SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: LIAISON® XL MUREX Anti-HBs
LIAISON® XL MUREX Control Anti-HBs
LIAISON® XL MUREX Anti-HBs Verifiers

Device Procode: LOM

Applicant's Name and Address: DiaSorin Inc.
1951 Northwestern Avenue
Stillwater, MN 55082

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180039

Date of FDA Notice of Approval: February 21, 2020

II. INDICATIONS FOR USE

The LIAISON XL MUREX Anti-HBs is an *in vitro* chemiluminescent immunoassay (CLIA) for the qualitative and quantitative determination of antibody to hepatitis B surface antigen (anti-HBs) in human adult and pediatric (2 – 21 years) serum and plasma (lithium and sodium heparin and K_2 EDTA) including separator tubes, on the LIAISON XL Analyzer. Assay results in conjunction with other hepatitis B virus (HBV) serological markers and clinical information may be used as an aid in the diagnosis of HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection. The assay results may be used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown.

The assay is not approved for use in screening blood, plasma or tissue donors.

The LIAISON XL MUREX Control Anti-HBs (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON XL MUREX Anti-HBs assay. The performance characteristics of LIAISON XL MUREX Control Anti-HBs have not been established for any other assays or instrument platforms.

The LIAISON XL MUREX Anti-HBs Verifiers (level 1, 2, 3, and level 4) are assayed quality control materials intended for the quantitative verification of calibration and reportable range of the LIAISON XL MUREX Anti-HBs assay. The performance

characteristics of LIAISON XL MUREX Anti-HBs Verifiers have not been established in connection with any other assay or instrument platforms.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LIAISON XL MUREX Anti-HBs labeling.

V. DEVICE DESCRIPTION

Kit Components

Reagents: The LIAISON XL MUREX Anti-HBs is an *in vitro* diagnostic device consisting of four (4) reagents provided in individual compartments within a plastic container called the Reagent Integral. The assay configuration allows performance of 100 tests.

The assay is comprised of the following components:

- 1 vial of Magnetic particles coated with HBsAg obtained in *mammalian cells* by the recombinant DNA technology (balanced *ad* and *ay* subtypes), BSA, Phosphate buffer (PBS), < 0.1% sodium azide.
- 1 vial Calibrator 1 containing Human plasma containing low levels of anti-HBs fetal calf serum, EDTA and 0.2% ProClin® 300, preservatives.
- 1 vial Calibrator 2 containing human plasma with high levels of anti-HBs fetal calf serum, EDTA. 0.2% ProClin® 300, preservatives, and an inert blue dye.
- 1 vial Conjugate containing Heat-treated Human HBsAg (balanced *ad* and *ay* subtypes) conjugated to an isoluminol derivative, BSA, phosphate buffer (PBS), EDTA, 0.2% ProClin® 300, preservatives, and an inert blue dye.

Controls: LIAISON XL MUREX Control Anti-HBs set consists of 2 levels (positive and negative) ready to use controls. Each control solution allows at least 20 tests to be performed. The control set is an additional material required to perform the test.
The controls are comprised of the following components:

- 2 vials of Negative control containing Human serum without anti-HBs antibodies with 0.2% ProClin® 300 and preservatives
- 2 vials of Positive control containing Human plasma with anti-HBs antibodies, 0.2% ProClin® 300 and preservatives

Verifiers: LIAISON XL MUREX Anti-HBs Verifier set consists of 4 levels (A-D) ready to use verifiers. Each verifier solution allows at least 20 tests to be performed. The Verifier set is an additional material required to perform the test.

The Verifiers are comprised of the following components:

- 1 vial per level A to D, containing Human plasma with 4 different levels of anti-HBs, 0.2 ProClin® and preservatives.

In addition, the following Analyzer and accessories are required for performing the LIAISON XL MUREX Anti-HBs, LIAISON XL MUREX Control Anti-HBs and the LIAISON XL MUREX Anti-HBs Verifiers:

- LIAISON XL Analyzer is a fully automated chemiluminescent analyzer, performing the complete sample processing steps of the chemiluminescent assay and interprets the results.
- LIAISON Wash/System Liquid (10x) - phosphate buffer solution, < 0.1% sodium azide.
- LIAISON XL Starter Kit – catalyst in 4% sodium hydroxide solution and 0.12% hydrogen peroxide solution

Assay Principle

The qualitative and quantitative determination of anti-HBs is a direct, sandwich chemiluminescence immunoassay (CLIA). Anti-HBs present in samples, calibrators, or controls binds to the solid phase and HBsAg conjugate, thus forming a sandwich. After the incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-HBsAg conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of anti-HBs concentration present in the sample.

