Number of Specimens Tested	Positive Percent Agreement	Negative Percent Agreement[a]
Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection (US Population)	2,016	100.00% (16/16)	99.50% (1,990/2,000)
Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection (Vietnam Population)	300	NA	99.00% (297/300)
Individuals Diagnosed With Acute HBV Infection	11	100.00% (11/11)	NA
Preselected IgM Anti-HBc Positive Specimens	25	100.00% (23/23)	0.00% (0/2)
Pediatric Population	100	NA	100.00% (100/100)

NA = Not Applicable

[a] Of the 15 discordant specimens, 11 were classified as chronic based on the four-marker HBV reference results.

The 2,316 specimens from individuals at increased risk of HBV infection and individuals with signs and symptoms of hepatitis infection (Populations 1 and 2) were also sent to an external reference laboratory for HBV reference marker testing by FDA-approved reference assays for the detection of HBsAg, anti-HBc IgM, total anti-HBc, and anti-HBs. These specimens were assigned an HBV classification using the results for the four HBV reference markers and the modification of the serological criteria established by the National Center of Infectious Diseases (CDC) for diagnosing HBV infection.

The number of specimens in each HBV classification category is presented in Tables 9 and 10. A comparison of AxSYM CORE-M 2.0 results versus the reference IgM anti-HBc assay results by HBV classification category is presented in Tables 11 and 12. The percent agreement between AxSYM CORE-M 2.0 and the reference IgM anti-HBc assay by HBV classification category is summarized in Tables 13 and 14.

Two thousand sixteen specimens were prospectively collected in the United States at specimen collection sites located in Galveston, TX (39.29%); Dallas, TX (5.80%); Miami, FL (4.51%); St. Petersburg, FL (4.17%); Chicago, IL (8.18%); and Denver, CO (6.10%); or were obtained from a specimen vendor at the following three locations: Colton, CA (5.85%); Plymouth, MA (16.91%); and High Point, NC (9.18%) (Population 1). Three hundred specimens were also prospectively collected in Vietnam (Population 2) by a specimen vendor.

Population 1 was 52.83% Caucasian, 28.52% African American, 14.68% Hispanic, 1.98% Asian, and 0.45% American Indian/Alaska Native, with the remaining 1.54% represented by other ethnic groups. The population was 52.53% female and 47.47% male and ranged in age from 18 to 83 years. Testing of these specimens occurred at Clinical Testing Site 1 located in Port Jefferson, NY (39.29%); Clinical Testing Site 2 located in Dallas, TX (40.13%); and Clinical Testing Site 3 located in Raritan, NJ (20.59%).

Population 2 was Vietnamese (100.00%). The population was 53.33% female and 46.67% male and ranged in age from 18 to 68 years. Testing of these specimens occurred at a clinical testing site located in Raritan, NJ.

Table 9
HBV Classification for Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection (Population 1)

HBV Reference Markers					HBV Classification
Number of Specimens	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
2	+	–	–	–	Early Acute
7	+	+	+	–	Acute
1	+	+	+	I	Chronic
2	+	–	+	+	Chronic
35	+	–	+	–	Chronic
1	+	–	–	+	Chronic

2	+	–	+	I	Chronic
1	+	+	+	+	Late Acute/Recovering
4	–	+	+	+	Recovering Acute
3	–	+	+	I	Early Recovery
193	–	–	+	+	Immune Due to Natural Infection
31	–	–	+	I	Distantly Immune/Anti-HBs Unknown
107	–	–	+	–	Distantly Immune/Anti-HBs Not Detected
507	–	–	–	+	Immune Due to HBV Vaccination
66	–	–	–	I	Unknown
1,054	–	–	–	–	Susceptible
2,016					**Total**

I = Indeterminate

Table 10
HBV Classification for Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection (Population 2)

HBV Reference Markers					HBV Classification
Number of Specimens	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
1	+	–	–	–	Early Acute
3	+	–	+	+	Chronic
119	+	–	+	–	Chronic
2	+	–	–	+	Chronic
3	+	–	+	I	Chronic
72	–	–	+	+	Immune Due to Natural Infection
5	–	–	+	I	Distantly Immune/Anti-HBs Unknown
15	–	–	+	–	Distantly Immune/Anti-HBs Not Detected
41	–	–	–	+	Immune Due to HBV Vaccination
39	–	–	–	–	Susceptible
300					**Total**

I = Indeterminate

Table 11
Comparison of AxSYM CORE-M 2.0 Results With Reference IgM Anti-HBc Assay Results by HBV Classification (Population 1)

