

Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name: Reagent system for the measurement of antibodies against hepatitis B core antigen

Device Trade Name: IMMULITE[®] Anti-HBc
IMMULITE[®] 2000 Anti-HBc

Applicant's Name and Address: Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, California 90045-5597

Premarket Approval Application (PMA) Number: P010051

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: July 24, 2002

II. INDICATIONS FOR USE

IMMULITE Anti-HBc

The IMMULITE Anti-HBc is a solid-phase chemiluminescent enzyme immunoassay designed for use on the IMMULITE automated immunoassay analyzer for the qualitative detection of total antibodies against hepatitis B core antigen (anti-HBc) in human serum or plasma (EDTA, heparinized, citrate). It is intended for *in vitro* diagnostic use for the presumptive laboratory diagnosis of ongoing or previous hepatitis B virus infection.

IMMULITE 2000 Anti-HBc

The IMMULITE 2000 Anti-HBc is a solid-phase chemiluminescent enzyme immunoassay designed for use on the IMMULITE 2000 automated immunoassay analyzer for the qualitative detection of total antibodies against hepatitis B core antigen (anti-HBc) in human serum or plasma (EDTA, heparinized, citrate). It is intended for *in vitro* diagnostic use for the laboratory diagnosis of ongoing or previous hepatitis B virus infection.

III. DEVICE DESCRIPTION

The IMMULITE and IMMULITE 2000 Anti-HBc kits are the subject of this PMA. Data for each assay is presented separately in this document.

The IMMULITE and IMMULITE 2000 Anti-HBc kits are solid phase, two step chemiluminescent enzyme immunoassays designed for use on the automated IMMULITE and IMMULITE 2000 analyzers, for the qualitative measurement of total antibodies against hepatitis B core antigen (HBcAg) in human serum or plasma. The kits are intended for *in vitro* use as an aid in the determination of a prior immune status to the hepatitis B virus.

The kits' solid phase is a polystyrene bead coated with purified recombinant HBcAg. The patient sample and a protein-based buffer are simultaneously introduced into the Test Unit and incubated for approximately 30 minutes at 37 °C with intermittent agitation. During this time, anti-HBc in the patient sample binds to the recombinant HBcAg-coated bead. Unbound serum is then removed by a centrifugal wash. An alkaline phosphatase-labeled monoclonal anti-HBc antibody is introduced, and the reaction tube is incubated with agitation for another 30 minute cycle, during which time the monoclonal antibody binds to unoccupied sites on the recombinant HBcAg-coated bead. The unbound enzyme conjugate is removed by a centrifugal wash. After the wash, a chemiluminescent substrate is added, and the reaction tube is incubated with agitation for a further 5 – 10 minutes.

The chemiluminescent substrate is a phosphate ester of adamantyl dioxetane which undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex and the resulting photon output, measured as cps by the photomultiplier tube, are inversely related to the presence of antibodies to HBcAg in the sample. A qualitative result is then obtained by comparing the patient results to an established cutoff

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no known contraindications for the IMMULITE Anti-HBc and the IMMULITE 2000 Anti-HBc assay.

Warning and precautions for users of the IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc assays are stated in the product labeling.

V. ALTERNATIVE PRACTICES OR PROCEDURES

Commercially available, FDA licensed or approved serological tests have been used to measure antibodies against hepatitis B core antigen in individuals suspected of having hepatitis. When patient test results are used in combination with other serological markers expressed during the three phases of incubation, the presence of HBV virus can

be determined.

VI. MARKETING HISTORY

IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc have been marketed internationally as an aid in the determination of acute and chronic hepatitis B virus infection since July 1996. IMMULITE and IMMULITE 2000 Anti-HBc have received European Union CE Mark approval and have been marketed in Europe since June 2001. The devices have not been withdrawn from any country for reasons related to safety and effectiveness.

VII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

As an *in vitro* diagnostic test system, there is no direct adverse effect of IMMULITE and IMMULITE 2000 Anti-HBc assays on the health of the patient. The possibility of erroneous test results due to test malfunctions or operator errors exists. A false non-reactive result would make the patients unnecessarily receive a vaccine, vaccine booster, hyperimmune globulin, or be considered not to have recovered from an HBV infection when in fact they have recovered.

Blood specimens obtained from a subject infected with hepatitis B prior to the appearance of an antibody titer have the potential to misdiagnose the patient as not being infected. Additionally, specimens obtained after the disappearance of anti-HBc IgM antibodies, in the absence of test results for other hepatitis B markers, may lead to misdiagnosis of a hepatitis B infected patient.

