

Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name: Hepatitis B Surface Antigen
Hepatitis B Surface Antigen Confirmatory

Device Trade Name: ARCHITECT® HBsAg Reagent Kit
ARCHITECT® HBsAg Calibrators
ARCHITECT® HBsAg Controls
ARCHITECT® HBsAg Confirmatory Reagent Kit
ARCHITECT® HBsAg Confirmatory Manual Diluent

Name and Address of Applicant: Abbott Laboratories
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Premarket Approval Application (PMA) Number: P060007

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: September 07, 2006

II. INDICATIONS FOR USE

ARCHITECT HBsAg Reagent Kit

The ARCHITECT HBsAg assay is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of hepatitis B surface antigen (HBsAg) in human adult and pediatric serum and plasma (dipotassium EDTA). The assay may also be used to screen for HBV infection in pregnant females to identify neonates who are at risk of acquiring hepatitis B during the perinatal period. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with the hepatitis B virus (HBV) (state of infection or associated disease not determined) in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection.

ARCHITECT HBsAg Calibrators

The ARCHITECT HBsAg Calibrators are used for calibration of the ARCHITECT i System when the system is used for the qualitative detection of hepatitis B surface antigen (HBsAg) using the ARCHITECT HBsAg and HBsAg Confirmatory Reagent Kits. The performance of the ARCHITECT HBsAg Calibrators has not been established with any other HBsAg assays.

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ARCHITECT HBsAg Controls

The ARCHITECT HBsAg Controls are used for monitoring the performance of the ARCHITECT i System (reagents, calibrators, and instrument) when used for the qualitative detection of hepatitis B surface antigen (HBsAg) using the ARCHITECT HBsAg and HBsAg Confirmatory assays. The performance of the ARCHITECT HBsAg Controls has not been established with any other HBsAg assays.

ARCHITECT HBsAg Confirmatory Reagent Kit

The ARCHITECT HBsAg Confirmatory assay is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative confirmation of the presence of hepatitis B surface antigen (HBsAg) in human adult and pediatric serum and plasma (dipotassium EDTA) that have been found to be repeatedly reactive by ARCHITECT HBsAg. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide evidence of infection with the hepatitis B virus (HBV) (state of infection or associated disease not determined) in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection.

ARCHITECT HBsAg Confirmatory Manual Diluent

The ARCHITECT HBsAg Confirmatory Manual Diluent is used for manually diluting specimens for testing on the ARCHITECT i System using the ARCHITECT HBsAg Confirmatory Reagent Kit. The performance of the ARCHITECT HBsAg Confirmatory Manual Diluent has not been established with any other HBsAg assays.

III. CONTRAINDICATIONS: None known

IV. WARNINGS AND PRECAUTIONS: For in vitro diagnostic use only. Warnings and precautions for ARCHITECT HBsAg Reagent Kit, ARCHITECT HBsAg Calibrators, ARCHITECT HBsAg Controls, ARCHITECT HBsAg Confirmatory Reagent Kit, and ARCHITECT HBsAg Confirmatory Manual Diluent are stated in the respective product labeling.

V. DEVICE DESCRIPTION

Kit Configurations and Components

For detection of hepatitis B surface antigen, the ARCHITECT HBsAg Reagent Kit is comprised of the following:

- ARCHITECT HBsAg Microparticles: 1 or 4 Bottle(s) (6.6 mL/27.0 mL) anti-HBs (mouse, monoclonal, IgM, IgG) coated microparticles in MES buffer

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with protein additives (152 μ M bovine serum albumin, 10.0% bovine calf serum) and surfactant. Minimum concentration: 0.0675% solids. Preservatives: ProClin[®] 300 and ProClin 950.

- ARCHITECT HBsAg Conjugate: 1 or 4 Bottle(s) (5.9 mL/26.3 mL) anti-HBs (goat, IgG) acridinium-labeled conjugate in MES buffer with protein additives (30.3 μ M bovine serum albumin, 12.5% bovine calf serum, 2.0% human plasma) and surfactant. Minimum concentration: 0.25 μ g/mL. Preservative: ProClin 300. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.

For the confirmation of the presence of hepatitis B surface antigen, the ARCHITECT HBsAg Confirmatory Reagent Kit is comprised of the following four components:

- ARCHITECT HBsAg Confirmatory Microparticles: 1 Bottle (6.6 mL) anti-HBs (mouse, monoclonal, IgM, IgG) coated microparticles in MES buffer with protein additives (152 μ M bovine serum albumin, 10.0% bovine calf serum) and surfactant. Minimum concentration: 0.0675% solids. Preservatives: ProClin[®] 300 and ProClin 950.
- ARCHITECT HBsAg Confirmatory Conjugate: 1 Bottle (5.9 mL) anti-HBs (goat, IgG) acridinium-labeled conjugate in MES buffer with protein additives (30.3 μ M bovine serum albumin, 12.5% bovine calf serum, 2.0% human plasma) and surfactant. Minimum concentration: 0.25 μ g/mL. Preservative: ProClin 300. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.
- ARCHITECT HBsAg Confirmatory Pretreatment 1: 1 Bottle (2.4 mL) Pretreatment 1 contains recalcified human plasma and surfactant. Preservatives: sodium azide and ProClin 950. The human plasma is reactive for anti-HBs and nonreactive for HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.
- ARCHITECT HBsAg Confirmatory Pretreatment 2: 1 Bottle (2.4 mL) Pretreatment 2 contains recalcified human plasma and surfactant. Preservatives: antimicrobial agent, ProClin 300, and ProClin 950. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.

ARCHITECT HBsAg Calibrators contain:

- Calibrator 1 is phosphate buffer with protein (bovine albumin and human plasma) additives. Preservatives: antimicrobial agent, ProClin[®] 300, and ProClin 950. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.
- Calibrator 2 contains inactivated purified HBsAg (subtype *ad*) in phosphate buffer with protein (bovine albumin and human plasma) additives. Preservatives: antimicrobial agent, ProClin 300, and ProClin 950. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV. Calibrator 2 is reactive for HBsAg.

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ARCHITECT HBsAg Controls contain:

- The negative control is recalcified human plasma. Preservative: antimicrobial agent, ProClin[®] 300, and ProClin 950. The negative control is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.
- The positive control contains inactivated purified HBsAg (subtypes *adlay*) in phosphate buffer with protein additives (5% bovine albumin and 7.5% human plasma). The positive control is blue and contains Acid Blue No. 9 dye. Preservatives: antimicrobial agent, ProClin 300, and ProClin 950. The positive control is reactive for HBsAg. The human plasma is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.

The following component is required for the ARCHITECT HBsAg Confirmatory Reagent Kit:

- Manual Diluent contains recalcified human plasma. Preservatives: antimicrobial agent, ProClin[®] 300, and ProClin 950. The manual diluent is nonreactive for anti-HBs, HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV.

In addition, the following components are required:

- ARCHITECT *i* System is an analyzer designed to perform fully-automated immunoassay tests based on the use of CMIA detection technology.
- ARCHITECT *i* Pre-Trigger Solution contains 1.32% (w/v) hydrogen peroxide.
- ARCHITECT *i* Trigger Solution contains 0.35N sodium hydroxide.
- ARCHITECT *i* Wash Buffer contains phosphate buffered saline solution with preservative.

Assay Principle and Format:

ARCHITECT HBsAg

The ARCHITECT HBsAg assay is a two-step immunoassay for the qualitative detection of HBsAg in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample and anti-HBs coated paramagnetic microparticles are combined. HBsAg present in the sample binds to the anti-HBs coated microparticles. After washing, acridinium-labeled anti-HBs conjugate is added in the second step and combines with any HBsAg bound to the microparticles. 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 HBsAg in the sample and the RLUs detected by the ARCHITECT *i* System optics.

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The presence or absence of HBsAg in the sample is determined by comparing the chemiluminescent signal in the reaction to the cutoff signal determined from an active ARCHITECT HBsAg calibration curve. If the chemiluminescent signal of the sample is greater than or equal to the cutoff signal, the sample is considered reactive for HBsAg. If the chemiluminescent signal is less than the cutoff, the sample is considered negative for HBsAg.

