

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION:

Device Generic Name: Antibody to Hepatitis B Surface Antigen (anti-HBs)

Device Trade Name: ARCHITECT® AUSAB® Reagent Kit
ARCHITECT® AUSAB® Calibrators
ARCHITECT® AUSAB® 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: P050051

Date of Notice of Approval to the Applicant: June 1, 2006

II. INDICATIONS FOR USE:

ARCHITECT® AUSAB® Reagent Kit

The ARCHITECT AUSAB assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of antibody to hepatitis B surface antigen (anti-HBs) in human adult and pediatric serum and plasma (dipotassium EDTA, lithium heparin, and sodium heparin) and neonatal serum. It is intended for quantitative measurement of antibody response following hepatitis B virus (HBV) vaccination, determination of HBV immune status, and for the laboratory diagnosis of HBV disease associated with HBV infection when used in conjunction with other laboratory results and clinical information.

ARCHITECT® AUSAB® Calibrators

The ARCHITECT AUSAB Calibrators are used to calibrate the ARCHITECT i System when the system is used for the quantitative determination of antibody to hepatitis B surface antigen (anti-HBs) using the ARCHITECT AUSAB Reagent Kit. The performance of the ARCHITECT AUSAB Calibrators has not been established with any other anti-HBs assays.

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ARCHITECT® AUSAB® Controls

The ARCHITECT AUSAB Controls are used for monitoring the performance of the ARCHITECT *i* System when used for the quantitative determination of antibody to hepatitis B surface antigen (anti-HBs) using the ARCHITECT AUSAB Reagent Kit. The performance of the ARCHITECT AUSAB Controls has not been established with any other anti-HBs assays.

III. CONTRAINDICATIONS: None known.

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

Warnings and precautions for ARCHITECT AUSAB Reagent Kit, ARCHITECT AUSAB Calibrators, and ARCHITECT AUSAB Controls are stated in the respective product labeling.

V. DEVICE DESCRIPTION:

Kit Configurations and Components

For detection of antibodies to hepatitis B virus, the ARCHITECT AUSAB Reagent Kit is composed of the following two components:

- o ARCHITECT AUSAB Microparticles: 1 or 4 Bottle(s) (4.56 mL/16.80 mL) hepatitis B surface (*E. coli*, recombinant) antigen (subtypes *ad* and *ay*) coated microparticles in TRIS buffer with protein (bovine) stabilizers (76 µM). Minimum concentration: 0.125% solids. Preservatives: antimicrobial agents.
- o ARCHITECT AUSAB Conjugate: 1 or 4 Bottle(s) (5.9 mL/26.3 mL) hepatitis B surface (*E. coli*, recombinant) antigen (subtypes *ad* and *ay*) acridinium-labeled conjugate in MES buffer with protein (112.5 g/L bovine serum and 102.7 g/L human plasma) stabilizers. Minimum concentration: 0.10 µg/mL. Preservatives: antimicrobial agents.

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In addition, the following components are required for the ARCHITECT AUSAB Reagent Kit:

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

The ARCHITECT AUSAB Calibrator Kit is composed of:

- o ARCHITECT AUSAB Calibrator A: recalcified anti-HBs negative human plasma. Preservatives: sodium azide and ProClin[®] 950.
- o ARCHITECT AUSAB Calibrators B – F: recalcified anti-HBs positive human plasma in recalcified anti-HBs negative human plasma. Preservatives: sodium azide and ProClin 950.

The ARCHITECT AUSAB Control Kit is composed of:

- o ARCHITECT AUSAB Negative Control: recalcified anti-HBs negative human plasma. Preservatives: sodium azide and ProClin[®] 950.
- o ARCHITECT AUSAB Positive Control: recalcified anti-HBs positive human plasma in recalcified anti-HBs negative human plasma. The positive control is blue and contains Acid Blue No. 9 dye. Preservatives: sodium azide and ProClin 950.

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Assay Principle and Format

The ARCHITECT AUSAB assay is a two-step immunoassay for the quantitative determination of anti-HBs in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex[®].

In the first step, sample and recombinant hepatitis B virus surface antigen (rHBsAg) coated paramagnetic microparticles are combined. Anti-HBs present in the sample binds to the rHBsAg coated microparticles. After washing, acridinium-labeled rHBsAg conjugate 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 direct relationship exists between the amount of anti-HBs in the sample and the RLUs detected by the ARCHITECT *i* optical system. The concentration of anti-HBs in the sample is determined using an active ARCHITECT AUSAB calibration curve.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Determining the presence of HBV in patients may be achieved by using a variety of commercially available, FDA-approved, serological tests. When these test results are used in combination with a physician's assessment and other laboratory test results, HBV immune status can be identified.