The risk of incorrect test results is inherent with all *in vitro* diagnostic products. Therefore, the above potential risks are not unusual in the laboratory setting. Appropriate warnings for each of these risks are contained in the labeling and package insert instructions. Standard good laboratory practices are considered sufficient to minimize risks to the end user.

VIII. SUMMARY OF NON CLINICAL STUDIES

Analytical Specificity

Analytical specificity was evaluated at two clinical sites in the United States and one European site. In the United States, serum specimens from 17 subgroups of patients with potentially cross-reacting microorganisms or conditions were tested by IMMULITE Anti-HBc, IMMULITE 2000 Anti-HBc, and a commercially available enzyme immunoassay for anti-HBc (Kit A), and the results are listed in the package insert.

In the European study, eight specimens from antinuclear antibody (ANA) positive patients and 28 specimens from patients with positive rheumatoid factor (RF) were tested by IMMULITE Anti-HBc. IMMULITE Anti-HBc test results were all negative for the

eight ANA specimens. IMMULITE Anti-HBc test results were negative for 25/28 RF specimens and positive for 3/28 RF specimens.

The specimens were also tested by IMMULITE 2000 Anti-HBc, and the results are listed in the package insert.

In the European study, eight specimens from antinuclear antibody (ANA) positive patients were tested by IMMULITE 2000 Anti-HBc. IMMULITE 2000 Anti-HBc test results were negative for all eight ANA specimens.

Analytical Sensitivity

Based on studies with serial dilution of Paul Erlich Institute reference material Anti-HBc IgG 100 U/mL, the analytical sensitivity (last positive dilution) for IMMULITE 2000 Anti-HBc is 0.42 PEI U/mL. The 95% confidence interval at this level (0.42 PEI IU/mL) is 0.37 - 0.48 PEI U/mL precision of IMMULITE and IMMULITE 2000 Anti-HBc.

Precision

Precision studies for the IMMULITE and IMMULITE 2000 Anti-HBc assays were conducted at three sites. Three controls and six patient samples with different hepatitis B core antibody levels representing negative, high negative, around the cutoff, low positive, medium positive and high positive samples were evaluated. All controls and samples were tested in duplicate by three different IMMULITE Anti-HBc kit lots and one IMMULITE 2000 Anti-HBc kit lot for a total of 40 runs at each of the three sites.

Statistics including the means, standard deviations, intra-assay and total precision were based on the adjustor to sample CPS ratios in the summary shown below.

EDTA, heparin and sodium citrate samples were assayed in duplicate in three runs on three days at three U.S. sites for three lots of IMMULITE Anti-HBc and one lot of IMMULITE 2000 Anti-HBc. The median total variance of coefficients (EDTA, 4.9%; heparin, 4.4%; sodium citrate, 5.5%) demonstrated that these alternative sample types do not affect the precision of IMMULITE and IMMULITE 2000 Anti-HBc.

The IMMULITE 2000 Anti-HBc lot-to-lot precision has not been evaluated. Because the lot-to-lot precision of the assay had previously been established, and the Stability studies included three lots, no additional data was required.

Effects of Anticoagulants

The measurement of specimens is not significantly affected by the presence of heparin. IMMULITE 2000 Anti-HBc results were negative for 23/26 and positive for 3/26 RF specimens. EDTA, heparin, and sodium citrate samples were assayed in duplicate in three runs on three days at three U.S. sites for three lots of IMMULITE Anti-HBc and one lot of IMMULITE 2000 Anti-HBc. The median total variance of coefficients (EDTA, 4.9%; heparin, 4.4%; sodium citrate, 5.5%) demonstrated that these alternative sample types do not affect the sodium citrate, or EDTA anti-coagulants, as shown in a study

(Study 1) that included 57 specimens collected into plain, heparinized, sodium citrate, and EDTA vacutainer tubes. Data graphs are in the package insert. The following is a summary showing cutoff-to-signal ratios with correlation regression ($r =$).