ARCHITECT HBsAg Confirmatory

The ARCHITECT HBsAg Confirmatory assay is a two-step pretreatment immunoassay for the confirmation of the presence of HBsAg in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

Sample and Pretreatment 1 (Reagent 1) are combined in a reaction vessel (RV) and incubated. When HBsAg is present in the sample, it is neutralized by the HBs antibody in Pretreatment 1 (Reagent 1). An aliquot of the pretreated sample and anti-HBs coated paramagnetic microparticles are combined in another RV and incubated. Any non-neutralized HBsAg present in the sample binds to the anti-HBs coated microparticles. The neutralized HBsAg is blocked from binding to the anti-HBs coated microparticles. After washing, acridinium-labeled anti-HBs conjugate is added to the reaction mixture and incubated. 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 HBsAg in the sample and the RLU detected by the ARCHITECT *i* System optics.

This sequence is repeated for the sample and Pretreatment 2 (Reagent 2), except Pretreatment 2 (Reagent 2) does not neutralize HBsAg in the sample.

If the signal for the non-neutralized sample (incubated with Pretreatment 2 [Reagent 2]) result is greater than or equal to the cutoff ($S/CO \cdot 0.80$) and the RLU of the neutralized sample (incubated with Pretreatment 1 [Reagent 1]) is reduced by at least 50% compared to the non-neutralized sample, the sample is considered confirmed positive for HBsAg.

VI. ALTERNATE PRACTICES AND PROCEDURES

Determining the presence of HBsAg in individuals may be achieved by using a variety of commercially available, FDA licensed serological tests. Additionally, when test results are used in combination with a physician's assessment and supplemental clinical laboratory serological and biochemical testing, infection with HBV can be identified.

VII. MARKETING HISTORY

ARCHITECT HBsAg, List No. 1L80, and ARCHITECT HBsAg Confirmatory, List No. 1L81, have not been marketed in any other country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as indicated or human error in use of the device may lead to a false result. A false positive result using an HBsAg assay is not considered a patient or public health concern as a positive result in a clinical lab setting is usually followed up with supplemental testing. Either additional HBV marker testing is performed or an HBsAg positive result is confirmed by neutralization. An exception to this is using HBsAg tests to screen pregnant women for the presence of HBsAg. This testing helps to determine if a neonate is at high risk of acquiring HBV during the prenatal period. Pregnant women are tested during an early prenatal visit. If they are HBsAg nonreactive during this testing, and at high risk for HBV infection, they are re-tested during the third trimester. If the result is positive, it is recommended that hepatitis B immune globulin (HBIG) and vaccine be provided to the newborn within 12 hours of birth. If an assay is false positive and the newborn receives HBIG, the newborn would be exposed to the risks of receiving a human source product.

The risks of a false negative result in a diagnostic setting are highest when testing pregnant women because HBsAg may be the only marker used. If the result is negative then the child is vaccinated within 2 months of birth. If the result is incorrect (false negative), then the neonate is at a higher risk of acute and chronic HBV infection, since HBIG and vaccine would not be provided within 12 hours of birth.

In addition, from time to time false negative results due to gene mutation have been reported for the HBsAg assays produced by a number of different manufacturers. Because of the complexity of the mutations that can occur, no manufacturer can guarantee to detect all infectious donors and patients.

A false positive result using an HBsAg confirmatory neutralization procedure is not considered a patient or public health concern because in order for a false positive to occur, the control sample (non-neutralized result) and the percent neutralization (in the neutralized tube) would both have to be incorrect for a reported false positive result. If this situation were to occur, the implications would be the same as described for false positive results for HBsAg assays.

A false negative result using an HBsAg confirmatory neutralization procedure could occur if the neutralized sample were incorrect either due to a falsely increased signal with the neutralized sample, or due to some other malfunction, laboratory or technician error when assayed. A falsely increased signal could be

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interpreted as a failure to neutralize. If this situation were to occur, the implications would be the same as described for false negative results for HBsAg.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical studies were conducted at Abbott Laboratories to evaluate the performance characteristics of the ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory assays.

Analytical sensitivity

The sensitivity of the ARCHITECT HBsAg assay is designed to be ≤ 0.2 ng/mL. The sensitivity of the ARCHITECT HBsAg assay was evaluated using a 17-member sensitivity panel consisting of eight HBsAg subtype ad members, eight HBsAg subtype ay members, and a nonreactive blank. The panel members were tested in replicates of five using three reagent lots across two instruments. The HBsAg level at the assay's cutoff was estimated from a linear regression analysis. The data are summarized in the following table.

Analytical Sensitivity (ng/mL) of ARCHITECT HBsAg

Sample	Mean Sensitivity (ng/mL)	Mean Sensitivity (Approximate IU/mL)	Upper One-sided 95% Confidence Limit (ng/mL)
HBsAg Sensitivity Panel (subtype ad)	0.15	0.03	0.18
HBsAg Sensitivity Panel (subtype ay)	0.13	0.02	0.15

In addition, the sensitivity of the ARCHITECT HBsAg assay was evaluated using serial dilutions of the WHO 1st International Standard. The dilutions ranged from 0.0195 to 2.5 IU/mL. Recalcified nonreactive human plasma was used as the diluent and represented the 0 IU/mL sample. The dilutions were tested in replicates of five using three reagent lots across two instruments. The HBsAg level at the assay's cutoff was estimated from a linear regression analysis. The data are summarized in the following table.

Analytical Sensitivity (IU/mL) of ARCHITECT HBsAg

Sample	Mean Sensitivity (Approximate IU/mL)	Upper One-sided 95% Confidence Limit (IU/mL)
Dilutions of WHO HBsAg Standard	0.02	0.03

The ability to confirm a low positive (0.249 ng/mL) panel member was verified for the ARCHITECT HBsAg Confirmatory assay. Abbott HBsAg Sensitivity Panel Member 9108L0002 (ayF) with a concentration of 0.249 ng/mL was tested in replicates of six with each of two reagent lots on two instruments (one *i* 2000 and one *i* 2000SR) for a total of four reagent lot/instrument combinations. Each panel replicate was confirmed positive using the ARCHITECT HBsAg Confirmatory assay.

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Analytical Specificity

The ARCHITECT HBsAg assay was evaluated for potential cross-reactivity for specimens from individuals with medical conditions unrelated to HBV infection. A total of 161 specimens from 17 different categories were tested. The first 13 of 17 categories were antibody, antigen, or PCR positive. One hundred fifty-nine specimens were nonreactive and two specimens were reactive by ARCHITECT HBsAg. One of the two reactive specimens was confirmed positive for HBsAg by ARCHITECT HBsAg Confirmatory. The data are summarized by final interpretation in the following table.

Category	n	Comparator HBsAg Assay					
		Negative			Positive		
		ARCHITECT			ARCHITECT		
		NR ^a	RR ^a	POS ^a	NR ^a	RR ^a	POS ^a
Cytomegalovirus (Anti-CMV Positive)	9	9	0	0	0	0	0
Epstein-Barr Virus (Anti-EBV Positive)	10	10	0	0	0	0	0
Hepatitis A Virus (Anti-HAV Positive)	10	10	0 ^a	0	0	0	0
Hepatitis C Virus (Anti-HCV Positive)	10	9	0	1	0	0	0
Herpes Simplex Virus (HSV) IgG	10	10	0	0	0	0	0
Human Anti-Mouse Antibodies (HAMA)	10	10	0	0	0	0	0
Human Immunodeficiency Virus (Anti-HIV-1 Positive)	10	9	1	0	0	0	0
Parvovirus B19 Infection	9	9	0	0	0	0	0
Rheumatoid Factor Positive	10	10	0	0	0	0	0
Rubella	10	10	0	0	0	0	0
Syphilis	10	10	0	0	0	0	0
Systemic Lupus Erythematosus (SLE)	10	10	0	0	0	0	0
Toxoplasmosis IgG Positive	8	8	0	0	0	0	0
Influenza Vaccine Recipient	10	10	0	0	0	0	0
Non-Viral Liver Disease: Alcoholic Liver Disease	10	10	0	0	0	0	0
Non-Viral Liver Disease: Hepatocellular Carcinoma	5	5	0	0	0	0	0
Non-Viral Liver Disease: Obstructive Jaundice	10	10	0	0	0	0	0
Total	161	159	1	1	0	0	0

^a NR = Nonreactive, RR = Repeatedly Reactive Not Confirmed, POS = Positive

Interference

At the concentrations listed below, the ARCHITECT HBsAg assay showed interference from bilirubin, total protein, hemoglobin, and triglycerides for high negative samples (targeted to an S/CO of 0.80) of ≤ 0.11 S/CO and low positive samples (targeted to an S/CO of 1.20) of $\leq 10\%$.

