

Summary of Safety and Effectiveness Data

Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION:

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

Device Trade Name: ARCHITECT[®] CORE-M[™] Reagent Kit
ARCHITECT[®] CORE-M[™] Calibrators
ARCHITECT[®] CORE-M[™] Controls

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

Premarket Approval Application (PMA) Number: P060035

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: November 6, 2007

II. INDICATIONS FOR USE:

Reagent Kit

The ARCHITECT CORE-M assay is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) in human adult and pediatric serum or plasma (dipotassium EDTA, lithium heparin, and sodium heparin) and neonatal serum. A test for IgM anti-HBc is indicated as an aid in the diagnosis of acute or recent hepatitis B virus (HBV) infection in conjunction with other laboratory results and clinical information.

Calibrators

The ARCHITECT CORE-M Calibrators are used for the calibration of the ARCHITECT *i* System when the system is used for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) using the ARCHITECT CORE-M Reagent Kit. The performance of the ARCHITECT CORE-M Calibrators has not been established with any other IgM anti-HBc assays.

Summary of Safety and Effectiveness Data

Controls

The ARCHITECT CORE-M Controls are used for monitoring the performance of the ARCHITECT *i* System when used for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) in human adult serum and plasma when using the ARCHITECT CORE-M Reagent Kit. The performance of the ARCHITECT CORE-M 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 ARCHITECT CORE-M Reagent Kit, ARCHITECT CORE-M Calibrators, and ARCHITECT CORE-M Controls are stated in the respective product labeling.

V. DEVICE DESCRIPTION:

Kit Configurations and Components

For detection of IgM antibody to hepatitis B core antigen, the ARCHITECT CORE-M Reagent Kit is composed of the following two components:

- o ARCHITECT CORE-M Microparticles: 1 or 4 Bottle(s) (5.6 mL)
Anti-human IgM (mouse, monoclonal) coated microparticles in TRIS buffer with protein (1.0% bovine serum albumin and 2.5% goat IgG) additives. Minimum concentration: 0.12% solids. Preservatives: antimicrobial agents.
- o ARCHITECT CORE-M Conjugate: 1 or 4 Bottle(s) (5.9 mL)
Acridinium-labeled hepatitis B virus core antigen (*E. coli*, recombinant) conjugate in succinate buffer with protein (2.5% bovine serum albumin and 2.0% bovine calf serum) additives. Minimum concentration: 0.4 µg/mL. Preservatives: antimicrobial agents.

Summary of Safety and Effectiveness Data

In addition, the following components are required for the ARCHITECT CORE-M Reagent Kit:

- o ARCHITECT *i* System is an analyzer designed to perform automated immunoassay tests based on the use of CMIA detection technology.
- o ARCHITECT CORE-M Calibrators, which consists of calibrator 1 and calibrator 2 for the calibration of the instrument.
- o ARCHITECT CORE-M Controls (or other control material), which consist of a negative control and a positive control.
- o ARCHITECT *i* Pre-Trigger Solution contains 1.32% (w/v) hydrogen peroxide.
- o ARCHITECT *i* Trigger Solution contains 0.35N sodium hydroxide.
- o ARCHITECT *i* Wash Buffer contains phosphate buffered saline solution with preservative.

The ARCHITECT CORE-M Calibrators contain:

- o 1 Bottle (4 mL) of Calibrator 1, which is recalcified IgM anti-HBc negative human plasma.
- o 1 Bottle (4 mL) of Calibrator 2, which is IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma.
- o ProClin[®] 950, ProClin 300, and other antimicrobial agents are used as preservatives in Calibrator 1 and Calibrator 2.

The ARCHITECT CORE-M Controls contain:

- o 1 Bottle (4 mL) of Negative Control, which is recalcified IgM anti-HBc negative human plasma.
- o 1 Bottle (4 mL) of Positive Control, which is IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma.
- o The positive control is blue and contains Acid Blue No. 9 dye.
- o ProClin 950, ProClin 300, and other antimicrobial agents are used as preservatives in the Negative Control and Positive Control.

Summary of Safety and Effectiveness Data

Assay Principle and Format

The ARCHITECT CORE-M assay is a two-step immunoassay for the qualitative detection of IgM anti-HBc in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample is prediluted with wash buffer. The prediluted sample and anti-human IgM (mouse, monoclonal) coated paramagnetic microparticles are combined. Human IgM present in the sample binds to the anti-human IgM (mouse, monoclonal) coated microparticles. After washing, the anti-HBc specific IgM binds to the acridinium-labeled recombinant hepatitis B virus core antigen (rHBcAg) conjugate that is added in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A relationship exists between the amount of IgM-anti-HBc in the sample and the RLUs detected by the ARCHITECT *i* optics.

The presence or absence of IgM anti-HBc in the specimen is determined by comparing the chemiluminescent signal in the reaction to the cutoff signal determined from an active ARCHITECT CORE-M calibration curve.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patient medical history and thorough physical examinations, including hepatitis serology, determination of liver enzyme levels, and liver biopsy evaluation, will provide further information regarding the status of HBV infection.

Alternate procedures for the detection of HBV in human serum and plasma depend on the detection of HBV deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) assays or nucleic acid testing (NAT), or the detection of HBV antibodies or antigens by commercially available assays that are licensed or approved in the United States.

VII. MARKETING HISTORY

ARCHITECT CORE-M, List No. 6L23, has not been marketed in any other country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ARCHITECT CORE-M assay, together with Calibrators and Quality Control materials, 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. This assay is used as an aid in the diagnosis of individuals with acute or recent HBV infection in conjunction with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

A false nonreactive result does not exclude the possibility of exposure to HBV. A nonreactive result may be due to antibody levels below the detection limits of this assay. Since this assay is used in combination with other HBV assays, a nonreactive result cannot be considered a public health risk, as the individual would be tested with other methodologies if signs and symptoms are indicative of HBV 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 B virus marker assays to define the clinical status of the patient.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical studies were performed at Abbott Laboratories to evaluate the performance characteristics of the ARCHITECT CORE-M assay. The studies are described below.