VII. MARKETING HISTORY

ARCHITECT AUSAB, List No. 1L82, has not been marketed in any other country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ARCHITECT AUSAB 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 chronic HBV infection and in the determination of the vaccination status of HBV infected individuals 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

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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 PRECLINICAL STUDIES

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

Tube Type Interference

A study was conducted to evaluate which anticoagulants (blood collection tube types) are acceptable for use with the ARCHITECT AUSAB assay. Sample sets of human specimens were collected in the control tube type (glass serum) and the blood collection tube types selected for evaluation. Half of the sample sets were from vaccinee donors with an anti-HBs concentration within the analytical measurement range of the assay and half of the sample sets were from anti-HBs negative donors. The blood collection tubes for the anti-HBs negative sample sets were supplemented with anti-HBs positive stock from HBV recovered donors to a target concentration within the analytical measurement range of the assay. The control and test samples were tested.

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

**Table 1
ARCHITECT AUSAB
Tube Type Interference
Distribution of Differences**

Evaluation Tube Type	Distribution of %Differences		
	< 10%	≥ 10% to ≤ 20%	> 20%
Glass Serum Separator	81.8% (36/44)	15.9% (7/44)	2.3% (1/44)
Plastic Serum	79.5% (35/44)	18.2% (8/44)	2.3% (1/44)
Plastic Serum Separator	79.5% (35/44)	20.5% (9/44)	0.0% (0/44)
Plastic Lithium Heparin Plasma Separator	86.0% (37/43)	14.0% (6/43)	0.0% (0/43)
Plastic Sodium Heparin	85.7% (36/42)	14.3% (6/42)	0.0% (0/42)

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Evaluation Tube Type	Distribution of %Differences		
	< 10%	≥ 10% to ≤ 20%	> 20%
Plastic Dipotassium EDTA	78.0% (32/41)	19.5% (8/41)	2.4% (1/41)

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The data support the use of the following blood collection tube types in the ARCHITECT AUSAB assay:

Glass tubes

- o Serum
- o Serum separator

Plastic tubes

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

Interferences – Bilirubin, Hemoglobin, Total Protein, and Triglycerides

A study was conducted to evaluate the susceptibility of the ARCHITECT AUSAB assay to potentially interfering substances based on guidance from the Clinical Laboratory Standards Institute (CLSI) document EP7-A.

Bilirubin test samples were prepared by supplementing a high negative and a low positive sample with bilirubin (conjugated and unconjugated) at ≥ 20 mg/dL (targeted to 22 mg/dL). Hemoglobin test samples were prepared by supplementing a high negative and a low positive sample 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 an HBV negative serum pool and supplementing with anti-HBs positive stock from HBV recovered donors to yield two test samples with different analyte levels (8.00 and 12.0 mIU/mL). Triglyceride test samples were prepared by supplementing a high negative and a low positive sample with Liposyn[®] III at ≥ 3000 mg/dL (targeted to 3300 mg/dL). Control samples were prepared for each test sample at each analyte level. The control and test samples were tested.

At the concentrations listed below, bilirubin, hemoglobin, total protein, and triglycerides showed less than 10% interference in the ARCHITECT AUSAB assay for high negative samples targeted to 8.0 mIU/mL (concentration range: 6.0 to 9.9 mIU/mL) and low positive samples targeted to 12.0 mIU/mL (concentration range: 10.0 to 14.0 mIU/mL):

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

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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 AUSAB assay. Sample sets of human specimens were collected in each of the blood collection tube types. The samples were tested at time point 0 and after being stored at 2 to 8°C for ≥ 7 days, at room temperature (study performed at 21 to 22°C) for ≥ 3 days, and after being subjected to three freeze/thaw cycles. Specimens that were stored at the room temperature condition and 2 to 8°C condition were tested from the blood collection tubes, as on the clot, cells, or gel represents worst-case condition. The specimens that were subjected to the freeze/thaw conditions were tested off the clot.

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

- o stored at 2 to 8°C for up to 7 days
- o stored at room temperature (study performed at 21°C to 22°C) 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 AUSAB assay. A low positive sample pool was prepared at a target concentration of 12 mIU/mL (range: 10.0 mIU/mL to 14.0 mIU/mL). The sample pool was tested using one lot of reagents, one lot of calibrator, and one lot of controls on two instruments. Time point 0 consisted of testing the sample pool immediately after pipetting. Time point 1 consisted of testing the sample pool after being stored on board the instrument for longer than 3 hours.

The data support sample storage of up to 3 hours on board the ARCHITECT *i* System when tested with the ARCHITECT AUSAB assay.

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Within-Laboratory Precision

A 20-day precision study was conducted to evaluate the precision performance of the ARCHITECT AUSAB assay based on guidance from the CLSI document EP5-A2. Testing was performed using three ARCHITECT AUSAB reagent lots, three calibrator lots, and one control lot on two instruments. The ARCHITECT AUSAB Negative Control, Positive Control, and six panels were assayed in replicates of two at two separate times of day for 20 testing days.

The ARCHITECT AUSAB assay demonstrated acceptable precision. The results are summarized in Table 2.