Interferent	Interferent Concentration
Bilirubin	≤ 20 mg/dL
Total Protein	≤ 12 g/dL
Hemoglobin	≤ 400 mg/dL
Triglycerides	≤ 1100 mg/dL

In addition, high negative (0.80 S/CO target) and low positive (1.20 S/CO target) serum samples were supplemented with viral or parasitic antigens (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, rubella, varicella-zoster virus, and *Toxoplasma gondii*) and with bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*). The viral or parasitic antigens were spiked to 1 ng/mL and 1 μ g/mL. The bacteria were supplemented to 10^{5-6} , 10^{3-4} , and 10^{2-3} colony-forming units per mL. All samples were tested in replicates of 22. All replicates of the high negative samples (0.80 S/CO target) remained nonreactive and all replicates of the low positive samples (1.20 S/CO target) remained reactive.

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Tube Type Matrix Comparison

The following tube types are acceptable for use with the ARCHITECT HBsAg assay:

Glass: serum and serum separator

Plastic: serum, serum separator, dipotassium EDTA

On average, the tube types listed in the table below showed less than a 10% difference when compared to the control tube type (glass serum) for high negative samples (S/CO range: 0.60 to 0.99) and low positive samples (S/CO range: 1.00 to 1.40). The ARCHITECT HBsAg assay showed the following distribution of percent differences when compared to the glass serum tube type.

Tube Type	Distribution of the Differences		
	< 10%	≥ 10% to ≤ 20%	> 20%
Glass Serum Separator	82.2% (37/45)	13.3% (6/45)	4.4% (2/45)
Plastic Serum	87.0% (40/46)	10.9% (5/46)	2.2% (1/46)
Plastic Serum Separator	82.6% (38/46)	10.9% (5/46)	6.5% (3/46)
Plastic Dipotassium EDTA	89.1% (41/46)	8.7% (4/46)	2.2% (1/46)

Seroconversion Panels

To determine the seroconversion sensitivity, 15 HBV seroconversion panels obtained from commercial vendors were tested using the ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory assays. HBsAg was first detected by the ARCHITECT HBsAg assay and confirmed by the ARCHITECT HBsAg Confirmatory assay 5 to 35 days earlier than it was first detected by the comparator assays in nine seroconversion panel sets and coincident with the first day detected by the comparator assays in six seroconversion panel sets. The data are summarized in the following table.

Panel ID	Days to HBsAg Reactive Result from Initial Draw Date		Difference in Days to HBsAg Reactive Result (Comparator – ARCHITECT)
	Comparator HBsAg Assay	ARCHITECT HBsAg Assay	
PHM903	17	10	7
PHM909	14	9	5
PHM915	54	19	35
PHM916	69	62	7
PHM917	43	43	0
PHM920	26	26	0
PHM923	21	15	6
6271	12	7	5
6272	115	97	18
6273	25	25	0
6274	167	156	9
6275	22	22	0
0994/3457	14	4	10
26982/14399	0	0	0
43527/3453	0	0	0

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HBsAg Mutant Detection

The hepatitis B virus, unlike other DNA viruses, replicates through reverse transcription. The reverse transcription process lacks proofreading capability; therefore, HBV is subject to a mutation rate 10 times higher than the mutation rate of other DNA viruses. Some of these mutations may cause changes in the antigenic structure of HBsAg, resulting in epitopes that are no longer recognized by anti-HBs. HBsAg mutants have been reported in a wide range of patient populations, including blood donors, vaccine recipients, renal dialysis patients, orthotopic liver transplant recipients, infants born to HBsAg-positive mothers, and patients undergoing nucleoside analog treatment for HBV. HBsAg mutations may result in a less favorable outcome in some patients and false negative results in some HBsAg assays.

The immunodominant “a” determinant portion of the HBsAg protein spans the region bound by amino acids 100–158. This region includes at least two antigenic loops; the second loop (amino acids 139–147) binds a large proportion of anti-HBs in immune serum. Immunological pressure by anti-HBs, whether induced by natural infection, vaccination, or therapeutic administration, may be a method by which HBsAg mutants are selected. The most frequent and stable mutation reported is the glycine to arginine mutation at amino acid position 145 (Gly 145 to Arg) in the second loop of the “a” determinant.

A panel of 26 recombinant HBsAg mutant samples were prepared to a concentration of approximately 2 ng/mL and tested by ARCHITECT HBsAg. One of the 24 “a” determinant samples was nonreactive by ARCHITECT HBsAg. All of the remaining 25 samples were repeatedly reactive by the ARCHITECT HBsAg assay and confirmed positive by the ARCHITECT HBsAg Confirmatory assay. The data are summarized in the following table.

Mutant	ARCHITECT HBsAg Results	ARCHITECT HBsAg Confirmatory Final Interpretation	Mutant	ARCHITECT HBsAg Results	ARCHITECT HBsAg Confirmatory Final Interpretation
Asn 40 to Ser	Repeatedly Reactive	Positive	Pro 142 to Ser	Repeatedly Reactive	Positive
Pro 111 to Thr	Repeatedly Reactive	Positive	Asp 144 to Ala	Repeatedly Reactive	Positive
Thr Thr 115, 116 to Ile Ile	Repeatedly Reactive	Positive	Gly 145 to Ala	Repeatedly Reactive	Positive
Thr 118 to Ser	Repeatedly Reactive	Positive	Gly 145 to Arg	Repeatedly Reactive	Positive
Thr 123 to Ala	Nonreactive	NA	Gly 145 to Lys	Repeatedly Reactive	Positive
Thr 123 to Ile	Repeatedly Reactive	Positive	Thr 126 to Ser + Gly 145 to Arg	Repeatedly Reactive	Positive
Asn 40 to Ser + Thr 123 to Ile	Repeatedly Reactive	Positive	Pro 142 to Leu + Gly 145 to Arg	Repeatedly Reactive	Positive
Gln 129 to His	Repeatedly Reactive	Positive	Pro 142 to Ser + Gly 145 to Arg	Repeatedly Reactive	Positive
Thr 131 to Ile	Repeatedly Reactive	Positive	Asp 144 to Ala + Gly 145 to Arg	Repeatedly Reactive	Positive
Met 133 to Leu	Repeatedly Reactive	Positive	Thr 148 to His	Repeatedly Reactive	Positive
Phe 134 to Ala	Repeatedly Reactive	Positive	Ser 154 to Trp	Repeatedly Reactive	Positive
Pro 135 to Ser	Repeatedly Reactive	Positive	Ser 155 to Tyr	Repeatedly Reactive	Positive
Pro 142 to Leu	Repeatedly Reactive	Positive	Met Met Met 197, 198, 199 to Ser Ser Ser	Repeatedly Reactive	Positive

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HBV Genotype Detection

The ARCHITECT HBsAg assay is designed to detect HBV genotypes A through G. A study was performed to evaluate the ability of the ARCHITECT HBsAg assay to detect different HBV genotypes by testing a commercially-available genotype panel containing genotypes A through G. All genotypes were detected by ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory. The data are summarized in the following table.

Genotype	Number of Genotypes Tested	Number of ARCHITECT HBsAg Reactive/ ARCHITECT HBsAg Confirmatory Positive
A	5	5
B	1	1
C	7	7
D	3	3
E	6	5 ^a
F	11	11
G	1	1
Total	34	33

^a One genotype E sample was nonreactive by ARCHITECT HBsAg and an FDA-licensed HBsAg assay.

Within Laboratory Precision

A 20-day precision study was performed for the ARCHITECT HBsAg assay that was conducted at Abbott Laboratories using three ARCHITECT HBsAg assay reagent lots, three calibrator lots, one control lot, and two instruments. Two controls and two panels were assayed in replicates of two at two separate times of day for 20 different days. The data are summarized in the following table.