Assay Cutoff Determination

The presence or absence of IgM antibody to hepatitis B virus core antigen (IgM anti-HBc) in the sample is determined by comparing the chemiluminescent signal in the reaction to the cutoff RLU determined from an active ARCHITECT CORE-M calibration. The ARCHITECT CORE-M assay results are expressed as the ratio of the sample RLU to the cutoff RLU (S/CO). The S/CO is calculated using the equation:

$$S/CO = \text{Sample RLU} / \text{Cutoff RLU}$$

Summary of Safety and Effectiveness Data

The cutoff signal for the ARCHITECT Anti-HBc IgM assay is calculated by subtracting the Calibrator 1 mean RLU from Calibrator 2 mean RLU and multiplying the result by a constant value (*i.e.*, cutoff multiplier factor of 0.75). The product is then added to the Calibrator 1 mean RLU to achieve the cutoff RLU:

$$\text{Cutoff RLU} = [(\text{Calibrator 2 mean RLU} - \text{Calibrator 1 mean RLU}) \times 0.75] \\ + \text{Calibrator 1 mean RLU}$$

The ARCHITECT Anti-HBc IgM assay results for a total of 1,433 specimens were used in the ROC analysis. The sensitivity was evaluated using 273 diagnosed acute specimens. The specificity of the assay was evaluated based on 920 normal population and a population consisting of normal (n=920) and chronic (n=240). Based on this analysis, the S/CO research value of 4.0 was selected which yielded 100% sensitivity at a specificity of 100% for sensitivity population and 96.4% specificity for normal+chronic population. The S/CO (research value) of 4.0 was translated into the cut-off multiplier of 0.75 in the ARCHITECT CORE-M assay (List no.6L23).

The seroconversion detection sensitivity of the ARCHITECT CORE-M assay (List No. 6L23) was verified utilizing the cutoff multiplier of 0.75 and found to be acceptable when compared to the FDA-approved comparator IgM anti-HBc assay.

A clinical investigation was performed for the ARCHITECT CORE-M assay (List No. 6L23). The percent agreement between the ARCHITECT CORE-M assay (List No. 6L23) and the comparator IgM anti-HBc assay was evaluated and the data support the selected assay cutoff and grayzone for the ARCHITECT CORE-M assay (List No. 6L23) and thus the following cutoff calculation:

$$\text{Cutoff RLU} = [(\text{Calibrator 2 mean RLU} - \text{Calibrator 1 mean RLU}) \times 0.75] \\ + \text{Calibrator 1 mean RLU}$$

Summary of Safety and Effectiveness Data

Tube Type Interference

A study was conducted to evaluate which anticoagulants (blood collection tube types) are acceptable for use with the ARCHITECT CORE-M assay. Sample sets of human specimens were collected in the control tube type (plastic serum) and the blood collection tube types selected for evaluation. The blood collection tubes for the sample sets were supplemented with IgM anti-HBc positive plasma to prepare high negative samples (targeted to 0.80 S/CO) and low positive samples (targeted to 1.20 S/CO) and were tested.

The data support the use of the following blood collection tube types in the ARCHITECT CORE-M assay:

Glass tubes

- o Serum

Plastic tubes

- o Serum
- o Serum separator
- o Dipotassium EDTA
- o Sodium heparin
- o Lithium heparin plasma separator

On average, the tube types evaluated showed less than a 10% difference when compared to the control tube type (plastic serum). The distribution of the percent differences per tube type is listed in Table 1 below.

Table 1
ARCHITECT CORE-M Tube Type Matrix Comparison
Distribution of Absolute Percent Differences

Tube Type	Distribution of Absolute Percent Differences		
	< 10%	≥ 10% to ≤ 20%	> 20%
Glass Serum	87.8% (36/41)	12.2% (5/41)	0.0% (0/41)
Plastic Serum Separator	82.9% (34/41)	14.6% (6/41)	2.4% (1/41)
Plastic Dipotassium EDTA	80.5% (33/41)	17.1% (7/41)	2.4% (1/41)
Plastic Sodium Heparin	82.9% (34/41)	14.6% (6/41)	2.4% (1/41)
Plastic Lithium Heparin Plasma Separator	80.5% (33/41)	17.1% (7/41)	2.4% (1/41)

Summary of Safety and Effectiveness Data

Sample Stability of Serum and Plasma

A study was conducted to evaluate the sample storage temperatures and number of freeze/thaw cycles for each blood collection tube type acceptable for use with the ARCHITECT CORE-M assay. Sample sets of human specimens were collected in each of the blood collection tube types and supplemented with IgM anti-HBc positive stock (targeted at 1.1 S/CO). The samples were tested at baseline (time point 1) and after being stored at 2 to 8°C for ≥ 7 days, at 24 to 30°C for ≥ 3 days, or after being subjected to three freeze/thaw cycles. Specimens that were stored at the 24 to 30°C condition and 2 to 8°C condition were tested from the blood collection tubes, as on the clot represents worst-case condition (*i.e.* specimen contact with the red blood cells). The specimens that were subjected to the freeze/thaw conditions were tested off the clot.

The data demonstrate that human serum (collected in glass or plastic tubes, or plastic serum separator tubes) or plasma collected in dipotassium EDTA, lithium heparin plasma separator, or sodium heparin tubes may be used with the ARCHITECT CORE-M assay when:

- o stored at 2 to 8°C for up to 7 days
- o stored at 24 to 30°C (room temperature) for up to 3 days
- o subjected to up to 3 freeze/thaw cycles

Sample On Board Stability

A study was conducted to evaluate samples when stored on the ARCHITECT *i* System (on board storage) and tested using the ARCHITECT CORE-M assay. High negative samples (targeted to 0.80 S/CO) and low positive samples (targeted to 1.20 S/CO) were tested using one lot of reagents, one lot of calibrators, and one lot of controls on two instruments (one *i* 2000 and one *i* 2000_{SR}). Time point 1 consisted of testing the two analyte levels immediately after pipetting the samples. Time point 2 consisted of testing the two analyte levels after being stored on board the instrument for at least 3 hours.

The data support sample storage of up to 3 hours on board the ARCHITECT *i* System when tested using the ARCHITECT CORE-M assay.

Summary of Safety and Effectiveness Data

Within-Laboratory Precision (20-day Precision)

A 20-day precision study was conducted to evaluate the precision performance of the ARCHITECT CORE-M assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) document EP5-A2 and to confirm that the ARCHITECT CORE-M assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}. Testing was performed using three ARCHITECT CORE-M reagent lots, three calibrator lots, and one control lot on two instruments (one *i* 2000 and one *i* 2000_{SR}). The ARCHITECT CORE-M Negative Control (NC) and Positive Control (PC), high negative panel (targeted to 0.80 S/CO) and low positive panel (targeted to 1.20 S/CO) were assayed in replicates of three at two separate times of day for 20 testing days.

The ARCHITECT CORE-M assay demonstrated acceptable precision. The data confirm that the ARCHITECT CORE-M assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}. The results are summarized in Table 2 on page 11.