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Table 2
ARCHITECT AUSAB
Within-Laboratory Precision Study - Overall Precision

Instrument	Sample	n	Grand Mean (mIU/ mL)	Within-Run		Within-Day		Within-Laboratory Precision (Total)	
				SD	%CV	SD	%CV	SD	%CV
1	Negative Control	240	0.15	0.135	NA	0.136	NA	0.150	NA
	Positive Control	240	14.99	0.499	3.3	0.572	3.8	0.811	5.4
	Panel 1	240	7.55	0.339	4.5	0.339	4.5	0.467	6.2
	Panel 2	240	11.32	0.471	4.2	0.479	4.2	0.666	5.9
	Panel 3	240	49.71	1.407	2.8	1.733	3.5	2.656	5.3
	Panel 4	240	98.24	2.845	2.9	3.497	3.6	5.040	5.1
	Panel 5	240	497.89	13.496	2.7	17.405	3.5	26.504	5.3
	Panel 6	240	837.29	21.876	2.6	25.947	3.1	45.386	5.4
2	Negative Control	240	0.16	0.180	NA	0.180	NA	0.180	NA
	Positive Control	240	15.70	0.496	3.2	0.669	4.3	0.907	5.8
	Panel 1	240	8.18	0.507	6.2	0.544	6.7	0.667	8.2
	Panel 2	240	12.25	0.564	4.6	0.573	4.7	0.776	6.3
	Panel 3	240	51.63	1.388	2.7	1.735	3.4	2.557	5.0
	Panel 4	240	101.84	2.457	2.4	3.229	3.2	4.871	4.8
	Panel 5	240	511.13	12.171	2.4	16.383	3.2	24.991	4.9
	Panel 6	240	852.69	24.829	2.9	33.928	4.0	51.692	6.1

NA = not applicable

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Analytical Specificity

A study was conducted to evaluate the ARCHITECT AUSAB assay for potential cross-reactivity with specimens from individuals with medical conditions unrelated to HBV infection. Specimens with various medical conditions were obtained and tested with the ARCHITECT AUSAB assay and a comparator anti-HBs assay. The final results for each of the specimens were compared between the two assays. Specimen results that were discordant between the two assays utilized supplemental testing results.

For the medical conditions evaluated, the ARCHITECT AUSAB assay demonstrated no more potential cross-reactivity than the comparator device. The data are summarized in Table 3.

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Table 3
Reactivity of the ARCHITECT AUSAB Assay in Individuals with Medical Conditions Unrelated to HBV Infection

Category	No. of Specimens	Comparator anti-HBs assay					
		Negative			Positive		
		ARCHITECT			ARCHITECT		
		NR ^a	GZ ^a	R ^a	NR ^a	GZ ^a	R ^a
Cytomegalovirus (anti-CMV positive)	9	4	0	0	0	0	5
Epstein-Barr Virus (anti-EBV positive)	9	2	0	0	0	0	7
Hepatitis A Virus (anti-HAV positive)	10	9	0	0	0	0	1
Hepatitis C Virus (anti-HCV positive)	10	6	0	0	0	0	4
Human immunodeficiency Virus (anti-HIV-1 positive)	10	6	0	0	0	0	4
Herpes Simplex Virus (anti-HSV positive)	6	4	0	0	0	0	2
Elevated Bilirubin	9	9	0	0	0	0	0
Elevated Protein	8	5	0	0	0	0	3
Human Anti-Mouse Antibodies (HAMA) positive	10	10	0	0	0	0	0
Influenza vaccine recipient	10	4	0	0	0	0	6
Multiparous Female	10	10	0	0	0	0	0
Non-viral liver disease	8	6	0	0	0	0	2
Rheumatoid factor positive	6	5	0	0	0	0	1
Rubella antibody positive	10	7	0	0	0	0	3
Syphilis	10	5	0	0	0	0	5
Toxoplasmosis IgG positive	9	5	0	0	0	0	4
Varicella Zoster Virus (VZV) positive	7	4	0	0	1 ^b	0	2
Yeast infection	9	6	0	0	0	0	3
<i>Total</i>	<i>160</i>	<i>107</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>52</i>

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

^b The final interpretation of the VZV positive specimen was anti-HBs negative when tested using the supplemental AUSAB enzyme immunoassay.

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WHO Standard Linearity

A study was conducted to evaluate the linearity performance of the ARCHITECT AUSAB assay calibrated with Abbott internal calibrators using dilutions of the World Health Organization (WHO) standard in anti-HBs negative plasma.

The linear regression slopes for the WHO Standard samples up to 250 mIU/mL and 800 mIU/mL were 1.05. The ARCHITECT AUSAB assay demonstrated acceptable WHO standard linearity.

Dilution Linearity

A study was conducted to evaluate the dilution linearity performance of the ARCHITECT AUSAB assay by preparing 8 serial dilutions of 8 positive specimen pools. The dilutions were prepared with a negative specimen pool.

Each dilution series yielded a correlation coefficient of ≥ 0.90 . The ARCHITECT AUSAB assay demonstrated acceptable dilution linearity.