Inst.	Sample	n	Grand Mean S/CO	Within-Run		Within Day		Within Laboratory Precision (Total)	
				SD	%CV	SD	%CV	SD	%CV
1	Negative Control	240	0.52	0.029	NA	0.031	NA	0.035	NA
	Positive Control	240	4.00	0.078	2.0	0.099	2.5	0.147	3.7
	High Negative Panel	240	0.74	0.036	5.0	0.036	5.0	0.046	6.3
	Low Positive Panel	240	1.15	0.042	3.7	0.043	3.8	0.059	5.1
2	Negative Control	240	0.56	0.038	NA	0.038	NA	0.039	NA
	Positive Control	240	4.02	0.159	4.0	0.176	4.4	0.206	5.1
	High Negative Panel	240	0.83	0.073	8.9	0.076	9.2	0.078	9.5
	Low Positive Panel	240	1.24	0.074	6.0	0.076	6.2	0.082	6.6

NA = not applicable

System Reproducibility

A five-day precision study was performed for the ARCHITECT HBsAg assay that was conducted at three clinical testing sites using three ARCHITECT HBsAg assay reagent, calibrator, and control lots per site. Two controls and two panels were assayed in replicates of four at two separate times of day for five days. The data are summarized in the following table.

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Sample	n	Grand Mean S/CO	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 Component of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative Control	360	0.59	0.051	NA	0.051	NA	0.054	NA	0.072	NA	0.101	NA	0.111	NA
Positive Control	360	4.25	0.183	4.3	0.186	4.4	0.195	4.6	0.216	5.1	0.254	6.0	0.254	6.0
High Negative Panel	360	0.83	0.066	7.9	0.066	8.0	0.068	8.1	0.100	12.0	0.107	12.9	0.128	15.4
Low Positive Panel	360	1.25	0.079	6.3	0.084	6.8	0.096	7.7	0.148	11.8	0.124	10.0	0.162	13.0

NA = not applicable

Sample Stability of Serum and Plasma

A study was conducted to evaluate the number of freeze/thaw cycles for each blood collection tube type acceptable for use with the ARCHITECT HBsAg assay.

The data demonstrate that human serum (including serum collected in serum separator tubes) or plasma collected in dipotassium EDTA tubes may be used with the ARCHITECT HBsAg assay when subjected to up to three 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 HBsAg assay on two instruments (one *i* 2000 and one *i* 2000_{SR}).

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

Calibration Curve Storage

A study was conducted to evaluate the acceptability of an ARCHITECT HBsAg calibration curve stored on the ARCHITECT *i* System for a minimum of 30 days. Testing was performed on two instruments (one *i* 2000 and one *i* 2000_{SR}) using three lots of reagents and calibrators, and one lot of controls. The ARCHITECT HBsAg Negative Control and Positive Control were tested 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 HBsAg calibration curve on the ARCHITECT *i* System for a minimum of 30 days. The data demonstrate that the ARCHITECT HBsAg assay can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}.

Summary of Safety and Effectiveness Data

Instrument Percent Agreement

A study was performed to demonstrate that the ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory assays can be used on the ARCHITECT *i* 2000 and the ARCHITECT *i* 2000_{SR} systems. Surplus serum specimens were obtained from two commercial vendors. Specimens were tested with two lots of ARCHITECT HBsAg reagents and one lot each of calibrators and controls on each ARCHITECT instrument system (one *i* 2000 and one *i* 2000_{SR}).

The negative percent agreement was 100.0% and the positive percent agreement was 99.6%. The 95% confidence intervals for the negative percent agreement were 99.28 % to 100.00%. The 95% confidence intervals for the positive percent agreement were 98.59% to 99.95%.

The data demonstrate that the ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory assays can be used on the ARCHITECT *i* 2000 and *i* 2000_{SR}.

Reagent On Board Evaluation

A study was performed to evaluate the performance of the ARCHITECT HBsAg reagents when stored on board the ARCHITECT *i* System while the instrument was in continuous running mode (on board evaluation). A minimum of 17 time points were performed over a 35-day period, with the last time point performed on day 35.

The time point mean S/CO values of each sample for all lots of the control and test reagent kits conformed to 1-2S/3-1S and 1-2S/7T Westgard rules. The data support a 30-day reagent storage of the ARCHITECT HBsAg reagent kit on board the ARCHITECT *i* System while the instrument is in continuous running mode.

Within-Assay Sample Carryover

A study was performed to evaluate the susceptibility of the ARCHITECT HBsAg assay to within-assay sample carryover. A singlicate from each of 34 sample cups containing HBsAg negative sample was tested to serve as a sample that was not exposed to potential sample carryover (protected sample). This was followed by a singlicate of the high positive sample (high sample), then by a singlicate from each of three sample cups to serve as samples exposed to potential sample carryover (unprotected sample). This sequence of high sample followed by three replicates of unprotected sample was repeated an additional 33 times for a total of 34 iterations.

The mean parts per million (ppm) of the unprotected low sample was 0.28 ppm. Carryover of the ARCHITECT HBsAg assay meets the ≤ 0.35 ppm requirement.

Summary of Safety and Effectiveness Data

ARCHITECT HBsAg High Dose Hook Effect

A study was performed to characterize the performance of the ARCHITECT HBsAg assay when used to test specimens containing high levels of HBsAg that have the potential to cause a high dose hook effect. Two HBsAg-positive stocks were serially diluted with HBsAg-negative plasma and tested using the ARCHITECT HBsAg assay.

The undiluted samples of both HBsAg-positive stocks were reactive by the ARCHITECT HBsAg assay. The data demonstrate that the ARCHITECT HBsAg assay is not susceptible to interference from specimens with high levels of HBsAg.

Microbial Challenge Characterization Evaluation

The Microbial Challenge Characterization (MCC) evaluation for the ARCHITECT HBsAg Reagents, Calibrators, and Controls and ARCHITECT HBsAg Confirmatory Reagents and Manual Diluent* consists of an Antimicrobial Effectiveness Testing (AET) evaluation, which establishes the level of antimicrobial protection provided by the preservative system, and a Microbial Interference Characterization (MIC) evaluation, which demonstrates the effect of microbial bioburden and/or its by-products on assay performance. The MCC evaluation integrates the results from both AET and MIC to determine that the product is adequately protected.

* The ARCHITECT HBsAg Confirmatory Manual Diluent and the ARCHITECT HBsAg Negative Control formulations are identical. Therefore, the results from the ARCHITECT HBsAg Negative Control AET and MIC studies apply to the ARCHITECT HBsAg Confirmatory Manual Diluent, and separate AET and MIC studies were not performed for the ARCHITECT HBsAg Confirmatory Manual Diluent.

Summary of Safety and Effectiveness Data

The following six microbial organisms were used in all AET and MIC studies:

Candida albicans (*C. albicans*)
Aspergillus niger (*A. niger*)
Escherichia coli (*E. coli*)
Pseudomonas aeruginosa (*P. aeruginosa*)
Pseudomonas fluorescens (*P. fluorescens*)
Staphylococcus aureus (*S. aureus*)

ARCHITECT HBsAg Reagents, Calibrators, and Controls and ARCHITECT HBsAg Confirmatory Reagents and Manual Diluent AET Evaluation

A study was conducted to demonstrate the antimicrobial effectiveness of the preservative system for the ARCHITECT HBsAg Reagents, Calibrators, and Controls and ARCHITECT HBsAg Confirmatory Reagents and Manual Diluent.[†] The reagents, calibrators, and controls were inoculated at a concentration of 10^5 to 10^6 CFU/mL with each of the six microbial organisms.

A control condition was prepared for each of the on-test materials by inoculating the materials with sterile saline. On Days 14 and 28, the uninoculated and inoculated materials were plated onto agar petri plates, incubated, and examined for growth. The number of colony forming units were counted within and on the surface of the plate medium. For all materials, the results were *cidal* for all of the microbial groups tested.