Table 2
ARCHITECT CORE-M Precision (20-Day)
Overall Precision – Three Reagent Lots

Instrument	Sample	n	Mean S/CO	Within-Run		Within-Laboratory Precision (Total)	
				SD	%CV	SD	%CV
1	Positive Control	360	3.20	0.127	4.0	0.137	4.3
	Low positive panel	359	1.21	0.049	4.0	0.052	4.3
	High negative panel	359	0.83	0.032	3.9	0.035	4.2
	Negative Control	360	0.04	0.005	N/A	0.005	N/A
2	Positive Control	360	3.13	0.131	4.2	0.141	4.5
	High negative panel	359	0.80	0.035	4.4	0.040	5.0
	Low positive panel	358	1.18	0.052	4.4	0.057	4.8
	Negative Control	356	0.03	0.005	N/A	0.005	N/A

N/A = not applicable

Summary of Safety and Effectiveness Data

Analytical Specificity

A study was conducted to evaluate the ARCHITECT CORE-M assay for potential cross-reactivity with specimens from individuals with medical conditions unrelated to HBV infection. Specimens with various medical conditions were tested using the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay. The final results for each of the specimens were compared between the two assays. Specimen results that were discordant between the two assays were sent to an external reference laboratory for supplemental testing with FDA-approved assays.

For the medical conditions evaluated, the ARCHITECT CORE-M assay demonstrated no potential cross-reactivity with specimens from individuals with medical conditions unrelated to HBV. The data are summarized in Table 3 on page 13.

Summary of Safety and Effectiveness Data

Table 3
ARCHITECT CORE-M versus Comparator IgM anti-HBc Assay
Final Results by Category

Category	N ^a	Comparator IgM Anti-HBc Assay					
		Nonreactive			Reactive		
		ARCHITECT CORE-M			ARCHITECT CORE-M		
		NR ^b	GZ ^b	R ^b	NR ^b	GZ ^b	R ^b
Anti-nuclear antibody (ANA)	10	10	0	0	0	0	0
Cytomegalovirus (anti-CMV positive)	10	10	0	0	0	0	0
Elevated IgG	10	10	0	0	0	0	0
Elevated IgM	5	5	0	0	0	0	0
Epstein-Barr virus (anti-EBV positive)	10	10	0	0	0	0	0
HBV vaccine recipient	8	8	0	0	0	0	0
Hepatitis A virus (anti-HAV IgM positive)	10	10	0	0	0	0	0
Hepatitis C virus (anti-HCV positive)	10	10	0	0	0	0	0
Herpes simplex virus (anti-HSV positive) IgG	4	4	0	0	0	0	0
Human anti-mouse antibodies (HAMA) positive	7	7	0	0	0	0	0
Human immunodeficiency virus (anti-HIV-1 positive)	10	10	0	0	0	0	0
Human immunodeficiency virus (anti-HIV-2 positive)	10	10	0	0	0	0	0
Influenza vaccine recipient	10	10	0	0	0	0	0
Multiparous female	10	10	0	0	0	0	0
Multiple myeloma	2	2	0	0	0	0	0
Mumps virus	10	10	0	0	0	0	0
Non-Hodgkin's lymphoma	6	6	0	0	0	0	0
Non-viral liver disease	12	12	0	0	0	0	0
Rheumatoid factor positive	10	9	0	0	1 ^c	0	0
Rubella	10	10	0	0	0	0	0
Rubeola virus	9	9	0	0	0	0	0
Syphilis	10	10	0	0	0	0	0
Systemic lupus erythematosus (SLE)	9	9	0	0	0	0	0
Toxoplasmosis IgG positive	9	9	0	0	0	0	0
Varicella zoster virus (anti-VZV positive)	4	4	0	0	0	0	0
Yeast Infection	7	7	0	0	0	0	0
Total	222	221	0	0	1	0	0

^a Number of specimens tested per category

^b NR = Nonreactive, GZ = Grayzone, R = Reactive

^c This specimen was tested and determined to be reactive for HBsAg, but did not confirm; negative for total anti-HBc; and positive for anti-HBs. A second FDA-approved IgM anti-HBc assay was performed and the specimen was determined to be negative.

Summary of Safety and Effectiveness Data

Interferences – Bilirubin, Hemoglobin, Total Protein, and Triglycerides

A study was conducted to evaluate the susceptibility of the ARCHITECT CORE-M assay to potentially interfering substances based on guidance from the CLSI document EP7-A2.

A bilirubin test sample was prepared by supplementing the high negative and low positive samples with bilirubin (conjugated and unconjugated) at > 20 mg/dL (targeted to 22 mg/dL). A hemoglobin test sample was prepared by supplementing the high negative and low positive samples with hemolysate at > 500 mg/dL (targeted to 550 mg/dL). A high protein test sample (> 12 g/dL [targeted to 13.2 g/dL]) was prepared by concentrating a nonreactive, normal protein specimen and supplementing with IgM anti-HBc positive stock to yield two test samples with different analyte levels (0.80 and 1.20 S/CO). A triglyceride test sample was prepared by supplementing the high negative and low positive samples with Liposyn[®] III at > 3000 mg/dL (targeted to 3300 mg/dL). Reference samples were prepared for each test sample at each analyte level. The reference and test samples were tested.

At the concentrations listed below, bilirubin, hemoglobin, total protein, and triglycerides showed less than 10% interference in the ARCHITECT CORE-M assay for high negative samples targeted to 0.80 S/CO (S/CO range: 0.60 to 0.99) and low positive samples targeted to 1.20 S/CO (S/CO range: 1.00 to 1.40):

- o Bilirubin (≤ 20 mg/dL)
- o Hemoglobin (≤ 500 mg/dL)
- o Total Protein (≤ 12 g/dL)
- o Triglycerides (≤ 3000 mg/dL)

Summary of Safety and Effectiveness Data

Seroconversion Panels

The ability of the ARCHITECT CORE-M assay to detect IgM anti-HBc was evaluated by testing eight seroconversion panels obtained from two commercial vendors.

The results were compared to the results of an FDA-approved IgM anti-HBc assay (reference). IgM anti-HBc was detected by ARCHITECT CORE-M coincident with the reference IgM anti-HBc assay in eight panels.

The profiles of the eight seroconversion panels were characteristic of an acute HBV infection progressing to eventual recovery and immunity to HBV. ARCHITECT CORE-M detected IgM anti-HBc following detection of HBsAg in all panels during the acute stage of disease.

IgM anti-HBc remained detectable over a range of two to ten months in the eight panels. The overall ARCHITECT CORE-M results were consistent with the known serological profile of each panel.

Neonate Serum

A study was conducted to evaluate whether neonate samples may be tested with the ARCHITECT CORE-M assay. Cord blood serum was used as a surrogate for neonate serum. Twenty-one matched cord blood and maternal serum samples were spiked with IgM anti-HBc positive stock to yield a high negative sample (target S/CO 0.80) and a low positive sample (target S/CO 1.20).