	Reference IgM Anti-HBc Assay Result[a]						
	+			–			
	AxSYM CORE-M 2.0 Result						
HBV Classification	+	GZR	–	+	GZR	–	Total
Early Acute	0	0	0	0	0	2	2
Acute	7	0	0	0	0	0	7
Chronic	1	0	0	1[b]	5[c]	34	41
Late Acute/Recovering	1	0	0	0	0	0	1

Recovering Acute	3	1	0	0	0	0	4
Early Recovery	3	0	0	0	0	0	3
Immune Due to Natural Infection	0	0	0	0	2[d]	191	193
Distantly Immune/Anti-HBs Unknown	0	0	0	0	0	31	31
Distantly Immune/Anti-HBs Not Detected	0	0	0	0	1[e]	106	107
Immune Due to HBV Vaccination	0	0	0	0	0	507	507
Unknown	0	0	0	0	1[f]	65	66
Susceptible	0	0	0	0	0	1,054	1,054
Total	**15**	**1**	**0**	**1**	**9**	**1,990**	**2,016**

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert, if required.
[b] This specimen was tested and determined to be positive for anti-HBe and HBV DNA.
[c] Three specimens were tested and determined to be positive for HBeAg and HBV DNA; two specimens were positive for anti-HBe and HBV DNA.
[d] These specimens were tested and determined to be positive for anti-HBe and gray zone reactive by an FDA-approved IgM anti-HBc assay.
[e] This specimen was tested and determined to be positive for anti-HBe and gray zone reactive by an FDA-approved IgM anti-HBc assay.
[f] This specimen was tested and determined to be reactive by an FDA-approved IgM anti-HBc assay.

Table 12
Comparison of AxSYM CORE-M 2.0 Results with Reference IgM Anti-HBc Assay Results by HBV Classification (Population 2)

	Reference IgM Anti-HBc Assay Result[a]						
	+			–			
	AxSYM CORE-M 2.0 Result						
HBV Classification	**+**	**GZR**	**–**	**+**	**GZR**	**–**	**Total**
Early Acute	0	0	0	0	0	1	1
Chronic	0	0	0	0	3[b]	124	127
Immune Due to Natural Infection	0	0	0	0	0	72	72
Distantly Immune/Anti-HBs Unknown	0	0	0	0	0	5	5
Distantly Immune/Anti-HBs Not Detected	0	0	0	0	0	15	15
Immune Due to HBV Vaccination	0	0	0	0	0	41	41
Susceptible	0	0	0	0	0	39	39
Total	**0**	**0**	**0**	**0**	**3**	**297**	**300**

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert, if required.
[b] Two specimens were tested and determined to be positive for HBeAg and HBV DNA, and one specimen was positive for anti-HBe and HBV DNA.

Table 13
Percent Agreement between AxSYM CORE-M 2.0 Results and Reference IgM Anti-HBc Assay Results Summarized by HBV Classification (Population 1)

HBV Classification	Positive Percent Agreement	95% Confidence Interval	Negative Percent Agreement	95% Confidence Interval
Early Acute	NA	NA	2/2 (100.00%)	[15.81%, 100.00%]
Acute	7/7 (100.00%)	[59.04%, 100.00%]	NA	NA
Chronic	1/1 (100.00%)	[2.50%, 100.00%]	34/40 (85.00%)	[70.16%, 94.29%]
Late Acute/Recovering	1/1 (100.00%)	[2.50%, 100.00%]	NA	NA

Recovering Acute	4/4 (100.00%)	[39.76%, 100.00%]	NA	NA
Early Recovery	3/3 (100.00%)	[29.24%, 100.00%]	NA	NA
Immune Due to Natural Infection	NA	NA	191/193 (98.96%)	[96.31%, 99.87%]
Distantly Immune/Anti-HBs Unknown	NA	NA	31/31 (100.00%)	[88.78%, 100.00%]
Distantly Immune/Anti-HBs Not Detected	NA	NA	106/107 (99.07%)	[94.90%, 99.98%]
Immune Due to HBV Vaccination	NA	NA	507/507 (100.00%)	[99.28%, 100.00%]
Unknown	NA	NA	65/66 (98.48%)	[91.84%, 99.96%]
Susceptible	NA	NA	1,054/1,054 (100.00%)	[99.65%, 100.00%]
Overall	**16/16 (100.00%)**	**[79.41%, 100.00%]**	**1,990/2,000 (99.50%)**	**[99.08%, 99.76%]**