Calibration Curve Storage

A study was conducted to evaluate the acceptability of an ARCHITECT AUSAB calibration curve stored on the ARCHITECT *i* System for a minimum of 30 days. Testing was performed using three ARCHITECT AUSAB reagent lots, three calibrator lots, and one control lot on two instruments. Each reagent lot was matched with a different calibrator lot. A single calibration per reagent lot was performed on each instrument and the calibration curve generated was stored on each instrument for the duration of the study. The ARCHITECT AUSAB Negative Control and Positive Control were assayed in replicates of two, 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 least 31 days after calibration.

The data support the storage of an ARCHITECT AUSAB calibration curve on the ARCHITECT *i* System for a minimum of 30 days.

Neonate Serum

A study was conducted to determine performance characteristics of neonatal samples when tested using the ARCHITECT AUSAB assay. Twenty-one neonate serum (cord blood) specimens were tested using the ARCHITECT AUSAB assay and three comparator anti-HBs assays. The results for each of the specimens were compared to the consensus result. Specimen results that were discordant between the assays utilized supplemental testing results.

One discordant specimen, 5 concordant reactive specimens, and 15 concordant nonreactive specimens were observed.

Verification of Dilution

A study was conducted to evaluate the performance of specimens diluted by the ARCHITECT *i* system versus specimens diluted manually. Positive specimens manually diluted 1:100 with negative serum, auto diluted 1:15 with on board ARCHITECT Wash Buffer, and manually diluted 1:100 with ARCHITECT Multi-Assay Manual Diluent were tested.

The mean % recovery of the manual dilutions with negative serum versus the auto dilutions was 115.17%. The mean % recovery of the manual dilutions with negative serum versus the manual dilutions with manual diluent was 99.07%. The ARCHITECT AUSAB demonstrated acceptable auto and manual dilution performance.

Limit of Blank, Limit of Detection, and Limit of Quantitation

A study was conducted to evaluate the Limit of Blank (LoB), Limit of Detection (LoD), and the Limit of Quantitation (LoQ) of the ARCHITECT AUSAB assay based on guidance from the CLSI document EP17-A. Testing was performed using three ARCHITECT AUSAB reagent lots, one calibrator lot, and one control lot on four instruments. Samples were prepared at concentrations ranging from 0.0 mIU/mL to 3.5 mIU/mL. Five runs with all reagent lot/instrument combinations were performed across a minimum of two days. For each run, one replicate of each sample was tested from each of two sample cups for a total of six replicates per sample.

The ARCHITECT AUSAB assay demonstrated a LoB of 0.82 mIU/mL, a LoD of 1.21 mIU/mL, and a LoQ of 3.00 mIU/mL.

High Dose Hook Effect

A study was conducted to characterize the performance of the ARCHITECT AUSAB assay when used to test specimens containing high levels of anti-HBs that have the potential to cause a high dose hook effect. Three unique stocks of recalcified anti-HBs positive human plasma with an ARCHITECT AUSAB concentration > 100,000 mIU/mL were each serially diluted with recalcified anti-HBs negative human plasma and tested on the ARCHITECT *i* System.

The data demonstrate that the ARCHITECT AUSAB assay is not susceptible to interference from specimens with high levels of anti-HBs.

ARCHITECT AUSAB Microbial Challenge Characterization

A Microbial Challenge Characterization (MCC) evaluation was performed according to USP requirements for Antimicrobial Effectiveness testing for the ARCHITECT AUSAB 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.

Reagent, Calibrator, and Control Developmental Stability

The developmental stability is an on-going study to establish the stability (shelf-life integrity) of the ARCHITECT AUSAB 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 stability study.

Stability testing is performed on three lots of 100-test kit reagents, three lots of 500-test kit reagents, three lots of calibrators, and three lots of controls.

The developmental stability is scheduled to continue for a maximum of 15 months (with a minimum of 6 months). Six months of stability data has been obtained for the reagents, calibrators, and controls, which supports 6 months of expiration dating.

Reagent Transport Stability

A study was conducted to support the stability of the ARCHITECT AUSAB Reagents following simulated transport stress conditions. One 100-test kit lot and one 500-test kit lot of the ARCHITECT AUSAB Reagents were tested after being subjected to simulated transport stress.

The data support the stability of the ARCHITECT AUSAB Reagents following transport at ambient temperatures.

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Calibrator and Control Transport Stability

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

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

X. SUMMARY OF CLINICAL STUDIES

A multi-center study was conducted to evaluate the efficacy of the ARCHITECT AUSAB assay for the quantitative detection of anti-HBs in human adult and pediatric serum and plasma and neonatal serum as measured by precision and method comparison.

System Reproducibility

A study was conducted to validate the precision performance of the ARCHITECT AUSAB assay based on guidance from the CLSI document EP15-A2. Three lots of ARCHITECT AUSAB Reagents, Calibrators, and Controls were tested per site. The ARCHITECT AUSAB Negative Control and Positive Control, and a high negative panel member (Panel 1, targeted to 8.00 mIU/mL) and low positive panel member (Panel 2, targeted to 12.00 mIU/mL) were tested using two replicates of each of two aliquots at two separate times per day for five days. The data are summarized in Table 4.