None of the samples were initially reactive. The data obtained upon spiking are summarized in the following table, showing the amount of bias for the cord blood serum samples from the matched maternal serum samples. For cord blood serum samples with > 10% bias, one sample exhibited negative bias and the remaining samples exhibited positive bias when compared to the matched maternal serum samples. The results are presented in Table 4 below.

Table 4
ARCHITECT CORE-M Neonate Serum
Distribution of Percent Bias

Analyte Level S/CO	Distribution of % Bias			
	< 10%	≥ 10% to < 20%	≥ 20% to < 30%	≥ 30%
0.80	66.7% (14/21)	28.6% (6/21)	4.8% (1/21)	0.0% (0/21)
1.20	52.4% (11/21)	38.1% (8/21)	9.5% (2/21)	0.0% (0/21)

Summary of Safety and Effectiveness Data

Calibration Curve Storage

A study was conducted to evaluate the acceptability of an ARCHITECT CORE-M calibration curve stored on the ARCHITECT *i* System for a minimum of 30 days and to confirm that the ARCHITECT CORE-M assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}. Testing was performed using three ARCHITECT CORE-M reagent lots, three calibrator lots, and one control lot on two instruments (one *i* 2000 and one *i* 2000_{SR}). Each reagent lot was matched with a different calibrator lot. Calibrations were performed on each instrument for each reagent lot and the calibration curve generated was stored on each instrument for the duration of the study. The ARCHITECT CORE-M Negative Control and Positive Control were assayed in replicates of three, at two times per day, for a total of 20 time points across a minimum of 31 days. The last time point was performed at 34 days after calibration.

- The data support the storage of an ARCHITECT CORE-M calibration curve on the ARCHITECT *i* System for a minimum of 30 days. The data confirm that the ARCHITECT CORE-M assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}.

High Dose Hook Effect

A study was conducted to characterize the performance of the ARCHITECT CORE-M assay when used to test specimens containing high levels of IgM anti-HBc that have the potential to cause a high dose hook effect. Two unique stocks of IgM anti-HBc positive human were used for the study, where at least one of the stocks had an S/CO value of > 10 after a minimum of a 1:8 dilution. The two IgM anti-HBc positive human plasma stocks were each serially diluted with recalcified IgM anti-HBc negative human plasma and tested on the ARCHITECT *i* System.

The data demonstrate that the ARCHITECT CORE-M assay is not susceptible to interference from specimens with high levels of IgM anti-HBc.

Summary of Safety and Effectiveness Data

Instrument Percent Agreement

A study was conducted to confirm that the ARCHITECT CORE-M assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR} systems. One hundred and one IgM anti-HBc negative specimens and 162 IgM anti-HBc positive specimens were tested on two instruments (one *i* 2000 and one *i* 2000_{SR}) using a minimum of two lots of reagents and one lot of calibrators and controls. One replicate of each specimen was tested with the same reagent lot on both instruments.

The negative percent agreement was 100.0% with a 95% confidence interval of 96.41% to 100.00%. The positive percent agreement was 100.0% with a 95% confidence interval of 97.75 % to 100.00%. The ARCHITECT CORE-M assay demonstrated acceptable agreement between the ARCHITECT *i* 2000 and *i* 2000_{SR}.

Within-Assay Sample Carryover

A study was conducted to evaluate the susceptibility of within-assay sample carryover within the ARCHITECT CORE-M assay by comparing the results of a low IgM anti-HBc sample when tested before (protected) and after testing a high IgM anti-HBc sample (unprotected).

The difference between the protected low sample and the unprotected low sample mean S/CO values was 0.02 S/CO, indicating that no within-assay sample carryover was present. Therefore, the ARCHITECT CORE-M assay is not susceptible to within-assay sample carryover.

Summary of Safety and Effectiveness Data

Reagent, Calibrator, and Control Developmental Stability

The developmental stability is an on-going study to establish the stability (shelf-life integrity) of the ARCHITECT CORE-M Reagents, Calibrators, and Controls at the intended storage condition of 2 to 8°C and during on board storage (for reagents only).

In addition, the developmental stability includes the in-use and freeze/thaw conditions. The in-use condition for the reagents, calibrators, and controls simulates customer use over time. The freeze/thaw condition for the reagents, calibrators, and controls supports the transport simulation studies described below. Stability testing is performed on three lots of reagents, calibrators, and controls.

The developmental stability is scheduled to continue for a maximum of 15 months (with a minimum of 6 months). To date, the above stability conditions meet the stability action limits over the time period tested.

Reagent Transport Stability

A study was conducted to support the stability of the ARCHITECT CORE-M Reagents following simulated transport stress conditions. One lot of the ARCHITECT CORE-M Reagents was tested after being subjected to simulated transport stress.

The data support the stability of the ARCHITECT CORE-M Reagents following transport at ambient temperatures.

Summary of Safety and Effectiveness Data

Calibrator and Control Transport Stability

A study was conducted to support the stability of the ARCHITECT CORE-M Calibrator and Controls following simulated transport stress conditions. One lot each of the ARCHITECT CORE-M Calibrators and Controls was tested after being subjected to simulated transport stress.

The data support the stability of the ARCHITECT CORE-M Calibrators and Controls following transport at ambient temperatures.

ARCHITECT CORE-M Microbial Challenge Characterization

A Microbial Challenge Characterization (MCC) evaluation was performed for the ARCHITECT CORE-M Reagents, Calibrators, and Controls, which consisted of an Antimicrobial Effectiveness Testing (AET) evaluation and a Microbial Interference Characterization (MIC) evaluation. The MCC evaluation integrated the results from both AET and MIC, which determined that the product is adequately protected.

X. SUMMARY OF CLINICAL STUDIES

A multi-center study was conducted to evaluate the efficacy of the ARCHITECT CORE-M assay for the qualitative detection of IgM anti-HBc in human serum and plasma as measured by precision and method comparison.

System Reproducibility (5-day Precision)

A study was conducted to validate the precision performance of the ARCHITECT CORE-M assay based on guidance from the CLSI document EP15-A2.²¹ Three lots of ARCHITECT CORE-M Reagents, Calibrators, and Controls were tested per site. The ARCHITECT CORE-M Negative Control and Positive Control, and a high negative panel member (Panel 1) (targeted to 0.80 S/CO) and low positive panel member (Panel 2) (targeted to 1.20 S/CO) were assayed in replicates of four at two separate times per day for five days. The data are summarized in Table 5 on page 21 and in Table 6 on page 22.