IMMULITE Anti-HBc (in cutoff-to-signal ratio)

(Heparin) = $1.08 (\text{Serum}) + 0.006$ $r = 0.99$

(Na Citrate) = $1.10 (\text{Serum}) + 0.026$ $r = 0.95$

(EDTA) = $0.99 (\text{Serum}) + 0.034$ $r = 0.98$

In another study, 18 specimens collected into plain and sodium citrate vacutainer tubes were tested by IMMULITE Anti-HBc assay. By regression: (in cutoff-to-signal ratio)

(Na Citrate) = $1.14 (\text{Serum}) - 1.54$ $r = 0.97$

IMMULITE 2000 Anti-HBc (in cutoff-to-signal ratio)

(Heparin) = $0.98 (\text{Serum}) + 0.018$ $r = 0.99$

(Na Citrate) = $1.07 (\text{Serum}) + 0.027$ $r = 0.94$

(EDTA) = $0.97 (\text{Serum}) + 0.031$ $r = 0.99$

In another study, 18 specimens collected into plain and sodium citrate vacutainer tubes were tested by IMMULITE 2000 Anti-HBc assay. By regression: (in cutoff-to-signal ratio)

(Na Citrate) = $0.92 (\text{Serum}) + 0.776$ $r = 0.91$

Analytical Specificity

Analytical specificity was evaluated at two clinical sites in the United States and one European site. In the United States, serum specimens from 17 subgroups of patients with potentially cross-reacting microorganisms or conditions were tested by IMMULITE 2000 Anti-HBc and a commercially available enzyme immunoassay for anti-HBc (Kit A). The data is presented in the package insert.

In the European study, eight specimens from antinuclear antibody (ANA) positive patients were tested by IMMULITE 2000 Anti-HBc. IMMULITE 2000 Anti-HBc test results were negative for all eight ANA specimens.

Effects of Bilirubin, Lipemia and Hemolysis

To simulate moderate and severe icterus, different volumes of each of 5 patient samples ranging from very negative to high positive total antibodies against hepatitis B surface antigen were pipetted into lyophilized unconjugated bilirubin to achieve 3 levels of bilirubin concentrations (10, and 20 mg/dL) for each sample. The spiked and unspiked samples were assayed by the IMMULITE and IMMULITE 2000 Anti-HBc assays. In the IMMULITE Anti-HBc tests, the spiked samples had averages of 98%, and 90% recovery

for all samples for 10, and 20 mg/dL bilirubin concentrations, respectively. In the IMMULITE 2000 Anti-HBc tests, the spiked samples had averages of 96%, and 97% recovery for all samples for 10, and 20 mg/dL bilirubin concentrations, respectively. This study demonstrated that the measurement of antibodies against hepatitis B surface antigen was not affected by the presence of bilirubin up to 20 mg/dL.

To simulate mild, moderate and severe hemolysis, the same five samples were spiked with hemolysate to achieve final hemoglobin levels of 168, 252 and 504 mg/dL. The samples were assayed, both spiked and unspiked, by the IMMULITE and IMMULITE 2000 Anti-HBc assays. In both the IMMULITE and IMMULITE 2000 Anti-HBc tests, the low samples had significant increases in the antibodies against hepatitis B surface antigen when spiked with hemolysate. It was concluded that the measurement of antibodies against hepatitis B surface antigen may be affected by the presence of red blood cells. The results of hemolyzed samples should be interpreted with caution.

The same 6 samples were each spiked with 4 levels of triglycerides at 500, 1000, 2000 and 3000 mg/dL to evaluate the lipemia effect on the IMMULITE and IMMULITE 2000 Anti-HBc assays. Unspiked and spiked samples were tested by the IMMULITE and IMMULITE 2000 Anti-HBc assays. Since no significant increases of antibody levels were observed in the spiked samples with the increase of triglyceride levels, it was concluded that the measurement of antibodies to hepatitis surface antigen was not affected by the presence of lipemia (triglycerides up to 3000 mg/dL).

Hook Effect and Carryover

The hook effect study demonstrated that the IMMULITE and IMMULITE 2000 Anti-HBc assays did not have a hook effect up to at least 10,000 mIU/mL.

The carryover study demonstrated that the IMMULITE and IMMULITE 2000 Anti-HBc assays did not exhibit a carryover phenomenon when samples were preceded by a sample with a very high titer of antibodies against hepatitis B surface antigen.

Interfering Substances

A study was conducted to evaluate the effects of interfering substances on IMMULITE and IMMULITE 2000 Anti-HBc assays. Potential interfering substances that included common serum constituents, chemotherapeutic and other drugs were spiked into serum samples with 5 or 6 different levels of anti-HBc. Listed below are the substances and their test levels (concentration).