NA = Not Applicable

Table 14
Percent Agreement between AxSYM CORE-M 2.0 Results and Reference IgM Anti-HBc Assay Results Summarized by HBV Classification (Population 2)

HBV Classification	Positive Percent Agreement	95% Confidence Interval	Negative Percent Agreement	95% Confidence Interval
Early Acute	NA	NA	1/1 (100.00%)	[2.50%, 100.00%]
Chronic	NA	NA	124/127 (97.64%)	[93.25%, 99.51%]
Immune Due to Natural Infection	NA	NA	72/72 (100.00%)	[95.01%, 100.00%]
Distantly Immune/Anti-HBs Unknown	NA	NA	5/5 (100.00%)	[47.82%, 100.00%]
Distantly Immune/Anti-HBs Not Detected	NA	NA	15/15 (100.00%)	[78.20%, 100.00%]
Immune Due to HBV Vaccination	NA	NA	41/41 (100.00%)	[91.40%, 100.00%]
Susceptible	NA	NA	39/39 (100.00%)	[90.97%, 100.00%]
Overall	**NA**	**NA**	**297/300 (99.00%)**	**[97.11%, 99.79%]**

NA = Not Applicable

Potentially Cross-reacting Subgroups

A total of 492 specimens from Population 1 (US) were identified as anti-HCV reactive, and 11 specimens from Population 2 (Vietnam) were identified as anti-HAV IgM reactive. The AxSYM CORE-M 2.0 results were compared to the results of the reference IgM anti-HBc assay by HBV classification. A comparison of AxSYM CORE-M 2.0 results versus the reference IgM anti-HBc assay results by HBV classification category is presented in Tables 15 and 16.

Table 15
Comparison of AxSYM CORE-M 2.0 Results With Reference IgM Anti-HBc Assay Results by HBV Classification (Population 1)
Anti-HAV IgM Reactive Specimens

HBV Classification	Reference IgM Anti-HBc Assay Result[a]						Total
	+			-			
	AxSYM CORE-M 2.0 Result						
	+	GZR	-	+	GZR	-	
Early Acute	0	0	0	0	0	1	1
Acute	2	0	0	0	0	0	2
Chronic	0	0	0	0	0	5	5
Recovering Acute	3	1	0	0	0	0	4
Early Recovery	1	0	0	0	0	0	1
Immune Due to Natural Infection	0	0	0	0	1	87	88
Distantly Immune/Anti-HBs Unknown	0	0	0	0	0	26	26
Distantly Immune/Anti-HBs Not Detected	0	0	0	0	1	72	73
Immune Due to HBV Vaccination	0	0	0	0	0	70	70
Unknown	0	0	0	0	0	15	15
Susceptible	0	0	0	0	0	207	207
Grand Total	6	1	0	0	2	483	492

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert as required.

Table 16
Comparison of AxSYM CORE-M 2.0 Results With Reference IgM Anti-HBc Assay Results by HBV Classification (Population 2) Anti-HAV IgM Reactive Specimens

HBV Classification	Reference IgM Anti-HBc Assay Result[a]						Total
	+			-			
	AxSYM CORE-M 2.0 Result						
	+	GZR	-	+	GZR	-	
Chronic	0	0	0	0	0	3	3
Immune Due to Natural Infection	0	0	0	0	0	4	4
Immune Due to HBV Vaccination	0	0	0	0	0	1	1
Susceptible	0	0	0	0	0	3	3
Grand Total	0	0	0	0	0	11	11

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert as required.

Expected Results

Expected results were determined using the AxSYM CORE-M 2.0 results for individuals at increased risk of HBV infection living in the United States.

Of the prospective subjects participating in the investigation, 55.82% (1,313/2,352) were from individuals, living in the United States, who were at increased risk of HBV infection. All subjects were at risk of HBV infection due to lifestyle, behavior, occupation, or known exposure event but were asymptomatic and reported no current signs or symptoms of hepatitis. The population ranged in age from 18 to 75 years. A demographic summary of this population is presented in the following table:

	Total Number of Specimens (%)
Ethnicity:	
Caucasian	47.60
African American	36.25
Hispanic	12.72
Asian	1.45
American Indian/Alaska Native	0.46
Other	1.52
Gender:	
Female	62.15
Male	37.85

The AxSYM CORE-M 2.0 assay was reactive or gray zone reactive in 0.61% (8/1,313) of the individuals in this population. The percent of individuals at increased risk of HBV infection enrolled at each location and the percent of AxSYM CORE-M 2.0 reactive results observed from each location are presented in Table 17. The percent AxSYM CORE-M 2.0 reactive, gray zone reactive, and nonreactive results by age range and gender is presented in Table 18.