Table 5
ARCHITECT CORE-M
System Reproducibility (5-Day Precision)
All Sites, All Reagent Lots
Individual Variance Components

Sample	N	Grand Mean S/CO	Within-Run		Between-Run		Between-Day		Total ^a			Between-Lot		Between-Site		Overall ^b	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	%CV Upper CL ^c	SD	%CV	SD	%CV	SD	%CV
Panel 1	360	0.83	0.036	4.3	0.000	0.0	0.000	0.0	0.036	4.3	4.6	0.036	4.4	0.027	3.3	0.056	6.8
Panel 2	360	1.21	0.049	4.0	0.006	0.5	0.012	1.0	0.051	4.2	4.5	0.051	4.2	0.035	2.9	0.078	6.5
Negative Control	360	0.03	0.005	14.0	0.000	0.0	0.001	2.6	0.005	14.3	15.2	0.001	2.8	0.002	7.2	0.005	16.1
Positive Control	360	3.19	0.115	3.6	0.003	0.1	0.038	1.2	0.121	3.8	4.0	0.110	3.4	0.106	3.3	0.187	5.8

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

^b Overall variability contains within-run, between-run, between-day, between-lot, between-site and lot-site interaction variance components.

^c One-sided upper 95% confidence limit for % CV with degrees of freedom calculated by Satterthwaite's method.

Table 6
ARCHITECT CORE-M
System Reproducibility (5-Day Precision)
All Sites, All Reagent Lots
Cumulative Variance Components

Sample	n	Grand Mean S/CO	Within-Run		Within-Day		Within-Laboratory Precision (Total)		Precision with Additional Component of Between-Site ^a		Precision with Additional Component of Between-Lot ^a		Precision with Additional Components of Site and Lot (Overall) ^a	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Positive Control	360	3.19	0.115	3.6	0.115	3.6	0.121	3.8	0.160	5.0	0.163	5.1	0.187	5.8
Low Positive Panel	360	1.21	0.049	4.0	0.049	4.1	0.051	4.2	0.061	5.1	0.072	5.9	0.078	6.5
High Negative Panel	360	0.83	0.036	4.3	0.036	4.3	0.036	4.3	0.045	5.4	0.051	6.2	0.056	6.8
Negative Control	360	0.03	0.005	N/A	0.005	N/A	0.005	N/A	0.005	N/A	0.005	N/A	0.005	N/A

N/A = not applicable

^a Includes site-lot interaction variance component.

Method Comparison

Study Overview and Subject Population

A prospective multi-center study was conducted to evaluate the ability of the ARCHITECT CORE-M assay to detect IgM anti-HBc antibodies in specimens from an intended use diagnostic population.

Of the 2,159 specimens tested and analyzed in the ARCHITECT CORE-M clinical study, 1,207 specimens were from individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, disease state, or known exposure event and 545 specimens were from individuals exhibiting signs and symptoms of hepatitis infection living in the United States (Population One); 94 specimens were from individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, disease state, or known exposure event and 183 specimens were from individuals exhibiting signs and symptoms of hepatitis infection living in Vietnam (Population Two); 14 specimens were from individuals diagnosed with acute HBV infection; 16 specimens were pre-selected IgM anti-HBc positive specimens; and 100 surplus specimens were from a pediatric population.

The 2,159 specimens were collected from specimen collection sites or were purchased from specimen vendors. Each specimen was tested using the ARCHITECT CORE-M assay at one of the three clinical testing sites located in Galveston, TX; Hershey, PA; and Milwaukee, WI.

Each specimen was also tested with the comparator IgM anti-HBc assay at an external laboratory. Specimens from Population One, Population Two, and the acute and pre-selected IgM anti-HBc populations were also tested with three HBV reference assays. The comparator and reference assays were from a single manufacturer and during the clinical study, all comparator and reference testing was performed according to manufacturer's instructions.

HBV classification was then determined using the results from the HBV reference markers and a modification of the serological criteria established by the National Center of Infectious Disease (CDC) for diagnosing HBV infection, which is presented in Table 7 on page 24. Nineteen unique reference marker patterns are represented.

Summary of Safety and Effectiveness Data

Table 7
HBV Classification

HBV Reference Markers				HBV Classification
HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
+	–	–	–	Early Acute
+	+	+	–	Acute
+	+	+	I	Chronic
+	–	+	+	Chronic
+	–	+	–	Chronic
+	–	–	+	Chronic
+	–	+	I	Chronic*
+	+	+	+	Late Acute/Recovering*
–	+	+	+	Recovering Acute
–	+	+	–	Recovering Acute/Undetectable HBsAg
–	+	–	+	Recovering Acute [†]
–	+	–	–	Possible Recovering Acute/Undetectable HBsAg [†]
–	+	+	I	Early Recovery*
–	–	+	+	Immune Due to Natural Infection
–	–	+	I	Distantly Immune/Anti-HBs Unknown
–	–	+	–	Distantly Immune/ Anti-HBs Not Detected
–	–	–	+	Immune Due to HBV Vaccination
–	–	–	I	Unknown
–	–	–	–	Susceptible

+ = Positive/Reactive; – = Negative; I = Indeterminate

[†] Serological marker pattern was not observed during the clinical evaluation.

* Three additional serological marker patterns were observed during the clinical evaluation.

Summary of Safety and Effectiveness Data

The ARCHITECT CORE-M results were compared to the comparator IgM anti-HBc results. For specimens that were discordant between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay, supplemental testing was performed to better characterize the specimens. Supplemental testing was performed on different specimen aliquots at external reference laboratories.

Results by Specimen Classification

Following testing with the comparator IgM anti-HBc assay and the three reference HBV assays, specimens from Population One, Population Two, and the acute and pre-selected IgM anti-HBc populations were assigned an HBV classification using the reactive (+) and nonreactive (-) patterns.

The 17 unique reference marker patterns observed in the ARCHITECT CORE-M clinical study for Population One are presented in Table 8 on page 26. The 10 unique reference marker patterns observed in the ARCHITECT CORE-M clinical study for Population Two are presented in Table 9 on page 27.

Acute status was determined for all of the specimens in the acute and pre-selected IgM anti-HBc populations.