Table 4
ARCHITECT AUSAB
System Reproducibility (5-Day Precision Study)

Sample	n	Grand Mean (mIU/mL)	Within-Run		Within-Day		Within-Laboratory Precision (Total)		Precision with Additional Component of Between-Site		Precision with Additional Component of Between-Lot		Precision with Additional Components of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative Control	360	0.09	0.108	NA	0.110	NA	0.123	NA	0.136	NA	0.162	NA	0.168	NA
Positive Control	360	14.78	0.502	3.4	0.542	3.7	0.739	5.0	0.995	6.7	0.878	5.9	1.015	6.9
High Negative Panel	360	7.20	0.334	4.6	0.370	5.1	0.434	6.0	0.814	11.3	0.570	7.9	0.846	11.7
Low Positive Panel	360	10.84	0.453	4.2	0.497	4.6	0.602	5.6	1.066	9.8	0.826	7.6	1.136	10.5

NA = not applicable

Method Comparison

Clinical Performance

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

Of the 2,389 specimens tested and analyzed in the ARCHITECT AUSAB clinical study, 1,314 specimens were from individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, disease state, or known exposure event; 704 specimens were from individuals exhibiting signs and symptoms of a hepatitis infection; 211 specimens were from vaccine recipients; 40 matched pre- and post-vaccination specimens were from 20 hepatitis B vaccine recipients; and 120 surplus specimens were from a pediatric population.

The 2,389 specimens were collected from specimen collection sites or were purchased from specimen vendors. Of the 2,389 specimens, 2,018 were from the

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increased risk and signs and symptoms populations. The number and percent of specimens obtained from each specimen collection site/specimen vendor for the increased risk and signs and symptoms populations are listed in Table 5 below.

Table 5
Number and Percent of Specimens by Specimen Collection Sites/Specimen Vendors
for Increased Risk and Signs and Symptoms Populations

Collection Site/Vendor	Site/Location	Group (n)	Total (n)	Percent (%)
Collection Site				
Galveston, TX	1	794	2018	39.35
Dallas, TX	2	117	2018	5.80
Miami, FL	3	89	2018	4.41
St. Petersburg, FL	4	85	2018	4.21
Chicago, IL	5	166	2018	8.23
Denver, CO	6	123	2018	6.10
Collection Vendor				
Vendor 1: High Point, NC	1	185	2018	9.17
Vendor 1: Colton, CA	2	118	2018	5.85
Vendor 1: Plymouth, MA	3	341	2018	16.90

A demographic summary of the increased risk and signs and symptoms populations by race/ethnic group is provided in Table 6 below.

Table 6
Demographic Summary of Increased Risk and Signs and Symptoms Populations
by Race/Ethnic Group

Race/Ethnic Group	Group (n)	Total (n)	Percent (%)
African American	577	2018	28.59
American Indian/Alaska Native	9	2018	0.45
Asian	40	2018	1.98
Caucasian	1067	2018	52.87
Hispanic	295	2018	14.62
Other	30	2018	1.49

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Of the 2,018 increased risk and signs and symptoms subjects, 1,061 (52.58%) were female and 957 (47.42%) were male. The age was not reported for three subjects. Of the remaining 2,015 subjects, the mean age was 41 years (age range: 18 to 83 years).

Each specimen was tested using the ARCHITECT AUSAB assay at one of three clinical testing sites. Each of these specimens was also tested with a comparator anti-HBs assay method at ICON Laboratories. Specimens from the increased risk subgroup, and the signs and symptoms subgroup were also tested with FDA approved assays for HBsAg/HBsAg Confirmatory (where warranted), anti-HBc, and anti-HBc IgM to determine HBV classification. Post vaccine recipient specimens were also tested with an FDA approved anti-HBc assay. During the clinical study, all comparator and HBV classification testing was performed following manufacturers' instructions.

Testing was performed to determine the agreement of the investigational ARCHITECT AUSAB assay versus the comparator Anti-HBs assay. HBV Classification was determined based on the pattern of positive and negative results of four HBV serological markers: HBsAg, anti-HBc IgM, Total anti-HBc and anti-HBs. Nineteen unique reference marker patterns are represented. The classification being used is a modification of the National Centers of Infectious Diseases (CDC) interpretation of Viral Hepatitis B Panel testing.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Results by Specimen Classification

Following testing by a comparator anti-HBs assay and the reference HBV assays, as necessary, HBV classification was determined for the 2,018 specimens from the increased risk and signs and symptoms subgroups. HBV classification was based on the reference marker patterns presented in Table 7 below.

**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
-	+	+	-	Recovering Acute/Undetectable HBsAg
-	+	-	-	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

I = indeterminate

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

Comparison of Results

The ARCHITECT AUSAB assay results were compared to results from a comparator anti-HBs assay for each HBV classification for the increased risk and signs and symptoms subgroups. The comparison of ARCHITECT AUSAB results by HBV classification is presented in Table 8.