Interfering Substance	Concentration
HUMAN ALBUMIN	6 g/dL
ASCORBIC ACID	3 mg/dL
ALT	7000 U/L
AST	7000 U/L
ALK PHOSPHATASE	5000 U/L
CORTISONE	400 ug/dL
CYCLOSPORIN A	18.02 ug/dL
GANCICLOVIR	11.8 ug/mL
ETHANOL	350 mg/dL
INTRON A	2730 IU/mL
LAMIVUDINE	20 ug/mL
LDH	6000 U/L
NELFINAVIR	40 ug/mL

This study demonstrated that the measurement of antibodies against hepatitis B surface antigen by IMMULITE and IMMULITE 2000 Anti-HBc was not affected by the presence of any of the interfering substances listed up to the levels tested.

Stability

Stability studies for IMMULITE and IMMULITE 2000 Anti-HBc were conducted by using 3 lots of IMMULITE Anti-HBc, and one lot of IMMULITE 2000 Anti-HBc. The kits and components were subjected to different storage/stress conditions to simulate adverse conditions that might be encountered during shipment and use at clinical laboratories, to establish the long-term (shelf-life) claims, to approximate and support the real time stability and to test the robustness of individual components.

The studies demonstrated that the performance of IMMULITE and IMMULITE 2000 Anti-HBc assays was not affected if properly stored at package insert conditions for at least 720 days.

These studies also demonstrated that the performance of IMMULITE and IMMULITE 2000 Anti-HBc assays was not affected following initial stresses (37°C, or –20°C) for at least 720 days.

IX. SUMMARY OF CLINICAL STUDIES

Expected Values

Individuals acutely infected with the hepatitis B virus will exhibit anti-HBc approximately two weeks after the disappearance of HBsAg. This antibody response will reach peak levels after several months and gradually decline over a period of years. The majority of persons who have been vaccinated against HBV will also have detectable levels of anti-HBc.

Demographics and expected prevalence rates for different categories of subjects (apparently healthy individuals, HBV Chronic Patients, HBV Acute Patients and individuals at high risk or low risk of exposure to hepatitis B.) each of whom provided one specimen, from four clinical studies, one in the northwestern United States (Study 1), two in the southern United States (Study 3 using specimens from China and Study 4), and one in Europe, are summarized in the package insert.

Clinical Studies

The sponsor conducted clinical studies at four sites to assess the performance of the IMMULITE Anti-HBc assay and IMMULITE 2000 Anti-HBc. The study included 908 subjects, whose status was determined using FDA-approved or licensed hepatitis B assays (Reference markers), of those 139 specimens were evaluated in a comparison study. Only initial test results were reported in the analyses.

The data were analyzed using the test results obtained from the HBV reference serological marker assays, reactive(+)/ nonreactive(-). Specimen designation was based only on the HBV serological marker results for that particular specimen. No other laboratory or clinical information was used in the characterization process.

Site 1: Conducted in the northwestern United States, this study included 281 patients, consisting of 138 males and 88 females. Gender for 55 subjects was not reported. These subjects had an average age of 43 years, ranging from 21 to 85 years. Distributions of the ethnicity of the subjects are shown in the following table.

Ethnicity	<i>n</i>	%
African American	15	5.3%
Caucasian	169	60.1%
Hispanic	2	0.7%
Asian	32	11.4%
Other	3	1.1%
Unknown	60	21.4%
Total	281	100.0%

These subjects included acute and chronic hepatitis B patients, vaccinated individuals, pregnant women, and apparently healthy individuals, and patients with potentially cross-reactive substances and medical conditions.

A total of 281 specimens were prospectively (n=92) and retrospectively (n=189) collected and tested by FDA-approved or licensed hepatitis B assays for six HBV serological markers (HBsAg, Anti-HBc, Anti-HBs, Anti-HBc IgM, HBeAg, and Anti-HBe). Characterization based on single point specimens by the reference serological markers demonstrated 17 unique patterns:

Characterization based on single point specimens	Number of patients	HBV Reference Markers					
		HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc	Anti-HBe	Anti-HBs
Acute	2	+	–	–	–	–	–
Acute	1	+	+	–	–	–	–
Acute	32	+	–	+/-	+	+	–
Acute	34	+	+	+/-	+	–	–
Chronic	2	+	–	–	+	–	–
Chronic	3	+	+/-	–	+	+	+
Chronic	1	+	–	–	+	–	+
Chronic	1	+	+	+/-	+	–	+
Early Recovery	16	–	–	+/-	+	+	+
Early Recovery	4	–	–	–	+	+	–
Early Recovery	19	–	–	–	+	+/-	–
Early Recovery	1	–	–	+	+	+/-	+
HBV vaccine response	27	–	–	–	–	–	+
Not previously infected	120	–	–	–	–	–	–
Recovered	16	–	–	–	+/-	–	+
Recovered	1	–	+/-	–	+	–	+
Uninterpretable	1	–	+	–	–	–	–

Based on the above classifications the IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc results were compared to Kit A, a reference assay for the determination of anti-HBc. Data charts are presented in the package insert.