Table 8
HBV Classification for Increased Risk and Signs and Symptoms Population
(Population One)

HBV Classification	HBV Reference Markers				
	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	N
Early Acute	+	-	-	-	8
Acute	+	+	+	-	17
Chronic	+	+	+	I	1
Chronic	+	-	+	+	2
Chronic	+	-	+	-	51
Chronic	+	-	-	+	3
Recovering Acute	-	+	+	+	7
Recovering Acute/Undetectable HBsAg	-	+	+	-	2
Immune Due to Natural Infection	-	-	+	+	220
Distantly Immune/Anti-HBs Unknown	-	-	+	I	34
Distantly Immune/Anti-HBs Not Detected	-	-	+	-	107
Immune Due to HBV Vaccination	-	-	-	+	351
Susceptible	-	-	-	-	897
Late Acute/Recovering	+	+	+	+	1
Chronic	+	-	+	I	3
Early Recovery	-	+	+	I	3
Unknown	-	-	-	I	45
Total					1752

I = Indeterminate

Summary of Safety and Effectiveness Data

Table 9
HBV Classification for Increased Risk and Signs and Symptoms Population
(Population Two)

HBV Classification	HBV Reference Markers				
	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	N
Early Acute	+	-	-	-	1
Chronic	+	-	+	+	3
Chronic	+	-	+	-	107
Chronic	+	-	-	+	1
Immune Due to Natural Infection	-	-	+	+	67
Distantly Immune/Anti-HBs Unknown	-	-	+	I	5
Distantly Immune/Anti-HBs Not Detected	-	-	+	-	12
Immune Due to HBV Vaccination	-	-	-	+	41
Susceptible	-	-	-	-	37
Chronic	+	-	+	I	3
Total					277

I = Indeterminate

Comparison of Results

The ARCHITECT CORE-M assay results were compared to the comparator IgM anti-HBc assay results for Population One and Population Two. The data are presented in the Table 10 beginning on page 28 for Population One and in Table 11 on page 30 for Population Two.

Table 10
ARCHITECT CORE-M Results versus Comparator IgM Anti-HBc Results
Comparison for Increased Risk and Signs and Symptoms Population (Population One) by HBV Classification

HBV Classification	Comparator IgM Anti-HBc												Total	
	Reactive						Negative							
	ARCHITECT CORE-M						ARCHITECT CORE-M							
	Reactive		Grayzone		Nonreactive		Reactive		Grayzone		Nonreactive			
	N	%	N	%	N	%	N	%	N	%	N	%		
Early Acute	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	8	0.46	8	0.46
Acute	16	0.91	1 ^a	0.06	0	0.00	0	0.00	0	0.00	0	0.00	17	0.97
Chronic	1	0.06	0	0.00	0	0.00	0	0.00	4 ^d	0.23	55	3.14	60	3.42
Recovering Acute	7	0.40	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	7	0.40
Recovering Acute/Undetectable HBsAg	2	0.11	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.11
Immune Due to Natural Infection	0	0.00	0	0.00	0	0.00	14 ^b	0.80	5 ^e	0.29	201	11.47	220	12.56
Distantly Immune/Anti-HBs Unknown	0	0.00	0	0.00	0	0.00	0	0.00	1 ^f	0.06	33	1.88	34	1.94
Distantly Immune/Anti-HBs Not Detected	0	0.00	0	0.00	0	0.00	2 ^c	0.11	1 ^f	0.06	104	5.94	107	6.11
Immune Due to HBV Vaccination	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	351	20.03	351	20.03
Susceptible	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	897	51.20	897	51.20
Late Acute/Recovering	1	0.06	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.06
Early Recovery	3	0.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	3	0.17
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	45	2.57	45	2.57
Total	30	1.71	1	0.06	0	0.00	16	0.91	11	0.63	1694	96.69	1752	100.00

Continued on next page

Table 10 (Continued)
ARCHITECT CORE-M Results versus Comparator IgM Anti-HBc Results
Comparison for Increased Risk and Signs and Symptoms Population (Population One) by HBV Classification

- ^a This specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay.
- ^b Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and nonreactive by a second FDA-approved IgM anti-HBc assay. Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and grayzone by a second FDA approved IgM anti-HBc assay. Four specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. Five specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg, anti-HBe, and HBV DNA; and grayzone by a second FDA-approved IgM anti-HBc assay.
- ^c One specimen was tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg, anti-HBe, and HBV DNA; and grayzone by a second FDA-approved IgM anti-HBc assay.
- ^d Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay.
- ^e Four specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay.
- ^f These specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay.

Table 11
ARCHITECT CORE-M Results versus Comparator IgM Anti-HBc Results
Comparison for Increased Risk and Signs and Symptoms Population (Population Two) by HBV Classification

HBV Classification	Comparator IgM Anti-HBc												Total	
	Reactive						Negative							
	ARCHITECT CORE-M						ARCHITECT CORE-M							
	Reactive		Grayzone		Nonreactive		Reactive		Grayzone		Nonreactive			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Early Acute	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.36	1	0.36
Chronic	0	0.00	0	0.00	0	0.00	0	0.00	1 ^a	0.36	113	40.79	114	41.16
Immune Due to Natural Infection	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	67	24.19	67	24.19
Distantly Immune/Anti-HBs Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	5	1.81	5	1.81
Distantly Immune/Anti-HBs Not Detected	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	12	4.33	12	4.33
Immune Due to HBV Vaccination	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	41	14.80	41	14.80
Susceptible	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	37	13.36	37	13.36
Total	0	0.00	0	0.00	0	0.00	0	0.00	1	0.36	276	99.64	277	100.00

^a This specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay

Summary of Safety and Effectiveness Data

Percent Agreement

The negative percent agreement and positive percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay and their corresponding 95% exact confidence intervals were calculated for Population One, Population Two, and the acute and pre-selected IgM anti-HBc populations combined by HBV classification. For the purposes of calculating percent agreement, the ARCHITECT CORE-M grayzone results were assigned to the opposite clinical interpretation than that of the comparator IgM anti-HBc assay result.

The percent agreement between ARCHITECT CORE-M and the comparator IgM anti-HBc assay for Population One by HBV classification is presented in Table 12 on page 32. The percent agreement between ARCHITECT CORE-M and the comparator IgM anti-HBc assay for Population Two by HBV classification is presented in Table 13 on page 33.

For individuals diagnosed with acute HBV infection and for the pre-selected IgM anti-HBc positive specimens combined, the positive percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (30/30, with a 95% confidence interval of 88.43% to 100.00%).