Table 1: Initial Interpretation of Results for the LIAISON XL MUREX Anti-HBs is as follows:

Initial Result LIAISON XL Anti-HBs assay		
mIU/mL	**Results**	**Retest Procedure**
< 9.0	Negative	No retest is required.
9.0 < x < 11.0	Equivocal	Retest in duplicate with the LIAISON XL Anti-HBs assay.
≥ 11.0	Positive	No retest is required.

Table 2: Final Interpretation of Results for the LIAISON XL MUREX Anti-HBs is as follows:

Final Result LIAISON XL Anti-HBs assay		
Result After Retest	**Final Result**	**Clinical Interpretation of the Final Results**
Both retest results are <10 IU/mL	Negative	Anti-HBs concentration detected at < 10 mIU/mL. Individual is considered to be not immune to infection with HBV.
2 results out of 3 <10 IU/mL	Negative	Anti-HBs concentration detected at < 10 mIU/mL. Individual is considered to be not immune to infection with HBV.
2 results out of 3 ≥10 IU/mL	Positive	Anti-HBs concentration detected at ≥ 10 mIU/mL. Individual is considered to be immune to infection with HBV.
Both retest results are ≥10 IU/mL	Positive	Anti-HBs concentration detected at ≥ 10 mIU/mL. Individual is considered to be immune to infection with HBV.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection and quantitation of antibodies to hepatitis B surface antigen (Anti-HBs). There are currenty several FDA approved in vitro diagnostic tests commercially available for serological markers of hepatitis B virus (HBV) infection which, when used in conjunction with a patient's medical history, clinical examination and other laboratory findings, may be used as an aid in the diagnosis of HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection. The assay may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection in individuals prior to or following HBV vaccination or where vaccination status is unknown. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The LIAISON XL MUREX Anti-HBs assay (318220) and LIAISON XL MUREX Control Anti-HBs (318221) are essentially the same as the CE-marked LIAISON XL murex Anti-HBs assay (311220) and LIAISON XL murex Control Anti-HBs (311221) with some minor modifications to raw material manufacturing processes.

The LIAISON XL MUREX Anti-HBs assay (318220), LIAISON XL MUREX Control Anti-HBs (318221) and the LIAISON XL MUREX Anti-HBs Verifiers (318223) have not been marketed in the U.S. or any foreign country.

The CE-marked LIAISON XL murex Anti-HBs assay (311220) and LIAISON XL murex Control Anti-HBs (311221) have been marketed in multiple countries. These devices

have not been withdrawn from the market in any country for reasons relating to safety and effectiveness.

The following table includes a list all countries where the CE-marked versions have been marketed in the past year.

Table 3: Countries where CE Marked LIAISON XL murex Anti-HBs (311220) and LIAISON XL murex Control Anti-HBs (311221) is sold

Austria	Australia	Bangladesh
Belgium	Bulgaria	Brunei
Brazil	Bahamas	Switzerland
Chile	Colombia	Cyprus
Czech Republic	Germany	Denmark
Dominican Republic	Egypt	Spain
Finland	France	United Kingdom
Greece	Croatia	Hungary
Ireland	Israel	Iraq
Iran	Italy	Kuwait
Lebanon	Luxembourg	Morocco
Netherlands	Norway	Perù
Poland	Portugal	Paraguay
Romania	Saudi Arabia	Slovenia
Thailand	Tunisia	Turkey
South Africa		

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. The LIAISON XL MUREX Anti-HBs is intended for *in vitro* diagnostic use, and as a result, there is no direct adverse effect on the patient. Standard good laboratory practices are considered sufficient to minimize risks to the end user.

Failure of the product to perform as intended or human error in the use of the test may lead to a false result. Appropriate Warnings and Precautions for identified risks are contained in the labeling and assay Instructions for Use.