For the IMMULITE Anti-HBc the combined Total Positive agreement is 87.7% (114/130) with a 95% CI of 80.8 to 92.8%. The Negative agreement is 98.7% (149/151) with a 95% CI of 95.3 to 99.8%. The combined Total agreement is 93.6% (263/281) with a 95% CI of 90.1 to 96.2%.

For the IMMULITE 2000 Anti-HBc the combined Total Positive agreement is 88.7% (114/130) with a 95% CI of 80.8 to 92.8%. The Negative agreement is 99.3% (150/151) with a 95% CI of 96.4 to 100.0%. The Total agreement is 94.0% (264/281) with a 95% CI of 90.5 to 96.4%.

Site 2: Conducted in the northeastern United States, this study included 209 patients, consisting of 104 males, 103 females. Gender for two patients was not reported. These patients had an average age of 47 years, ranging from newborn to 93 years. Distributions of the ethnicity of the patients are shown in the following table.

Ethnicity	<i>N</i>	%
African American	21	10.0%
Caucasian	101	48.3%
Hispanic	3	1.4%
Asian	6	2.9%
Other	7	3.3%
Unknown	71	34.0%
Total	209	100.0%

Included were patients with potentially cross-reactive substances and medical conditions. A total of 209 retrospective specimens were collected and tested by FDA-approved or licensed hepatitis B assays for four HBV serological markers (HBsAg, Anti-HBc IgM, Anti-HBc, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated eight unique patterns:

Characterization based on single point specimens	No. of patients	HBV Reference Markers			
		HbsAg	Anti-HBc IgM	Anti-HBc	Anti-HBs
Acute	8	+	–	–	–
Acute	9	+	+/-	+	–
Chronic	2	+	–	+	+
Early recovery	33	–	+/-	+	+
Early recovery	17	–	–	+	–
HBV vaccine response	32	–	–	–	+
Not previously infected	107	–	–	–	–
Uninterpretable	1	+	–	–	+

Based on the above classifications the IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc results were compared to Kit A. Data charts are presented in the package insert.

For the IMMULITE Anti-HBs the combined Total Positive agreement is 91.8% (56/61) with a 95% CI of 81.9 to 97.3%. The Negative agreement is 99.3% (147/148) with a 95% CI of 96.3 to 100.0%. The combined Total agreement is 97.1% (203/209) with a 95% CI of 93.9 to 98.9%.

For the IMMULITE 2000 Anti-HBs the combined Total Positive agreement is 91.8% (56/61) with a 95% CI of 81.9 to 97.3%. The Negative agreement is 99.3% (147/148) with a 95% CI of 96.3 to 100.0%. The combined Total agreement is 97.1% (203/209) with a 95% CI of 93.9 to 98.9%.

Site 3: Specimens obtained from China were tested in the southern United States, this study included 79 patients and was comprised of 13 females and 55 males (gender for 11

patients was not reported) with an average age of 36 years, ranging from 18 to 82 years. These were prospectively recruited patients from a clinically well-characterized, homogeneous population: acute hepatitis B patients who presented with symptoms typical of acute hepatitis B such as jaundice, persistent fatigue, loss of appetite, pale stools and liver enlargement. Their ALT and AST results were significantly elevated at the time of diagnosis.

A total of 79 specimens were prospectively collected and tested using FDA-approved or licensed hepatitis B assays for six HBV serological markers (HBsAg, HBeAg, Anti-HBc IgM, Anti-HBc, Anti-HBeAg, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated 11 unique patterns:

Characterization based on single point specimens	Number of patients	HBV Reference Markers					
		HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc	Anti-HBe	Anti-HBs
Acute	23	+	–	+/-	+	+	–
Acute	8	+	+/-	+	+	+	–
Acute	1	+	–	+	+/-	–	–
Acute	35	+	+	+/-	+	–	–
Acute	4	+	+	+	+	–	+/-
Chronic	1	+	–	–	+	–	–
Chronic	3	+	+/-	–	+	+	–
Chronic	1	+	+	+/-	+	–	+
Chronic	1	+	+	+	+	+	+
Recovered	1	–	–	–	+/-	–	+
Uninterpretable	1	+	–	+	+	+	+

Based on the above classifications the IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc results were compared to Kit A. The data charts are presented in the package insert.