Table 8
ARCHITECT AUSAB Results versus Comparator Anti-HBs Assay Results
Comparison of Results for Increased Risk and Signs and Symptoms Subgroups
by HBV Classification

HBV Classification	Comparator anti-HBs Interpretation																		Total	
	Positive						Indeterminate						Negative							
	ARCHITECT AUSAB Interpretation						ARCHITECT AUSAB Interpretation						ARCHITECT AUSAB Interpretation							
	Reactive		Grayzone		Nonreactive		Reactive		Grayzone		Nonreactive		Reactive		Grayzone		Nonreactive			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
Early Acute	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.10	2	0.10
Acute	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	5	0.25	5	0.25
Late Acute/Recovering	0	0.00	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.05
Early Recovery	0	0.00	0	0.00	0	0.00	2	0.10	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	3	0.15
Recovering Acute	4	0.20	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	4	0.20
Chronic	3	0.15	0	0.00	0	0.00	2	0.10	0	0.00	2	0.10	0	0.00	0	0.00	35	1.73	42	2.08
Immune Due to Natural Infection	192	9.51	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	193	9.56
Distantly Immune/ Anti-HBs Unknown	0	0.00	0	0.00	0	0.00	21	1.04	6	0.30	4	0.20	0	0.00	0	0.00	0	0.00	31	1.54
Distantly Immune/ Anti-HBs Not Detected	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	13	0.64	11	0.55	83	4.11	107	5.30
Immune Due to HBV Vaccination	500	24.78	7	0.35	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	508	25.17
Unknown	0	0.00	0	0.00	0	0.00	34	1.68	17	0.84	15	0.74	0	0.00	0	0.00	0	0.00	66	3.27
Susceptible	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	12	0.59	4	0.20	1040	51.54	1056	52.33
<i>Total</i>	<i>699</i>	<i>34.64</i>	<i>8</i>	<i>0.40</i>	<i>2</i>	<i>0.10</i>	<i>59</i>	<i>2.92</i>	<i>23</i>	<i>1.14</i>	<i>22</i>	<i>1.09</i>	<i>25</i>	<i>1.24</i>	<i>15</i>	<i>0.74</i>	<i>1165</i>	<i>57.73</i>	<i>2018</i>	<i>100.00</i>

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Percent Agreement

The negative percent agreement and positive percent agreement between the ARCHITECT AUSAB assay result and a comparator anti-HBs assay result, and their corresponding 95% confidence intervals were calculated for the increased risk and signs and symptoms subgroups. The negative percent agreement for the increased risk and signs and symptoms subgroups combined was 96.68% (1,165/1,205) with a 95% confidence interval of 95.51% to 97.62%. The positive percent agreement for the increased risk and signs and symptoms subgroups combined was 98.59% (699/709) with a 95% confidence interval of 97.42% to 99.32%.

The negative percent agreement and positive percent agreement results for the increased risk and signs and symptoms subgroups by HBV classification are presented in Table 9.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table 9
ARCHITECT AUSAB Results versus Comparator Anti-HBs Assay Results
Percent Agreement
for Increased Risk and Signs and Symptoms Subgroups
by HBV Classification

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Early Acute	NA (0/0)	NA	100.00 (2/2)	15.81-100.00
Acute	NA (0/0)	NA	100.00 (5/5)	47.82-100.00
Late Acute/Recovering	0.00 (0/1)	0.00-97.50	NA (0/0)	NA
Early Recovery	NA (0/0)	NA	NA (0/0)	NA
Recovering Acute	100.00 (4/4)	39.76-100.00	NA (0/0)	NA
Chronic	100.00 (3/3)	29.24-100.00	100.00 (35/35)	90.00-100.00
Immune Due to Natural Infection	99.48 (192/193)	97.15-99.99	NA (0/0)	NA
Distantly Immune/Anti-HBs Unknown	NA (0/0)	NA	NA (0/0)	NA
Distantly Immune/Anti-HBs Not Detected	NA (0/0)	NA	77.57 (83/107)	68.49-85.07
Immune Due to HBV Vaccination	98.43 (500/508)	96.92-99.32	NA (0/0)	NA
Unknown	NA (0/0)	NA	NA (0/0)	NA
Susceptible	NA (0/0)	NA	98.48 (1040/1056)	97.55-99.13
TOTAL	98.59 (699/709)	97.42-99.32	96.68 (1165/1205)	95.51-97.62

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

The negative percent agreement for the vaccine recipient subgroup was 84.78% (39/46) with a 95% confidence interval of 71.13% to 93.66%. The positive percent agreement for the vaccine recipient subgroup was 100.00% (146/146) with a 95% confidence interval of 97.51% to 100.00%. This is presented in Table 10 below.