ARCHITECT HBsAg Reagents MIC Evaluation

A study was conducted to demonstrate the effect of microbial bioburden and/or its by-products on assay performance of the ARCHITECT HBsAg Reagents (Microparticles and Conjugate). The reagents were inoculated at a concentration of 10^3 to 10^4 CFU/mL with each of the six microbial organisms.

A control condition was prepared for each of the on-test materials by inoculating the materials with sterile saline. Within seven days after Day 35, testing of the uninoculated and inoculated conditions was initiated on the ARCHITECT *i* System. The ARCHITECT HBsAg Reagents (Microparticles and Conjugate) were *not sensitive* to any of the microbial organisms evaluated when inoculated at 10^3 to 10^4 CFU/mL.

[†] The ARCHITECT HBsAg Confirmatory Manual Diluent and the ARCHITECT HBsAg Negative Control formulations are identical. Therefore, the results from the ARCHITECT HBsAg Negative Control AET study apply to the ARCHITECT HBsAg Confirmatory Manual Diluent, and a separate AET study was not performed for the ARCHITECT HBsAg Confirmatory Manual Diluent.

Summary of Safety and Effectiveness Data

ARCHITECT HBsAg Calibrators and Controls and ARCHITECT HBsAg Confirmatory Manual Diluent[†] MIC Evaluation

A study was performed to demonstrate the effect of microbial bioburden and/or its by-products on assay performance of the ARCHITECT HBsAg Calibrator 1, Calibrator 2, Negative Control, and Positive Control and ARCHITECT HBsAg Confirmatory Manual Diluent. The reagents were inoculated at a concentration of 10^3 to 10^4 CFU/mL with each of the six microbial organisms.

A control condition was prepared for each of the on-test materials by inoculating the materials with sterile saline. Within seven days after Day 35, testing of the uninoculated and inoculated conditions was initiated on the ARCHITECT *i* System. The ARCHITECT HBsAg Calibrator 1, Calibrator 2, Negative Control, and Positive Control and the ARCHITECT HBsAg Confirmatory Manual Diluent were *not sensitive* to any of the microbial organisms evaluated when inoculated at 10^3 to 10^4 CFU/mL.

ARCHITECT HBsAg Confirmatory Reagents MIC Evaluation

A study was performed to demonstrate the effect of microbial bioburden and/or its by-products on the assay performance of the ARCHITECT HBsAg Confirmatory Reagents (Microparticles, Conjugate, Pretreatment 1, and Pretreatment 2). The reagents were inoculated at a concentration of 10^3 to 10^4 CFU/mL with each of the six microbial organisms.

A control condition was prepared for each of the on-test materials by inoculating the materials with sterile saline. Within seven days after Day 35, testing of the uninoculated and inoculated conditions was initiated on the ARCHITECT *i* System. The ARCHITECT HBsAg Confirmatory Reagents (Microparticles, Conjugate, Pretreatment 1, and Pretreatment 2) were *not sensitive* to any of the microbial organisms evaluated when inoculated at 10^3 to 10^4 CFU/mL.

For all reagents, calibrators, controls, and manual diluent, the AET results were *cidal* and the MIC results were *not sensitive*. In conclusion, the MCC results indicate that the ARCHITECT HBsAg Reagents, Calibrators, and Controls and ARCHITECT HBsAg Confirmatory Reagents and Manual Diluent are adequately protected.

[†] The ARCHITECT HBsAg Confirmatory Manual Diluent and the ARCHITECT HBsAg Negative Control formulations are identical. Therefore, the results from the ARCHITECT HBsAg Negative Control MIC study apply to the ARCHITECT HBsAg Confirmatory Manual Diluent, and a separate MIC study was not performed for the ARCHITECT HBsAg Confirmatory Manual Diluent.

Summary of Safety and Effectiveness Data

Stability Study Summaries

ARCHITECT HBsAg Reagent, Calibrators, and Control Developmental Stability

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

Stability testing is performed on three lots of 100-test kit reagents, three lots of 50Q-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). To date, 8 months of stability data have been obtained for the reagents, calibrators, and controls at the intended storage condition and stability data supporting 8 months has been obtained for the reagents at the on board storage condition. The data support 8 months of expiration dating for the ARCHITECT HBsAg Reagents, Calibrators, and Controls.

ARCHITECT HBsAg Confirmatory Reagent Developmental Stability

The developmental stability is an on-going study to establish the stability (shelf-life integrity) of the ARCHITECT HBsAg Confirmatory Reagents at the intended storage condition of 2 to 8°C and during on-board storage.

In addition, the developmental stability includes the in-use and freeze/thaw conditions. The in-use condition for the reagents simulates customer use over time. The freeze/thaw condition for the reagents supports the transport simulation study.

Stability testing is performed on three lots of reagents.

The developmental stability is scheduled to continue for a maximum of 15 months (with a minimum of 6 months). To date, 8 months of stability data have been obtained for the reagents at the intended storage and on board storage conditions. The data support 8 months of expiration dating for the ARCHITECT HBsAg Confirmatory Reagents.

Summary of Safety and Effectiveness Data

ARCHITECT HBsAg Confirmatory Manual Diluent Recommended Storage Stability

The ARCHITECT HBsAg Confirmatory Manual Diluent has the same formulation as the ARCHITECT HBsAg Negative Control found in the ARCHITECT HBsAg Controls. Therefore, the stability data used to support the stability of the ARCHITECT HBsAg Negative Control are also used to support the stability of the ARCHITECT HBsAg Confirmatory Manual Diluent.

ARCHITECT HBsAg Reagent Transport Temperature Simulation Stability

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

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

ARCHITECT HBsAg Calibrator and Control Transport Temperature Simulation Stability

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

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

ARCHITECT HBsAg Confirmatory Reagent Transport Temperature Simulation Stability

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

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

Summary of Safety and Effectiveness Data

ARCHITECT HBsAg Confirmatory Manual Diluent Transport Temperature Simulation Stability

The ARCHITECT HBsAg Confirmatory Manual Diluent has the same formulation as the ARCHITECT HBsAg Negative Control. Therefore, the data used to support the stability of the ARCHITECT HBsAg Negative Control during transport can be used to support the transport stability of the ARCHITECT HBsAg Confirmatory Manual Diluent.

X. SUMMARY OF CLINICAL STUDIES

Description of Patient Population

The 2946 specimens tested and analyzed in the ARCHITECT HBsAg and ARCHITECT HBsAg Confirmatory clinical study were prospectively collected from specimen collection sites or were purchased from specimen vendors as noted. The specimens comprised the following categories:

- 1313 specimens were from individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, disease state, or known exposure event;
- 690 specimens were from individuals exhibiting signs and symptoms of HBV infection;
- 49 specimens were from individuals diagnosed with acute or chronic HBV infection;
- 53 specimens were from individuals from Vietnam (initially diagnosed as having acute HBV infection based on subject medical history);
- 741 specimens were from pregnant females;
- 100 pediatric specimens were obtained retrospectively from commercial vendors; and
- 15 seroconversion panel members were obtained retrospectively from commercial vendors and subsequently classified as acute by four marker reference testing.

Study Design

Each specimen was tested using the ARCHITECT HBsAg assay and, if warranted, the ARCHITECT HBsAg Confirmatory assay at one of the three clinical testing sites. Each specimen was also tested with the HBsAg and HBsAg Confirmatory (where required) comparator methods.

Specimens from the increased risk, signs and symptoms, diagnosed acute HBV infection (including specimens from Vietnam) subgroups were also tested by the anti-HBc IgM, anti-HBc, and anti-HBs markers to determine HBV classification. During the clinical study, all comparator and HBV classification testing was performed following manufacturer's instructions. HBV classification was based on the reference marker patterns presented in Table 6 on page 24. The classification being used is a modification of the National Centers of Infectious

Summary of Safety and Effectiveness Data

Diseases of the Centers for Disease Control and Prevention (CDC) interpretation of Viral Hepatitis B Panel testing.

Supplemental testing was performed for specimen results that were discordant between the ARCHITECT HBsAg/ARCHITECT HBsAg Confirmatory assays and the comparator HBsAg/HBsAg Confirmatory assays to better characterize the specimen. Supplemental testing was performed for the following hepatitis markers: HBeAg, anti-HBe, anti-HBc IgM, anti-HBc, and anti-HBs. Testing was also performed using HBV polymerase chain reaction (PCR).