Summary of Safety and Effectiveness Data

Table 12
ARCHITECT CORE-M Results versus Comparator IgM Anti-HBc Results
Percent Agreement for Increased Risk and Signs and Symptoms Population
(Population One) by HBV Classification

HBV Classification	Positive Percent Agreement (%)	95% Confidence Interval	Negative Percent Agreement (%)	95% Confidence Interval
Early Acute	N/A	N/A	100.00 (8/8)	63.06-100.00
Acute	94.12 (16/17)	71.31-99.85	N/A	N/A
Chronic	100.00 (1/1)	2.50-100.00	93.22 (55/59)	83.54-98.12
Recovering Acute	100.00 (7/7)	59.04-100.00	N/A	N/A
Recovering Acute/Undetectable HBsAg	100.00 (2/2)	15.81-100.00	N/A	N/A
Immune Due to Natural Infection	N/A	N/A	91.36 (201/220)	86.84-94.72
Distantly Immune/Anti-HBs Unknown	N/A	N/A	97.06 (33/34)	84.67-99.93
Distantly Immune/Anti-HBs Not Detected	N/A	N/A	97.20 (104/107)	92.02-99.42
Immune Due to HBV Vaccination	N/A	N/A	100.00 (351/351)	98.95-100.00
Susceptible	N/A	N/A	100.00 (897/897)	99.59-100.00
Late Acute/Recovering	100.00 (1/1)	2.50-100.00	N/A	N/A
Early Recovery	100.00 (3/3)	29.24-100.00	N/A	N/A
Unknown	N/A	N/A	100.00 (45/45)	92.13-100.00
Total	96.77 (30/31)	83.30-99.92	98.43 (1694/1721)	97.73-98.96

NA = not applicable

Positive % agreement = $\frac{\text{No. of ARCHITECT CORE-M reactive results in agreement with the comparator IgM anti-HBc reactive results}}{\text{[Total number of comparator IgM anti-HBc reactive results]}} \times 100\%$

Negative % agreement = $\frac{\text{No. of ARCHITECT CORE-M nonreactive results in agreement with the comparator IgM anti-HBc negative results}}{\text{[Total number of comparator IgM anti-HBc negative results]}} \times 100\%$

45

Summary of Safety and Effectiveness Data

Table 13
ARCHITECT CORE-M Results versus Comparator IgM Anti-HBc Results
Percent Agreement for Increased Risk and Signs and Symptoms Population
(Population Two) by HBV Classification

HBV Classification	Positive Percent Agreement (%)	95% Confidence Interval	Negative Percent Agreement (%)	95% Confidence Interval
Early Acute	N/A	N/A	100.00 (1/1)	2.50-100.00
Chronic	N/A	N/A	99.12 (113/114)	95.21-99.98
Immune Due to Natural Infection	N/A	N/A	100.00 (67/67)	94.64-100.00
Distantly Immune/Anti-HBs Unknown	N/A	N/A	100.00 (5/5)	47.82-100.00
Distantly Immune/Anti-HBs Not Detected	N/A	N/A	100.00 (12/12)	73.54-100.00
Immune Due to HBV Vaccination	N/A	N/A	100.00 (41/41)	91.40-100.00
Susceptible	N/A	N/A	100.00 (37/37)	90.51-100.00
Total	N/A	N/A	99.64 (276/277)	98.01-99.99

NA = not applicable

Negative % agreement = $\frac{\text{No. of ARCHITECT CORE-M nonreactive results in agreement with the comparator IgM anti-HBc negative results}}{\text{Total number of comparator IgM anti-HBc negative results}} \times 100\%$

Percent of Positive Specimens

The percent of positive ARCHITECT CORE-M specimens for individuals diagnosed with acute HBV infection was 100.00% (14/14, with a 95% confidence interval of 76.84% to 100.00%). The percent of positive ARCHITECT CORE-M specimens for the pre-selected IgM anti-HBc positive specimens was 100.00% (16/16, with a 95% confidence interval of 79.41% to 100.00%).

Clinical Performance in a Pediatric Population

The performance of the ARCHITECT CORE-M assay in a pediatric population was evaluated by testing 100 surplus specimens from a pediatric population collected in Fall River, MA by a specimen vendor, and from the 125 prospectively-collected pediatric specimens from Population One, Population Two, and pre-selected positive specimens.

For the surplus pediatric specimens, the negative percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (100/100, with a 95% confidence interval of 96.38% to 100.00%).

For the prospectively-collected pediatric specimens, the positive percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (8/8, with a 95% confidence interval of 63.06% to 100.00%) and the negative percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 99.15% (116/117, with a 95% confidence interval of 95.33% to 99.98%).

Summary of Safety and Effectiveness Data

The distribution of the ARCHITECT CORE-M reactive, grayzone, and nonreactive results for the surplus pediatric population and prospectively-collected pediatric population is presented below in Table 14 and Table 15, respectively.

Table 14
ARCHITECT CORE-M Results by Age Range and Gender
for the Surplus Pediatric Population

Age Range	Gender	ARCHITECT CORE-M Result			Total
		Reactive N (%)	Grayzone N (%)	Nonreactive N (%)	
2 to 12 Years	Female	0 (0.00)	0 (0.00)	25 (100.00)	25
	Male	0 (0.00)	0 (0.00)	25 (100.00)	25
13 to 18 Years	Female	0 (0.00)	0 (0.00)	32 (100.00)	32
	Male	0 (0.00)	0 (0.00)	18 (100.00)	18
Total		0 (0.00)	0 (0.00)	100 (100.00)	100

Table 15
ARCHITECT CORE-M Results by Age Range and Gender
for the Prospective Pediatric Population

Age Range	Gender	ARCHITECT CORE-M Result			Total
		Reactive N (%)	Grayzone N (%)	Nonreactive N (%)	
2 to 12 Years	Male	1 (100.00)	0 (0.00)	0 (0.00)	1
13 to 18 Years	Female	1 (14.29)	0 (0.00)	6 (85.71)	7
	Male	1 (16.67)	0 (0.00)	5 (83.33)	6
19 to 21 Years	Female	1 (1.54)	0 (0.00)	64 (98.46)	65
	Male	5 (10.87)	0 (0.00)	41 (89.13)	46
Total		9 (7.20)	0 (0.00)	116 (92.80)	125

Summary of Safety and Effectiveness Data

Expected Results

Of the 2,059 prospectively-collected specimens tested in the ARCHITECT CORE-M clinical study, 1,207 were from individuals living in the United States with increased risk of HBV infection. All 1,207 were at risk for HBV due to lifestyle, behavior, occupation, or a known exposure event but were asymptomatic and reported no current signs or symptoms of hepatitis.

The 1,207 increased risk specimens from Population One were collected from specimen collection sites or were purchased from specimen vendors. Testing of these specimens was performed at three clinical sites located in Galveston, TX; Hershey, PA; and Milwaukee, WI.

A demographic summary of the increased risk population in Population One by race/ethnic group is provided in Table 16 below.