Table 10
ARCHITECT AUSAB Results versus Comparator Anti-HBs Assay Results
Percent Agreement for Vaccine Recipients Subgroup
n=211

ARCHITECT AUSAB Interpretation	Comparator Anti-HBs Interpretation		
	Positive	Indeterminate	Negative
Reactive	146 (A)	9 (B)	4 (C)
Grayzone	0 (D)	5 (E)	3 (F)
Nonreactive	0 (G)	5 (H)	39 (I)

Negative Percent Agreement = $(I / (C+F+I)) \times 100 = 84.78 \%$

Positive Percent Agreement = $(A / (A+D+G)) \times 100 = 100.00\%$

95% Confidence Interval for Negative Percent Agreement = (71.13 % , 93.66 %)

95% Confidence Interval for Positive Percent Agreement = (97.51 % , 100.00%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

The negative percent agreement for the pre- and post- vaccine recipients subgroup combined was 100.00% (22/22) with a 95% confidence interval of 84.56% to 100.00%. The positive percent agreement for the pre- and post- vaccine recipients subgroup combined was 100.00% (18/18) with a 95% confidence interval of 81.47% to 100.00%. This is presented in Table 11 below.

Table 11
ARCHITECT AUSAB Results versus Comparator Anti-HBs Assay Results
Percent Agreement for Pre- and Post- Vaccine Recipients Subgroup

Vaccination Status	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Pre-Vaccination	NA (0/0)	NA	100.00 (20/20)	83.16-100.00
Post-Vaccination	100.00 (18/18)	81.47-100.00	100.00 (2/2)	15.81-100.00
Combined	100.00 (18/18)	81.47-100.00	100.00 (22/22)	84.56-100.00

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

The negative percent agreement for the pediatric subgroup was: 92.68% (38/41) with a 95% confidence interval of 80.08% to 98.46%. The positive percent agreement for the pediatric subgroup was 93.44% (57/61) with a 95% confidence interval of 84.05% to 98.18%. This is presented in Table 12 below.

Table 12
ARCHITECT AUSAB Results versus Comparator Anti-HBs Assay Results
Percent Agreement for Pediatric Subgroup
n=120

ARCHITECT AUSAB Interpretation	Comparator Anti-HBs Interpretation		
	Positive	Indeterminate	Negative
Reactive	57 (A)	8 (B)	1 (C)
Grayzone	3 (D)	4 (E)	2 (F)
Nonreactive	1 (G)	6 (H)	38 (I)

Negative Percent Agreement = $(I / (C+F+I)) \times 100 = 92.68 \%$

Positive Percent Agreement = $(A / (A+D+G)) \times 100 = 93.44\%$

95% Confidence Interval for Negative Percent Agreement = (80.08 % , 98.46 %)

95% Confidence Interval for Positive Percent Agreement = (84.05 % , 98.18%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Expected Results (Increased Risk Population and Pediatric Populations)

In addition to precision and method comparison, demographic summaries of the expected results from the increased risk and pediatric populations are provided.

Increased Risk Population

Of the 2,389 specimens analyzed in the ARCHITECT AUSAB clinical investigation, a total of 1,314 specimens were from the individuals with 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 1,314 increased risk specimens were collected from specimen collection sites or were purchased from specimen vendors. The number and percent of specimens obtained from each collection site/vendor are listed in Table 13 below.

**Table 13
Number and Percent of Specimens by Specimen Collection Sites/Specimen Vendors
for Increased Risk Population**

Collection Site/Vendor	Site/Location	Group (n)	Total (n)	Percent (%)
Collection Site				
Galveston, TX	1	743	1314	56.54
Dallas, TX	2	59	1314	4.49
Miami, FL	3	52	1314	3.96
St. Petersburg, FL	4	56	1314	4.26
Chicago, IL	5	8	1314	0.61
Denver, CO	6	36	1314	2.74
Collection Vendor				
Vendor 1: High Point, NC	1	185	1314	14.08
Vendor 1: Colton, CA	2	76	1314	5.78
Vendor 1: Plymouth, MA	3	99	1314	7.53

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

A demographic summary of the increased risk specimen population by race/ethnic group is provided in Table 14 below.

Table 14
Demographic Summary of Increased Risk Population
by Race/Ethnic Group

Race/Ethnic Group	Group (n)	Total (n)	Percent (%)
African American	477	1314	36.30
American Indian/Alaska Native	6	1314	0.46
Asian	19	1314	1.45
Caucasian	625	1314	47.56
Hispanic	167	1314	12.71
Other	20	1314	1.52

Of the 1,314 subjects, 816 (62.10%) were female and 498 (37.90%) were male. The age was not reported for three subjects. Of the remaining 1,311 subjects, the mean age was 40 years (age range: 18 to 75 years).

The ARCHITECT AUSAB assay was reactive in 535 (40.72%) of the individuals in the increased risk population. The number and percent of ARCHITECT AUSAB reactive results observed at each collection location are presented in Table 15.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table 15
ARCHITECT AUSAB Percent Reactive Results by Collection Location for
the Increased Risk Population

Collection Site/Vendor	Site/Location	Reactive (n)	Total (n)	Percent Reactive (%)
Collection Site				
Galveston, TX	1	276	743	37.15
Dallas, TX	2	16	59	27.12
Miami, FL	3	33	52	63.46
St. Petersburg, FL	4	16	56	28.57
Chicago, IL	5	3	8	37.50
Denver, CO	6	24	36	66.67
Collection Vendor				
High Point, NC	1	103	185	55.68
Colton, CA	2	35	76	46.05
Plymouth, MA	3	29	99	29.29
	Total	535	1314	40.72

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

The distribution of ARCHITECT AUSAB reactive, grayzone, and nonreactive results by age range and gender is presented in Table 16 below.