Demographic Data and Expected Results for Increased Risk Population

Due to geographic locations or demographics, assay results obtained in individual laboratories may vary from the data presented. Of the 2946 specimens tested in the ARCHITECT HBsAg clinical study, 1313 specimens were from individuals with increased risk of HBV infection. All 1313 individuals 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. Testing of these specimens was performed at three clinical sites located in Galveston, TX; Hershey, PA; and Milwaukee, WI.

The increased risk population (n=1313) consisted of the following race/ethnic groups:

- 625 (47.60%) Caucasian
- 476 (36.25%) African-American
- 167 (12.72%) Hispanic
- 19 (1.45%) Asian
- 6 (0.46%) American Indian/Alaska Native
- 20 (1.52%) Other

The 1313 specimens from the increased risk population were obtained from the following collection locations:

- 742 (56.51%) from Galveston, TX
- 185 (14.09%) from High Point, NC
- 99 (7.54%) from Plymouth, MA
- 76 (5.79%) from Colton, CA
- 59 (4.49%) from Dallas, TX
- 56 (4.27%) from St. Petersburg, FL
- 52 (3.96%) from Miami, FL
- 36 (2.74%) from Denver, CO
- 8 (0.61%) from Chicago, IL

A total of 23 (1.75%) of the specimens in the increased risk population were reactive in the ARCHITECT HBsAg assay. The number of ARCHITECT HBsAg reactive results observed for the increased risk population at each collection location was:

- 9 of 742 (1.21%) from Galveston, TX
- 1 of 185 (0.54%) from High Point, NC
- 0 of 99 (0.00%) from Plymouth, MA
- 0 of 76 (0.00%) from Colton, CA

Summary of Safety and Effectiveness Data

6 of 59 (10.17%) from Dallas, TX
 3 of 56 (5.36%) from St. Petersburg, FL
 4 of 52 (7.69%) from Miami, FL
 0 of 36 (0.00%) from Denver, CO
 0 of 8 (0.00%) from Chicago, IL

Of the 1313 specimens, 815 (62.07%) were female and 498 (37.93%) were male. The age was not reported for three specimens. Of the remaining 1310 specimens, the mean age was 40 years (age range: 18 to 75 years). The distribution of ARCHITECT HBsAg reactive and nonreactive results among the increased risk population by age and gender (n=1310) is summarized in the following table.

Age Group (Years)	Gender	ARCHITECT HBsAg Result		Total
		Reactive n (%)	Nonreactive n (%)	
10 to 19	F	0 (0.00)	14 (100.00)	14
	M	0 (0.00)	11 (100.00)	11
20 to 29	F	2 (1.09)	182 (98.91)	184
	M	0 (0.00)	97 (100.00)	97
30 to 39	F	0 (0.00)	184 (100.00)	184
	M	5 (4.67)	102 (95.33)	107
40 to 49	F	4 (1.60)	246 (98.40)	250
	M	4 (2.52)	155 (97.48)	159
50 to 59	F	2 (1.46)	135 (98.54)	137
	M	5 (4.59)	104 (95.41)	109
60 to 69	F	0 (0.00)	35 (100.00)	35
	M	1 (8.33)	11 (91.67)	12
70 to 79	F	0 (0.00)	8 (100.00)	8
	M	0 (0.00)	3 (100.00)	3
Total		23 (1.76)	1287 (98.24)	1310†

† Age was not reported for three subjects.

Clinical Performance

A prospective multi-center study was conducted to evaluate the ability of the ARCHITECT HBsAg assay to detect HBsAg in a group of individuals that would normally be tested in a clinical situation. Of the 2946 specimens tested in the ARCHITECT HBsAg clinical study, 1313 specimens were obtained from individuals with increased risk of HBV infection due to lifestyle, behavior, occupation, or a known exposure event and 690 specimens were obtained from individuals exhibiting signs and symptoms of hepatitis infection.

Of the 2003 specimens from the increased risk and signs and symptoms populations, 1055 (52.67%) were female and 948 (47.33%) were male. Age was not reported for three specimens. Of the remaining 2000 specimens, the mean age was 41 years (age range: 18 to 83 years). Each specimen was tested using a comparator HBsAg assay and three HBV reference assays, each detecting a unique serological marker (anti-HBc IgM, total anti-HBc, and anti-HBs). The HBV classification was determined for each specimen based on the reactivity

Summary of Safety and Effectiveness Data

patterns of the four HBV serological marker results. The comparator and reference assays were from a single manufacturer, and testing was performed following manufacturer's instructions. Each specimen was also tested at one of three clinical sites located in Galveston, TX; Hershey, PA; or Milwaukee, WI, using the ARCHITECT HBsAg assay.

Results by Specimen Classification

Following testing with the comparator HBsAg assay and three reference HBV assays, the 2003 specimens from the increased risk and signs and symptoms population plus 117 individuals with acute or chronic HBV infection were assigned an HBV classification according to the following table. There were 15 unique reference marker patterns observed in the ARCHITECT HBsAg clinical study.

Number of Specimens	HBV Reference Markers				HBV Classification
	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
17	+	-	-	-	Early Acute
10	+	+	+	-	Acute
3	+	-	+	+	Chronic
85	+	-	+	-	Chronic
2	+	-	-	+	Chronic
3	+	-	+	I	Chronic
43	Presence of HBsAg \geq 6 Months				Chronic
1	+	+	+	+	Late Acute/Recovering
4	-	+	+	+	Recovering Acute
2	-	+	+	I	Early Recovery
192	-	-	+	+	Immune Due to Natural Infection
31	-	-	+	I	Distantly Immune/Anti-HBs Unknown
107	-	-	+	-	Distantly Immune/Anti-HBs Not Detected
504	-	-	-	+	Immune Due to HBV Vaccination
63	-	-	-	I	Unknown
1,053	-	-	-	-	Susceptible
2120					Total

+ = Positive/Reactive, - = Negative, I = Indeterminate

Comparison of Results

The following table compares the ARCHITECT HBsAg assay results with the comparator HBsAg/HBsAg Confirmatory assay final interpretation for each of the HBV classifications for the increased risk and signs and symptoms populations (n = 2003) plus individuals with acute or chronic HBV infection (n=117). The data are summarized in the following table.

HBV Classification	Comparator HBsAg/HBsAg Confirmatory Final Interpretation								Total	
	Positive [†]				Negative					
	ARCHITECT HBsAg Results [†]									
	Reactive		Nonreactive		Reactive		Nonreactive			
	n	%	n	%	n	%	n	%		
Early Acute	16	0.75	1 ^a	0.05	0	0.00	0	0.00	17	0.80
Acute	10	0.47	0	0.00	0	0.00	0	0.00	10	0.47

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Chronic	133	6.27	1 ^b	0.05	1 ^c	0.05	1	0.05	136	6.42
Late Acute/Recovering	1	0.05	0	0.00	0	0.00	0	0.00	1	0.05
Recovering Acute	0	0.00	0	0.00	0	0.00	4	0.19	4	0.19
Early Recovery	0	0.00	0	0.00	0	0.00	2	0.09	2	0.09
Immune Due to Natural Infection	0	0.00	0	0.00	0	0.00	192	9.06	192	9.06
Distantly Immune/Anti-HBs Unknown	0	0.00	0	0.00	0	0.00	31	1.46	31	1.46
Distantly Immune/Anti-HBs Not Detected	0	0.00	0	0.00	1 ^d	0.05	106	5.00	107	5.05
Immune Due to HBV Vaccination	0	0.00	0	0.00	1 ^e	0.05	503	23.73	504	23.77
Unknown	0	0.00	0	0.00	0	0.00	63	2.97	63	2.97
Susceptible	0	0.00	0	0.00	10 ^f	0.47	1043	49.20	1053	49.67
Total	160	7.55	2	0.09	13	0.61	1945	91.75	2120	100.00

[†] The comparator HBsAg final positive interpretation is based on the comparator HBsAg assay repeatedly reactive results or the comparator HBsAg confirmatory assay results, when required.

[‡] Includes retesting of initial reactives.

^a This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA.