Table 17
AxSYM CORE-M 2.0 Reactive Results by Specimen Collection Site or Specimen Vendor for Individuals at Increased Risk of HBV Infection

Specimen Collection Site/ Specimen Vendor	Percent of Individuals at Increased Risk of HBV Infection Enrolled at Each Location	Percent of AxSYM CORE-M 2.0 Reactive[a] Results Observed From Each Location
Site 1, Galveston, TX	56.51 (742/1,313)	0.54 (4/742)
Site 2, Dallas, TX	4.49 (59/1,313)	0.00 (0/59)
Site 3, Miami, FL	3.96 (52/1,313)	1.92 (1/52)
Site 4, St. Petersburg, FL	4.27 (56/1,313)	1.79 (1/56)
Site 5, Chicago, IL	0.61 (8/1,313)	0.00 (0/8)

Site 6, Denver, CO	2.74 (36/1,313)	0.00 (0/36)
Specimen Vendor 1 Location:		
Colton, CA	5.79 (76/1,313)	0.00 (0/76)
Plymouth, MA	7.54 (99/1,313)	1.01 (1/99)
High Point, NC	14.09 (185/1,313)	0.54 (1/185)

[a] Includes gray zone reactives.

Table 18
AxSYM CORE-M 2.0 Results by Age Range and Gender for Individuals at Increased Risk of HBV Infection

		AxSYM CORE-M 2.0 Result			
		+	GZR	–	
Age Range	Gender	Number of Specimens (%)	Number of Specimens (%)	Number of Specimens (%)	Total
10 to 19	Female	0 (0.00)	0 (0.00)	14 (100.00)	14
	Male	0 (0.00)	0 (0.00)	11 (100.00)	11
20 to 29	Female	0 (0.00)	1 (0.54)	183 (99.46)	184
	Male	1 (1.03)	0 (0.00)	96 (98.97)	97
30 to 39	Female	0 (0.00)	0 (0.00)	184 (100.00)	184
	Male	1 (0.93)	0 (0.00)	106 (99.07)	107
40 to 49	Female	1 (0.40)	1 (0.40)	249 (99.20)	251
	Male	0 (0.00)	0 (0.00)	159 (100.00)	159
50 to 59	Female	0 (0.00)	1 (0.73)	136 (99.27)	137
	Male	1 (0.93)	1 (0.93)	106 (98.15)	108
60 to 69	Female	0 (0.00)	0 (0.00)	35 (100.00)	35
	Male	0 (0.00)	0 (0.00)	12 (100.00)	12
70 to 79	Female	0 (0.00)	0 (0.00)	8 (100.00)	8
	Male	0 (0.00)	0 (0.00)	3 (100.00)	3
Unknown[a]	Female	0 (0.00)	0 (0.00)	3 (100.00)	3
	Total	**4 (0.30)**	**4 (0.30)**	**1,305 (99.39)**	**1,313**

GZR = Gray Zone Reactive

[a] Age was not provided for three subjects.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The data from the nonclinical studies demonstrated acceptable precision, analytical specificity, and seroconversion panel detection of the AxSYM CORE-M 2.0 assay when used according to the instructions for use as stated in the labeling, the warnings and precautions, and the Specimen Collection and Preparation for Analysis and Limitations sections of the labeling.

The clinical studies in this application indicate that the AxSYM CORE-M 2.0 assay is safe and effective when used according to the directions for use in the labeling.

RISK BENEFIT ANALYSIS

As a diagnostic test, the AxSYM CORE-M 2.0 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 HBV-infected individuals tested by the assay outweigh any potential adverse event or risk to the patient or user due to assay malfunction or operator error.

The potential risks encountered with this *in vitro* diagnostic test are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for the device. 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 AxSYM CORE-M 2.0 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 AxSYM CORE-M 2.0 assay has been demonstrated for use in determining if IgM antibodies to hepatitis B virus core antigen (IgM anti-HBc) are present in an individual's serum or plasma. A reasonable determination of effectiveness of the AxSYM CORE-M 2.0 assay for aiding in the diagnosis of acute or recent HBV infection in conjunction with other laboratory results and clinical information in suspected individuals 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 August 25, 2006.

The applicant's manufacturing facility was inspected on 5/8/06 (N. Chicago), 5/16/06 (Abbott Park), and 5/19/06 (Puerto Rico) 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.