Table 16
ARCHITECT AUSAB Results by Age Range and Gender
for Individuals at Increased Risk of HBV Infection

Age Group (Years) ^a	Gender	Reactive N (%)	Grayzone N (%)	Nonreactive N (%)	Total
10 to 19	Female	9 (64.29%)	1 (7.14%)	4 (28.57%)	14
	Male	7 (63.64%)	0 (0.00%)	4 (36.36%)	11
20 to 29	Female	82 (44.57%)	2 (1.09%)	100 (54.35%)	184
	Male	35 (36.08%)	1 (1.03%)	61 (62.89%)	97
30 to 39	Female	78 (42.39%)	1 (0.54%)	105 (57.07%)	184
	Male	33 (30.84%)	0 (0.00%)	74 (69.16%)	107
40 to 49	Female	106 (42.23%)	5 (1.99%)	140 (55.78%)	251
	Male	55 (34.59%)	1 (0.63%)	103 (64.78%)	159
50 to 59	Female	68 (49.64%)	3 (2.19%)	66 (48.18%)	137
	Male	30 (27.52%)	4 (3.67%)	75 (68.81%)	109
60 to 69	Female	23 (65.71%)	1 (2.86%)	11 (31.43%)	35
	Male	3 (25.00%)	0 (0.00%)	9 (75.00%)	12
70 to 79	Female	3 (37.50%)	1 (12.50%)	4 (50.00%)	8
	Male	2 (66.67%)	0 (0.00%)	1 (33.33%)	3
Total		534 (40.73%)	20 (1.53%)	757 (57.74%)	1311

^a Age was not reported for three subjects.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Pediatric Population

Of the 2,389 specimens tested and analyzed in the ARCHITECT AUSAB clinical investigation, 120 specimens were from a pediatric population. Specimens were obtained from ProMedDx, LLC, which collected the specimens from a collection site located in Fall River, MA. The specimens were obtained from children ages greater than 1 month to 18 years.

The distribution of ARCHITECT AUSAB reactive, grayzone, and nonreactive results by age range and gender is presented in Table 17 below.

Table 17
ARCHITECT AUSAB Results by Age Range and Gender
for Pediatric Population

Age Group (Years) ^a	Gender	Reactive N (%)	Grayzone N (%)	Nonreactive N (%)	Total
Under 2	Female	8 (80.00%)	1 (10.00%)	1 (10.00%)	10
	Male	12 (85.71%)	0 (0.00%)	2 (14.29%)	14
2 to 12	Female	12 (54.55%)	2 (9.09%)	8 (36.36%)	22
	Male	8 (21.05%)	5 (13.16%)	25 (65.79%)	38
13 to 18	Female	18 (75.00%)	1 (4.17%)	5 (20.83%)	24
	Male	8 (66.67%)	0 (0.00%)	4 (33.33%)	12
Total		66 (55.00%)	9 (7.50%)	45 (37.50%)	120

^a Children with ages under 2 are greater than 1 month old.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multi-centered clinical studies were conducted in the US to evaluate the ARCHITECT AUSAB anti-HBs assay. A method comparison was performed with a commercially available licensed assay to detect anti-HBs antibodies in specimens from an intended use diagnostic population.

Hepatitis B virus classification using the prospective population showed 19 unique reference marker patterns. The overall positive percent agreement between the ARCHITECT AUSAB assay and the reference assay was 98.6% (699/709) in the high risk, signs and symptoms, and vaccinated populations. The overall negative percent agreement between the ARCHITECT AUSAB assay and the reference assay was 96.7% (1165/1205) in the same population.

In the HBV vaccinated individuals, the positive agreement was 100% (146/146) and the negative percent agreement was 84.8% (39/46) with the comparison method.

The ability of the ARCHITECT AUSAB assay to detect the anti-HBs antibodies was demonstrated in pediatric and neonatal specimen testing.

Precision and reproducibility of the ARCHITECT AUSAB 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) and neonatal serum in the ARCHITECT AUSAB assay.

The results from both the non-clinical and clinical studies indicate that the ARCHITECT AUSAB assay can be used safely and effectively for the qualitative *in vitro* determination of anti-HBs antibodies in human serum and plasma. The assay may be used with other HBV serological markers to define the clinical status of patients known to be infected with HBV.

RISK BENEFIT ANALYSIS

As a diagnostic test, the ARCHITECT AUSAB 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

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

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 ARCHITECT AUSAB 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 ARCHITECT AUSAB has been demonstrated for use in determining if antibodies to the HBs antigen of the hepatitis B virus are present in an individual's serum or plasma. A reasonable determination of effectiveness of the ARCHITECT AUSAB assay for aiding in the diagnosis of immunity and status of HBV infection 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 June 1, 2006.

The applicant's manufacturing facility was inspected on 5/8/06 (N. Chicago), 5/16/06 (Abbott Park), & 5/19/04 (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.