A false positive result in a diagnostic setting includes improper patient management, including treatment for hepatitis B with antiviral medication. Antiviral medical has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are co-infected but undiagnosed with other viruses using the same antiviral medication, such as HIV, can lead to viral resistance; however, the chance of an undiagnosed co-infection in a patient tested for hepatitis B is exceedingly unlikely.

Furthermore, a false positive result when the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown includes leading a provider to falsely believe that a patient has been vaccinated in the past and/or has current immunity when the patient does not. This could lead to a patient inappropriately missing a vaccination.

Additionally and likely more importantly, because hepatitis B surface antibody is ordered as part of a panel in clinical practice, this risk will likely be mitigated as incongruous test results would lead a clinician to either retest the patient or further investigate the etiology of hepatitis. As the performance of the assay in the clinical trial suggests that false positive results will be uncommon, the true risk of a false negative is likely minimal.

A false negative result when the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown include potentially missing and undertreating a patient who has hepatitis B infection and whose clinical picture warrants antiviral treatment. Again, because hepatitis B surface antibody is ordered as part of a panel in clinical practice, the risk of missing and undertreating a patient who has hepatitis B infection will likely be mitigated as incongruous test results would lead a clinician to either retest the patient or further investigate the etiology of hepatitis. As the performance of the assay in the clinical trial suggests that false negative results will be uncommon, the true risk of a false negative is likely minimal.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Cut-off Determination

The cut-off was established internally at DiaSorin and verified by testing a total of 113 samples (55 known negative and 58 known positive). A Receiver Operating Characteristics (ROC) analysis was performed on the results of the specimens tested. The assay's cut-off was evaluated with the observed results to demonstrate that its selection represents the best level of specificity, without compromising the sensitivity.

The cut-off value at 10.0 mIU/mL is within the optimal range determined by the ROC curve to discriminate between negative and positive results.

The established cut-off Index is 10.0 mIU/mL, with an equivocal range of ± 10% (9.00 – 11.0 mIU/mL).

2. Sensitivity / Seroconversion Panels

   The seroconversion sensitivity of the LIAISON XL MUREX Anti-HBs assay has been demonstrated by testing 10 commercial seroconversion panels in comparison to a reference anti-HBs immunoassay in terms of number of days from initial draw to first positive sample, as well as the difference between the last negative results and the first positive results.

   The LIAISON XL MUREX Anti-HBs assay yielded a positive result sooner by one blood draw or more than the comparator assay in the 10 panels.

3. Analytical Sensitivity / Dilution Study with Standard

   The sensitivity of the LIAISON XL MUREX Anti-HBs assay was evaluated by preparing serial dilutions of the WHO Second International Standard for anti-hepatitis B surface antigen (anti-HBs) immunoglobulin, human NIBSC code 07/164 in serum and plasma negative anti-HBs.

   Dilutions were tested in five (5) replicates on one (1) kit lot and on one (1) LIAISON XL Analyzer. The LIAISON XL MUREX Anti-HBs assay demostrated linearity and accuracy between 3 and 500 mIU/ml.

4. Endogenous Interference

   The LIAISON XL MUREX Anti-HBs assay was tested for potential interference of high levels of endogenous substances including Triglycerides (3000 mg/dL), Hemoglobin (1000 mg/dL), Bilirubin (conjugated and unconjugated 20 mg/dL), Albumin (6000 mg/dL) and Cholesterol (350 mg/dL). Ten (10) negative samples or negative pools were spiked with an IgG anti-HBs high positive sample to achieve high negative, low positive and moderate samples. Samples were tested in 26 replicates each on one (1) kit lot. No interference was observed at the levels tested.

5. Analytical Specificity (Cross-Reactivity)

   A study was conducted to evaluate the LIAISON XL MUREX Anti-HBs assay for cross-reactivity with specimens from individuals with medical conditions unrelated to HBV infection. A total of 301 samples from 28 unrelated medical conditions were tested in singlicate on one (1) kit lot of LIAISON XL MUREX Anti-HBs and on a reference Anti-HBs assay.

   Of the 301 samples, no evidence of cross-reactivity was observed. The results of each potential cross-reactant are shown in in table below.