^b This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but positive for anti-HBs.

^c This specimen was tested and determined to be negative for anti-HBc IgM, but positive for anti-HBc and anti-HBs.

^d This specimen was tested and determined to be confirmed positive by the ARCHITECT HBsAg Confirmatory assay and determined to be negative for anti-HBc IgM, anti-HBs, HBeAg, and HBV DNA, but positive for anti-HBc and anti-HBe.

^e This specimen was tested and determined to be confirmed positive by the ARCHITECT HBsAg Confirmatory assay and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, and anti-HBe, but positive for anti-HBs and HBV DNA.

^f Five specimens were tested and determined to be repeatedly reactive, not confirmed by the ARCHITECT HBsAg Confirmatory assay and determined to be negative for anti-HBc IgM, anti-HBc, and anti-HBs; four specimens were tested and determined to be confirmed positive by the ARCHITECT HBsAg Confirmatory assay and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA; one specimen was tested and confirmed positive by the ARCHITECT HBsAg Confirmatory assay but determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, anti-HBe, and HBV DNA.

Percent Agreement

The table below summarizes the percent agreement between the ARCHITECT HBsAg assay results and the comparator HBsAg assay final interpretation for the increased risk and signs and symptoms populations by HBV classification (n=2003).

HBV Classification	Positive Percent Agreement	95% Confidence Interval	Negative Percent Agreement	95% Confidence Interval
Early Acute	50.00 (1/2)	1.26 - 98.74	—	—
Acute	100.00 (4/4)	39.76 - 100.00	—	—
Chronic	97.50 (39/40)	86.84 - 99.94	—	—
Late Acute/Recovering	100.00 (1/1)	2.50 - 100.00	—	—
Recovering Acute	—	—	100.00 (4/4)	39.76 - 100.00
Early Recovery	—	—	100.00 (2/2)	15.81 - 100.00
Immune Due to Natural Infection	—	—	100.00 (192/192)	98.10 - 100.00
Distantly Immune/Anti-HBs Unknown	—	—	100.00 (31/31)	88.78 - 100.00
Distantly Immune/Anti-HBs Not Detected	—	—	99.07 (106/107)	94.90 - 99.98
Immune Due to HBV Vaccination	—	—	99.80 (503/504)	98.90 - 99.99
Unknown	—	—	100.00 (63/63)	94.31 - 100.00
Susceptible	—	—	99.05 (1043/1053)	98.26 - 99.54
Total	95.74 (45/47)	85.46 - 99.48	99.39 (1944/1956)	98.93 - 99.68

Percent Agreement for Individuals With Acute or Chronic HBV Infection

ARCHITECT HBsAg performance was further evaluated using serum specimens that were: prospectively collected in the U.S. from six individuals clinically diagnosed with acute HBV infection and 43 individuals clinically diagnosed with chronic HBV infection defined by the presence of HBsAg for ≥ 6 months;

Summary of Safety and Effectiveness Data

prospectively collected in Vietnam from 53 individuals classified as chronic by four-marker HBV reference testing; and 15 seroconversion panel members classified as acute by four-marker HBV reference testing. The percent agreement between the ARCHITECT HBsAg assay results and the comparator HBsAg assay final interpretation for the individuals with acute and chronic HBV infection are presented in the table below. The percent agreement between the ARCHITECT HBsAg assay results and the comparator HBsAg assay final interpretation for the individuals with acute and chronic HBV infection (n=117) are presented in the table below.

Specimen Category	Positive Percent Agreement	95% Confidence Interval	Negative Percent Agreement	95% Confidence Interval
Individuals With Acute HBV Infection	21/21 (100.00)	83.89-100.00	NA	NA
Individuals With Chronic HBV Infection	94/94 (100.00)	96.15-100.00	1/2 (50.00)	1.26-98.74
Total	115/115 (100.00)	96.84-100.00	1/2 (50.00)	1.26-98.74

Clinical Performance in Pregnant Females

The performance of ARCHITECT HBsAg in detecting HBV infection in pregnant females was evaluated by testing prospectively-collected serum specimens from pregnant females at low risk or increased risk of HBV infection due to lifestyle, behavior, or known exposure event. Of the 2946 specimens tested in the ARCHITECT HBsAg clinical study, 741 were from a pregnant female population. The specimens were obtained from commercial vendors. The 741 specimens, from pregnant females ages 16 to 45 years, were collected from collection sites in Colton, CA (178); Plymouth, MA (7); and Los Angeles, CA (556). Testing of these specimens was performed at the clinical sites located in Galveston, TX and Milwaukee, WI. Of the pregnant female population, 4.18% were obtained during the first trimester, 45.21% during the second trimester, and 50.61% during the third trimester. The demographic profile of the pregnant female population is presented in the table below.

	Low Risk n (%)	Increased Risk n (%)	Total n (%)
TOTAL	548 (73.95)	193 (26.05)	741 (100.00)
TRIMESTER			
First	24 (4.38)	7 (3.63)	31 (4.18)
Second	261 (47.63)	74 (38.34)	335 (45.21)
Third	263 (47.99)	112 (58.03)	375 (50.61)
AGE			
16-31	323 (58.94)	159 (82.38)	482 (65.05)
32-45	225 (41.06)	34 (17.62)	259 (34.95)
RACE/ETHNIC GROUP			
Caucasian	10 (1.82)	41 (21.24)	51 (6.88)
African-American	52 (9.49)	24 (12.44)	76 (10.26)
Hispanic	468 (85.40)	120 (62.18)	588 (79.35)
Asian	16 (2.92)	0 (0.00)	16 (2.16)
American Indian/ Alaska Native	0 (0.00)	2 (1.04)	2 (0.27)
Other	2 (0.36)	6 (3.11)	8 (1.08)

Summary of Safety and Effectiveness Data

Agreement for Pregnant Females by Risk and Trimester

A comparison was performed between the ARCHITECT HBsAg assay results and the comparator HBsAg assay results using serum samples obtained from a total of 741 females at low risk or increased risk for HBV infection. Data were analyzed by risk and by trimester. The data are summarized in the tables below.

ARCHITECT and Comparator HBsAg Results by Trimester for Low Risk Pregnant Females

ARCHITECT HBsAg Results†	First Trimester			Second Trimester			Third Trimester		
	Comparator HBsAg Results‡		Total	Comparator HBsAg Results‡		Total	Comparator HBsAg Results‡		Total
	Positive	Negative		Positive	Negative		Positive	Negative	
Reactive	0	0	0	1	2 ^a	3	0	2 ^b	2
Nonreactive	0	24	24	0	258	258	0	261	261
Total	0	24	24	1	260	261	0	263	263

‡ Includes retesting and confirmatory testing performed according to the comparator package insert.

† Includes retesting of initial reactives.

^a One specimen was tested and determined to be repeatedly reactive, not confirmed by the ARCHITECT HBsAg Confirmatory assay but was not further tested. One specimen was tested and determined to be confirmed positive by the ARCHITECT HBsAg Confirmatory assay and was determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but positive for anti-HBs.

^b One specimen was tested and determined to be repeatedly reactive, not confirmed by the ARCHITECT HBsAg Confirmatory assay but was not further tested. One specimen was tested and determined to be confirmed positive by the ARCHITECT HBsAg Confirmatory assay and was determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but indeterminate for anti-HBs.

ARCHITECT and Comparator HBsAg Results by Trimester for Increased Risk Pregnant Females

ARCHITECT HBsAg Results†	First Trimester			Second Trimester			Third Trimester		
	Comparator HBsAg Results‡		Total	Comparator HBsAg Results‡		Total	Comparator HBsAg Results‡		Total
	Positive	Negative		Positive	Negative		Positive	Negative	
Reactive	0	0	0	0	0	0	1	1 ^a	2
Nonreactive	0	7	7	0	74	74	0	110	110
Total	0	7	7	0	74	74	1	111	112

‡ Includes retesting and confirmatory testing performed according to the comparator package insert.

† Includes retesting of initial reactives.

^a This specimen was tested and determined to be repeatedly reactive, not confirmed by the ARCHITECT HBsAg Confirmatory assay but was not further tested.