For the IMMULITE Anti-HBs the combined Total Positive agreement is 100.0% (79/79) with a 95% CI of 95.4 to 100.0%. There were no negative specimens therefore the Negative agreement could not be calculated.

For the IMMULITE 2000 Anti-HBs the combined Total Positive agreement is 100.0% (79/79) with a 95% CI = 95.4 to 100.0%. There were no negative specimens therefore the Negative agreement could not be calculated

Site 4: Conducted in the southern United States, this study included retrospectively collected specimens from 200 pregnant subjects. These subjects had an average age of 28 years, ranging from 17 to 41 years.

A total of 200 specimens were tested by FDA-approved hepatitis B assays for four HBV serological markers (HBsAg, Anti-HBc IgM, Anti-HBc, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated three unique patterns:

Characterization based on single point specimens	Number of subjects	HBV Reference Markers			
		HbsAg	Anti-HBc IgM	Anti-HBc	Anti-HBs
Early recovery	4	–	+/-	+	+
Early recovery	2	–	–	+	–
HBV vaccine response	42	–	–	–	+
Not previously infected	152*	–	–	–	–

*Two specimens were not tested for IMMULITE Anti HBc.

Based on the above classifications the IMMULITE Anti-HBc and IMMULITE 2000 Anti-HBc results were compared to Kit A. The data charts are presented in the package insert.

For the IMMULITE Anti-HBs the combined Total Positive agreement is 66.7% (4/6) with a 95% CI of 22.3 to 95.7%. The Negative agreement is 99.5% (191/192) with a 95% CI of 97.1 to 100.0%. The combined Total agreement is 98.5% (195/198) with a 95% CI of 95.6 to 99.7%.

For the IMMULITE 2000 Anti-HBs the combined Total Positive agreement is 66.7% (4/6) with a 95% CI of 22.3 to 95.7%. The Negative agreement is 100.0% (194/194) with a 95% CI of 98.1 to 100.0%. The combined Total agreement is 99.0% (198/200) with a 95% CI of 96.4 to 99.9%.

Site 5: In an additional study conducted at Diagnostic Products Corporation, IMMULITE Anti-HBc was compared to IMMULITE 2000 Anti-HBc. Presented below are the comparisons between IMMULITE and IMMULITE 2000 Anti-HBc on a total of 139 specimens.

IML Anti-HBc									Total
+			Ind			–			
IML 2000 Anti-HBc									
+	Ind	–	+	Ind	–	+	Ind	–	
78	0	1	0	0	0	0	0	60	139

Positive agreement = 100.0% (78/78)

95% CI = 95.4 to 100.0%

Negative agreement = 98.4% (60/61)

95% CI = 91.2 to 100.0%

Total agreement = 99.3% (138/139)

95% CI = 96.1 to 100.0%

X. CONCLUSIONS DRAWN FROM STUDIES

The data from both the non-clinical and clinical studies demonstrate acceptable performance is obtained with the IMMULITE and IMMULITE 2000 Anti-HBc assays when used as directed in the package insert.

Safety

As a diagnostic test, the anti-HBc Ag assay involves removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is removed. The misdiagnosis due to false negative or false positive results, or inappropriate use of the assay, can affect the safe use of the assay.

Benefit/Risk Analysis

The PMA studies provide reasonable assurance that the IMMULITE and IMMULITE 2000 Anti-HBs assay results may be used:

- As an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown.
- Along with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection.
- To allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis when etiology is unknown.
- As an indication of seroconversion from hepatitis B virus (HBV) infection.

The potential risks seen for these *in vitro* diagnostic tests are not unusual in the laboratory setting, and appropriate warnings for these risks are contained in the labeling and package insert instructions for these devices. Standard good laboratory practices are considered sufficient to minimize the risks to the end user.

The benefits to HBV-infected individuals tested by these devices outweigh any potential adverse event or risk to the patient or user due to device malfunction or operator error.

XI. PANEL RECOMMENDATION

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Microbiology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

XII. CDRH DECISION

The applicant's manufacturing facility was found to be in compliance with the Quality Systems Regulation (21 CFR 820).

FDA issued an approval order on July 24, 2002.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See labeling

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

Postapproval Requirements and Restrictions: See approval order.