Table 4: Summary of Cross-Reactivity Testing

		N° of observed negative results	
Potential cross reactant	**N° of expected negative samples**	**LIAISON XL MUREX Anti HBs**	**Reference Method**
Anti-nuclear antibodies (ANA)	10	10	10
Auto-immune hepatitis	10	10	10
C. trachomatis	11	11	11
CMV (anti-CMV IgG or IgM positive)	11	11	11
EBV (IgM positive)	11	11	11
Fatty liver disease	11	11	11
HAMA	11	11	11
Hemodialysis patient	11	11	11
Hepatitis A Virus (IgM positive)	11	11	11
Hepatitis C Virus (anti-HCV)	11	11	11
Hepatocellular carcinoma	11	11	11
HIV-1 (anti-HIV-1 positive)	11	11	11
HIV-2 (anti-HIV-2 positive)	11	11	11
HSV (anti-HSV IgG or IgM positive)	11	11	11
HTLV-1/2 (anti-HTLV positive)	11	11	11
IgG monoclonal gammopathy	11	11	11
IgM monoclonal gammopathy	10	10	10
Influenza vaccine recipients	11	11	11
Multiparous pregnancies	10	10	10
Multiple myeloma	11	11	11
Multiple transfusion recipients	10	10	10
N. gonorrhoea	11	11	11
Pregnancy 1st trimester	10	10	10
Pregnancy 2nd trimester	10	10	10
Pregnancy 3rd trimester	11	11	11
Rheumatoid Factor	11	11	11
T. pallidum **(anti-*T. pallidum* IgG and/or IgM positive)**	11	11	11
T.cruzi **(anti-*T. cruzi* positive)**	11	11	11

6. Sample Equivalence/Matrix Effect

Twenty-five (25) paired sets of matched serum (with and without gel SST) and plasma (lithium and sodium heparin and K_2EDTA) were tested to determine if these sample types provide equivalent results on the LIAISON XL MUREX Anti-HBs assay. Each sample was divided into three aliquots. Two sets of aliquots were spiked with an anti-HBs high positive sample to achieve two (2) levels of samples: high negative and low positive samples. The third set of aliquots was un-spiked to serve as control samples. The results of the negative and low positive samples did not change the classification of the expected result.

The results obtained on the serum-plasma paired samples indicate that there is equivalence among serum (with and without Gel SST), K_2-EDTA, Lithium Heparin and Sodium Heparin plasma, as indicate in the table below:

Sample Type	Slope	Intercept
Serum with Gel separator	0.987	0.138
K2-EDTA	0.971	-0.036
Lithium Heparin	1.023	-0.150
Sodium Heparin	0.998	-0.099

7. Carry-Over Study

The LIAISON XL Analyzer uses disposable tips for sample pipetting. A carry-over study was performed to evaluate the extent of carryover and the associated residual risk for signal carryover in the instrument's measuring cell as the result of a high signal-generating sample.

Two samples were used for this evaluation: one (1) anti-HBs negative human serum sample and one (1) human positive sample/pool with a high level of anti-HBs analyte. The samples were tested in singlicate in five (5) runs in the following sequence: High Pos, Neg, High Pos, Neg, High Pos, Neg, High Pos, Neg, High Pos, Neg.

All acceptance criteria were met, demonstrating that no significant amount of analyte is carried over from one sample reaction into the subsequent sample reactions.

8. Stability Studies

Sample Stability

Studies were performed to determine the storage stability of patient serum and plasma samples at storage temperatures of 2-8°C, room temperature (RT), -20 °C. A multiple freeze/thaw (F/T) study was also performed.

Serum and plasma samples tested contained Anti-HBs analyte levels of negative, high negative and low positive.

- 2-8 °C study – samples were tested unstressed (T=0), and again after 1, 2, 3, 4, 5, 7 and 8 days of storage at 2-8°C for 24 hours per day.
- room temperature study (RT) - samples were tested immediately after preparation and again after 1, 2, 3, 4, and 5 days of storage at RT for 24 hours each day.
- -20 °C study – samples were tested unstressed (T=0) and stored at -20 °C or lower for 1, 3, and 4 months.
- Freeze/Thaw (F/T) study – samples were tested unstressed (T=0) and after 1, 2, 3, 4, 5, 6, and 7 F/T cycles. Samples were frozen for 12-24 hours at -20°C or lower and thawed at room temperature.