Table 16
Demographic Summary of Increased Risk Population by Race/Ethnic Group
(Population One)

Race/Ethnic Group	N	Percent (%)
African American	396	32.81
American Indian/Alaska Native	4	0.33
Asian	26	2.15
Caucasian	582	48.22
Hispanic	176	14.58
Other	21	1.74
Unknown	2	0.17
Total	1207	100.00

Summary of Safety and Effectiveness Data

Of the 1,207 increased risk subjects in Population One, 645 (53.44%) were female and 562 (46.56%) were male. The age was not reported for one subject. Of the remaining 1,206 subjects, the mean age was 39 years (age range: 17 to 82 years).

The ARCHITECT CORE-M assay was reactive in 20 (1.66%) of the individuals in the increased risk population. The number and percent of ARCHITECT CORE-M reactive results observed at each collection location are presented in Table 17 below.

Table 17
Number and Percent of Reactive Results by Clinical Testing Site
for Increased Risk Population (Population One)

Specimen Collection Site/ Vendor Location	Percent of Specimen Enrolled at Each Site	Percent of Reactive Results at Each Site
Specimen Collection Site 1 Galveston, TX	34.55 (417/1207)	1.20 (5/417)
Specimen Collection Site 2 Dallas, TX	13.92 (168/1207)	1.19 (2/168)
Specimen Collection Site 3 Miami, FL	8.86 (107/1207)	0.93 (1/107)
Specimen Collection Site 4 St. Petersburg, FL	19.39 (234/1207)	2.99 (7/234)
Specimen Collection Site 5 Chicago, IL	3.89 (47/1207)	6.38 (3/47)
Specimen Collection Site 6 Denver, CO	3.73 (45/1207)	0.00 (0/45)
Specimen Vendor 1 Colton, CA	2.82 (34/1207)	0.00 (0/34)
Specimen Vendor 1 Plymouth, MA	10.02 (121/1207)	1.65 (2/121)
Specimen Vendor 1 High Point, NC	2.82 (34/1207)	0.00 (0/34)

Summary of Safety and Effectiveness Data

The distribution of ARCHITECT CORE-M reactive, grayzone, and nonreactive results by age range and gender is presented in Table 18 below.

Table 18
Results by Age Range and Gender
for Individuals at Increased Risk Population (Population One)

Age Range	Gender	ARCHITECT CORE-M Result			Total
		Reactive N (%)	Grayzone N (%)	Nonreactive N (%)	
10 to 19	Female	0 (0.00)	0 (0.00)	14 (100.00)	14
	Male	0 (0.00)	0 (0.00)	7 (100.00)	7
20 to 29	Female	4 (2.00)	1 (0.50)	195 (97.50)	200
	Male	2 (1.72)	1 (0.86)	113 (97.41)	116
30 to 39	Female	3 (2.00)	0 (0.00)	147 (98.00)	150
	Male	1 (0.66)	1 (0.66)	149 (98.68)	151
40 to 49	Female	3 (1.92)	2 (1.28)	151 (96.79)	156
	Male	2 (1.15)	1 (0.57)	171 (98.28)	174
50 to 59	Female	2 (2.06)	0 (0.00)	95 (97.94)	97
	Male	1 (1.11)	1 (1.11)	88 (97.78)	90
60 to 69	Female	2 (8.33)	0 (0.00)	22 (91.67)	24
	Male	0 (0.00)	0 (0.00)	15 (100.00)	15
70 to 79	Female	0 (0.00)	0 (0.00)	1 (100.00)	1
	Male	0 (0.00)	0 (0.00)	8 (100.00)	8
80 to 89	Female	0 (0.00)	0 (0.00)	3 (100.00)	3
Unknown	Male	0 (0.00)	0 (0.00)	1 (100.00)	1
Total		20 (1.66)	7 (0.58)	1180 (97.76)	1207

XI. CONCLUSIONS DRAWN FROM THE STUDIES

A multi-center study was conducted to demonstrate that the ARCHITECT CORE-M assay performs as intended in a diagnostic population. Of the 2,159 specimens tested in the ARCHITECT CORE-M clinical study, 1,752 specimens were from individuals at increased risk or with signs and symptoms of a hepatitis infection living in the United States (Population One); 277 specimens were from individuals at increased risk or with signs and symptoms of a hepatitis infection living in Vietnam (Population Two); 14 specimens were from individuals diagnosed with acute HBV infection; 16 specimens were pre-selected IgM anti-HBc positive specimens; and 100 specimens were from pediatric population. The specimens from Population One and Population Two were assigned an HBV classification and the ARCHITECT CORE-M results were compared to the comparator IgM anti-HBc results.

The overall positive percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 96.77% (30/31) for Population One. The overall negative percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 98.43% (1,694/1,721) in the same population.

The overall negative percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 99.64% (276/277) for Population Two.

The overall positive percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 100.00% (14/14) for the diagnosed acute HBV specimens and 100.00% (16/16) for the pre-selected positive specimens.

The overall positive percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 100% (8/8) for the prospectively-collected pediatric population and 100.00% (100/100) for the surplus pediatric population. The overall negative percent agreement between the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay was 99.15% (116/117) for the prospectively-collected pediatric population.

Precision and system reproducibility of the ARCHITECT CORE-M assay was established for within-run, within-day, within-lab, and between-sites.

Tube Type Interference study results support the use of human serum and plasma (dipotassium EDTA, lithium heparin, and sodium heparin) in the ARCHITECT CORE-M assay.

The ability of the ARCHITECT CORE-M assay to detect HBV infections was demonstrated with eight seroconversion panel evaluations.

Summary of Safety and Effectiveness Data

Studies with cord blood as a surrogate for neonate serum indicate comparable results with maternal serum.

The results from both the nonclinical and clinical studies indicate that the ARCHITECT CORE-M assay can be used safely and effectively for the qualitative *in vitro* determination of anti-HBc antibodies in human serum and plasma. The data also support the use of this assay as an aid in the diagnosis of acute or recent hepatitis B virus (HBV) infection in conjunction with other laboratory results and clinical information.

RISK BENEFIT ANALYSIS

As a diagnostic test, the ARCHITECT CORE-M 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 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 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 these devices. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user.

SAFETY

Based on the results of the nonclinical and clinical laboratory studies, the ARCHITECT CORE-M assay, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and pose minimal risk to the patient due to false test results.

EFFECTIVENESS

The effectiveness of the ARCHITECT CORE-M assay has been demonstrated for use in determining if IgM antibodies to the core antigen of the hepatitis B virus are present in an individual's serum or plasma. A reasonable determination of effectiveness of the ARCHITECT CORE-M assay for aiding in the diagnosis of acute or recent HBV 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 November 6, 2007.

The applicant's manufacturing facility was inspected on 5/2/07 (Abbott Park), & 7/20/07 (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.

Post-approval Requirements and Restrictions: See approval order.