Overall Summary and Percent Agreement for Pregnant Females

The table below summarizes the frequency of reactivity of the ARCHITECT HBsAg assay and the comparator HBsAg assay from a total of 741 females at low risk and increased risk for HBV infection.

ARCHITECT HBsAg Results†	Comparator HBsAg Results‡		Total n (%)
	Positive n (%)	Negative n (%)	
Reactive	2 (100.0)	5 (0.68)	7 (0.94)
Nonreactive	0 (0.00)	734 (99.32)	734 (99.06)
Total	2 (0.27)	739 (99.73)	741 (100.00)

‡ Includes retesting and confirmatory testing performed according to the comparator package insert.

† Includes retesting of initial reactives.

The table below summarizes the percent agreement between the ARCHITECT HBsAg assay results and the comparator HBsAg assay results for the pregnant female population and shows the 95% confidence intervals.

Subjects	Positive Percent	95% Confidence	Negative Percent	95% Confidence
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Summary of Safety and Effectiveness Data

	Agreement	Interval	Agreement	Interval
Pregnant Females	100.00% (2/2)	15.81 - 100.00	99.32% (734/739)	98.43 - 99.78

Clinical Performance in a Pediatric Population

Of the 2946 specimens tested in the ARCHITECT HBsAg clinical study, 100 specimens were from a pediatric population. The specimens were obtained from a commercial vendor, which collected the specimens from a collection site located in Fall River, MA. The specimens were obtained from children ages 2 to 18 years. Testing of these specimens was performed at the clinical site located in Galveston, TX.

The data are summarized by age and gender in the following table.

Age Group (Years)	Gender	Reactive n (%)	Nonreactive n (%)	Total
2 to 12	F	0 (0.00)	28 (100.00)	28
	M	0 (0.00)	22 (100.00)	22
13 to 18	F	0 (0.00)	41 (100.00)	41
	M	0 (0.00)	9 (100.00)	9
Total		0 (0.00)	100 (100.00)	100

Summary of Safety and Effectiveness Data

ARCHITECT HBsAg Confirmatory

In a multi-center study, 167 repeatedly reactive specimens that were tested using the ARCHITECT HBsAg assay were also tested with the ARCHITECT HBsAg Confirmatory assay. Of the 167 specimens, 157 were confirmed positive using the ARCHITECT HBsAg Confirmatory assay, and 149 were reported positive by the comparator assay. The data are summarized in the following table.

Specimen Category	Comparator HBsAg/HBsAg Confirmatory Final Interpretation								Total	
	Positive				Negative					
	ARCHITECT HBsAg/ ARCHITECT HBsAg Confirmatory Final Interpretation				ARCHITECT HBsAg/ ARCHITECT HBsAg Confirmatory Final Interpretation					
	Confirmed Positive		Repeatedly Reactive Not Confirmed		Confirmed Positive		Repeatedly Reactive Not Confirmed			
	n	%	n	%	n	%	n	%		
Individuals Diagnosed With Acute HBV Infection	6	3.59	0	0.00	0	0.00	0	0.00	6	3.59
Individuals Diagnosed With Chronic HBV Infection	41	24.55	0	0.00	1 ^c	0.60	0	0.00	42	25.15
Individuals At Increased Risk For HBV Infection	18	10.78	1 ^a	0.60	3 ^d	1.80	2	1.20	24	14.37
Individuals From Vietnam	53	31.74	0	0.00	0	0.00	0	0.00	53	31.74
Individuals With Signs And Symptoms Of Hepatitis Infection	27	16.17	1 ^b	0.60	4 ^e	2.40	3	1.80	35	20.96
Pregnant Females	2	1.20	0	0.00	2 ^f	1.20	3	1.80	7	4.19
TOTAL	147	88.02	2	1.20	10	5.99	8	4.79	167	100.0

^a This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but positive for anti-HBs.

^b This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA.

^c This specimen was tested and determined to be negative for anti-HBc IgM, HBeAg, and HBV DNA, but positive for anti-HBc, anti-HBs, and anti-HBe.

^d Two specimens were tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA; one specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, and anti-HBe, but positive for anti-HBs and HBV DNA.

^e Two specimens were tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA; one specimen was tested and determined to be negative for anti-HBc IgM, anti-HBs, HBeAg, and HBV DNA, but positive for anti-HBc and anti-HBe; one specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, anti-HBe, and HBV DNA.

^f One specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but indeterminate for anti-HBs; one specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but positive for anti-HBs.

Of the 167 specimens tested above, 59 specimens from the increased risk and signs and symptoms populations were classified by HBV infection. A comparison of the ARCHITECT HBsAg/HBsAg Confirmatory specimens versus the comparator HBsAg/HBsAg Confirmatory final interpretation by HBV classification are summarized in the following table.

HBV Classification	Comparator HBsAg/HBsAg Confirmatory Final Interpretation								Total	
	Positive				Negative					
	ARCHITECT HBsAg/ ARCHITECT HBsAg Confirmatory Final Interpretation				ARCHITECT HBsAg/ ARCHITECT HBsAg Confirmatory Final Interpretation					
	Confirmed Positive		Repeatedly Reactive Not Confirmed		Confirmed Positive		Repeatedly Reactive Not Confirmed			
	n	%	n	%	n	%	n	%		
Early Acute	1	1.69	1 ^a	1.69	0	0.00	0	0.00	2	3.39
Acute	4	6.78	0	0.00	0	0.00	0	0.00	4	6.78
Chronic	39	66.10	1 ^b	1.69	0	0.00	0	0.00	40	67.80

Summary of Safety and Effectiveness Data

Late Acute/Recovering	1	1.69	0	0.00	0	0.00	0	0.00	1	1.69
Distantly Immune/Anti-HBs Not Detected	0	0.00	0	0.00	1 ^c	1.69	0	0.00	1	1.69
Immune Due to HBV Vaccination	0	0.00	0	0.00	1 ^d	1.69	0	0.00	1	1.69
Susceptible	0	0.00	0	0.00	5 ^e	8.47	5	8.47	10	16.95
TOTAL	45	76.27	2	3.39	7	11.86	5	8.47	59	100.00

^a This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA.

^b This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, anti-HBe, and HBV DNA, but positive for anti-HBs.

^c This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBs, HBeAg, and HBV DNA, but positive for anti-HBc and anti-HBe.

^d This specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, HBeAg, and anti-HBe, but positive for anti-HBs and HBV DNA.

^e Four specimens were tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, and anti-HBe, but positive for HBV DNA; one specimen was tested and determined to be negative for anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, anti-HBe, and HBV DNA.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multi-centered clinical studies were conducted that showed the ARCHITECT HBsAg assay and the ARCHITECT HBsAg Confirmatory assay performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

The ability of the ARCHITECT HBsAg assay and the ARCHITECT HBsAg Confirmatory assay to detect HBV infections was demonstrated with the seroconversion panel evaluation. When the ARCHITECT HBsAg and the ARCHITECT HBsAg Confirmatory assay was compared to the reference assay results, the first reactive time point for the ARCHITECT assay occurred at the same time or earlier in all 15 panels tested.

The ARCHITECT HBsAg assay demonstrated acceptable precision estimates for within run, within day, within laboratory, between site, and between lot when these variables were introduced.

The ARCHITECT HBsAg Confirmatory assay demonstrated the ability to confirm the presence of HBsAg in positive samples from a variety of sources across a broad range of sample RLU/cutoff RLU (S/CO) values.

The results from both the non-clinical and clinical studies indicate that the ARCHITECT HBsAg assay and the ARCHITECT HBsAg Confirmatory assay can be used safely and effectively for the qualitative in vitro determination of HBsAg in human adult and pediatric serum and dipotassium EDTA plasma. The data also support the use of the assay to screen for HBV infection in pregnant females to identify neonates who are at risk of acquiring hepatitis B during the perinatal period. The ARCHITECT HBsAg assay and the ARCHITECT HBsAg Confirmatory assay may be used with other serological markers and clinical information to assess the clinical status of patients known or suspected of infection with HBV.

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 September 7, 2006.

The applicant's manufacturing facilities were inspected on 5/16/06 (Abbott Park), 5/8/06 (N. Chicago) and 5/19/06 (PR) 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.