The results of the studies indicate serum and plasma samples are stable for:

	Sample Stability Claims			
Sample Matrix	**Number of Freeze and Thaw Cycles**	**Storage at 2-8°C**	**Storage at -20°C**	**Storage at Room Temperature**
Serum	6	7 days	3 months	1 day
Plasma	1	7 days	3 months	1 day

Reagent Stability

Real-Time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON XL MUREX Anti-HBs assay. Three (3) lots of LIAISON XL MUREX Anti-HBs were stored at the recommended storage temperature of 2-8°C throughout the study. Performance was assessed against clinically relevant acceptance criteria using three (3) lots LIAISON XL MUREX Control Anti-HBs (positive and negative) and an internal stability panel consisting of eight (8) samples. Study results demonstrate that reagents are stable and continue to meet acceptance criteria ten (10) months after the date of manufacture for the LIAISON XL MUREX Anti-HBs.

Reagent On-Board

Stability studies were conducted to determine the length of time the LIAISON XL MUREX Anti-HBs Reagent Integral can be stored on-board the LIAISON XL Analyzer in the refrigerated area once opened.

One (1) lot of the LIAISON XL MUREX Anti-HBs assay was stored on-board the LIAISON XL Analyzer throughout the 13 weeks of the study. The LIAISON XL MUREX Control Anti-HBs (negative and positive) along with the internal stability panel were tested in duplicate at one (1) week intervals up to the 13 weeks.

The LIAISON XL MUREX Anti-HBs assay is stable on-board the LIAISON XL Analyzer for 6 weeks.

Reagent Open Use

The aim of this study was to assess the open use stability of the LIAISON XL MUREX Anti-HBs kit reagents by simulating normal conditions of use as specified in the instruction for use.

Testing of samples was performed in duplicate, on one (1) lot of LIAISON XL MUREX Anti-HBs and one (1) lot of LIAISON XL MUREX Control Anti-HBs. Results were calculated using the initial (time zero) assay calibration.

The opened Reagent Integral was then removed from the XL Analyzer and stored at 2-8 °C. Kit performance using the opened Reagent Integral was evaluated weekly up to 13 weeks.

The Reagent Integral is stable after opening for 6 weeks when stored at 2-8 °C.

Temperature Stress/Reagent Transport Study

The transport simulation tests were performed in order to verify that kit reagents maintain their properties during the shipment and delivery conditions to the customer. After being subjected to simulated stress conditions, testing was performed on 1 lot of LIAISON XL MUREX Anti-HBs at midlife and will be tested at expiration.

All testing performed meets acceptance criteria under various simulated transport conditions.

Calibrator Stability

The LIAISON XL MUREX Anti-HBs calibrators are included on the Reagent Integral. All studies for the Reagent Integral are applicable to the 2 levels of calibrators provided.

Calibration Interval Stability

The aim of this study was to assess stability of the product calibration by simulating normal condition of use as specified in the instruction for use.

A calibration was performed at time 0 and the Reagent Integral was stored on board the analyzer for the duration of the study. Kit performance was evaluated weekly up to nine (9) weeks by testing the stability panel and LIAISON XL MUREX Control Anti-HBs on one (1) lot of LIAISON XL MUREX Anti-HBs reagents. Results were generated using the initial (time zero) assay calibration and performance was assessed against clinically relevant acceptance criteria.

Results demonstrate that the LIAISON XL MUREX Anti-HBs calibration is stable for six (6) weeks.

Control stability

Real-time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON XL MUREX Control Anti-HBs and the LIAISON XL MUREX Anti-HBs Verifiers. Three lots of LIAISON XL MUREX Control Anti-HBs were stored at the recommended storage temperature of 2-8°C throughout the study.

Current results demonstrate that the positive and negative controls are stable and continue to meet acceptance criteria at eighteen (18) months.

Open use

The aim of this study was to assess stability of the opened Control vials by simulating normal conditions of use, as specified in the instruction for use. Testing was performed in duplicate, on one lot of LIAISON XL MUREX Control Anti-HBs.

LIAISON XL MUREX Control Anti-HBs (negative and positive) were within their established ranges and were assessed against clinically relevant acceptance criteria.

The LIAISON XL MUREX Control Anti-HBs (negative and positive) are stable for 6 weeks after opening when stored at 2-8 °C between uses.

Temperature Stress/Reagent Transport Study

The transport simulation tests were performed in order to ensure that kit Controls maintain their properties during the shipment and delivery conditions to the customer. After being subjected to simulated stress conditions testing was performed on 1 lot of LIAISON XL MUREX Control Anti-HBs.

All testing performed meets acceptance criteria under various simulated transport conditions.

9. Precision

Internal 20 Days

A precision/reproducibility study was carried out over a period of twenty (20) days on the LIAISON XL MUREX Anti-HBs assay using the LIAISON XL Analyzer. The CLSI document EP05-A3 was consulted in the preparation of the testing protocol. The testing was performed internally at DiaSorin S.p.A.

A coded panel of eight (8) serum-based samples consisting of 1 Negative, 1 High Negative, 1 Low Positive, 1 Moderate Positive and 4 Positive along with 3 lots of the LIAISON XL MUREX Control Anti-HBs (neg and pos) and 3 lots of the LIAISON XL MUREX Anti-HBs Verifiers were tested in 2 replicates per run, 2 runs per day for 20 days using 3 different LIAISON XL MUREX Anti-HBs assay reagents and spanning at least 2 calibration cycles.

The Repeatability of the combined 3 lots of LIAISON XL MUREX Anti-HBs ranged from 1.3% to 3.1%. The with-in Laboratory %CV of the combined 3 lots of LIAISON XL MUREX Anti-HBsc ranged from 4.2% to 15.1%. The results are shown below.

Table 5: Summary of Precision Study

LIAISON XL MUREX Anti-HBs Assay All 3 Lots Combined												
Sample ID	**N**	**Mean**	**Repeatability**		**Between-Run**		**Between-Day**		**Between-Lot**		**Within Laboratory**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Ctrl Neg #RS-764	240	*977	32.198	3.3%	7.269	0.7%	24.653	2.5%	20.068	2.1%	45.826	4.7%
Ctrl Neg #RS-765	240	*940	27.365	2.9%	13.132	1.4%	18.266	1.9%	17.476	1.9%	39.501	4.2%
Ctrl Neg #RS-766	240	*941	25.578	2.7%	17.607	1.9%	19.764	2.1%	20.353	2.2%	42.061	4.5%
Ctrl Pos #RS-767	240	51.9	0.825	1.6%	0.905	1.7%	0.694	1.3%	5.428	10.5%	5.608	10.8%
Ctrl Pos #RS-768	240	56.4	0.908	1.6%	1.012	1.8%	0.641	1.1%	4.215	7.5%	4.475	7.9%
Ctrl Pos #RS-769	240	53.7	0.890	1.7%	1.169	2.2%	0.578	1.1%	3.967	7.4%	4.269	8.0%
Cal Ver #RS-784 A	240	7.56	0.236	3.1%	0.154	2.0%	0.181	2.4%	0.95	12.6%	1.007	13.3%
Cal Ver #RS-784 B	240	20.1	0.396	2.0%	0.248	1.2%	0.364	1.8%	2.47	12.3%	2.54	12.6%
Cal Ver #RS-784 C	240	72.6	1.022	1.4%	0.681	0.9%	0.857	1.2%	6.809	9.4%	6.972	9.6%
Cal Ver #RS-784 D	240	237	2.973	1.3%	3.572	1.5%	2.681	1.1%	27.599	11.6%	28.116	11.9%
Cal Ver #RS-785 A	240	6.94	0.214	3.1%	0.103	1.5%	0.146	2.1%	0.658	9.5%	0.715	10.3%
Cal Ver #RS-785 B	240	18.3	0.412	2.3%	0.339	1.9%	0.375	2.1%	1.662	9.1%	1.786	9.8%
Cal Ver #RS-785 C	240	75.1	0.870	1.2%	1.042	1.4%	0.885	1.2%	4.376	5.8%	4.666	6.2%
Cal Ver #RS-785 D	240	238	3.747	1.6%	2.507	1.1%	3.324	1.4%	19.32	8.1%	20.116	8.5%
Cal Ver #RS-786 A	240	7.15	0.223	3.1%	0.080	1.1%	0.203	2.8%	0.7	9.8%	0.767	10.7%
Cal Ver #RS-786 B	240	19.4	0.371	1.9%	0.371	1.9%	0.289	1.5%	1.736	8.9%	1.836	9.5%
Cal Ver #RS-786 C	240	77.3	1.038	1.3%	0.935	1.2%	1.122	1.5%	5.436	7.0%	5.723	7.4%
Cal Ver #RS-786 D	240	251	4.106	1.6%	2.782	1.1%	3.584	1.4%	23.625	9.4%	24.404	9.7%
AHBS-1-U1	240	*1024	27.177	2.7%	18.492	1.8%	18.060	1.8%	22.522	2.2%	43.749	4.3%
AHBS-1-U2	240	7.32	0.205	2.8%	0.124	1.7%	0.135	1.8%	1.116	15.3%	1.149	15.7%
AHBS-1-U3	240	16.9	0.386	2.3%	0.618	3.7%	0.000	0.0%	1.841	10.9%	1.98	11.7%
AHBS-1-U4	240	26.9	0.457	1.7%	0.405	1.5%	0.556	2.1%	3.967	14.8%	4.052	15.1%
AHBS-1-U5	240	35.2	0.608	1.7%	0.675	1.9%	0.313	0.9%	2.234	6.4%	2.432	6.9%
AHBS-1-U6	240	76	1.385	1.8%	0.410	0.5%	1.062	1.4%	4.744	6.2%	5.071	6.7%
AHBS-1-U7	240	122	1.770	1.4%	1.288	1.1%	1.693	1.4%	14.523	11.9%	14.784	12.1%
AHBS-1-U8	240	289	4.745	1.6%	5.408	1.9%	3.250	1.1%	38.677	13.4%	39.475	13.6%

External Precision 5-day Study

A five (5) day precision/reproducibility study was conducted at two (2) external laboratories and at DiaSorin Inc. to verify the precision of the LIAISON® XL MUREX Anti-HBs assay. The CLSI document EP15-A3 was consulted in the preparation of the testing protocol. The coded panel, comprised of eight (8) frozen serum samples was the same panel used in the 20-day precision study.

The precision panel was tested at all three (3) sites on the LIAISON® XL Analyzer using six (6) replicates per run in one (1) run per day for five (5) operating days with multiple technicians performing the testing.

Table 6: Summary of Reproducibility Study

LIAISON XL MUREX Anti-HBs Assay All 3 Lots Combined												
Sample ID	**N**	**Mean**	**Repeatability**		**Between-Day/Run**		**Within Laboratory Precision**		**Between-sites/Lot**		**Reproducibility**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Ctrl Neg (All 3 lots)	90	780.611	28.577	3.7%	13.741	1.8%	31.710	4.1%	51.133	6.6%	60.167	7.7%
Ctrl Pos (All 3 lots)	90	53.777	1.313	2.4%	0.811	1.5%	1.543	2.9%	1.862	3.5%	2.418	4.5%
Cal Ver A (All 3 lots)	90	7.278	0.217	3.0%	0.082	1.1%	0.232	3.2%	0.227	3.1%	0.325	4.5%
Cal Ver B (All 3 lots)	90	19.269	0.527	2.7%	0.279	1.4%	0.596	3.1%	1.044	5.4%	1.202	6.2%
Cal Ver C (All 3 lots)	90	74.560	1.345	1.8%	1.253	1.7%	1.838	2.5%	1.200	1.6%	2.195	2.9%
Cal Ver D (All 3 lots)	90	242.422	4.881	2.0%	3.828	1.6%	6.203	2.6%	13.707	5.7%	15.045	6.2%
AHBS-1-U1	90	847.011	22.506	2.7%	14.415	1.7%	26.727	3.2%	54.888	6.5%	61.049	7.2%
AHBS-1-U2	90	7.119	0.260	3.6%	0.248	3.5%	0.359	5.0%	0.264	3.7%	0.445	6.3%
AHBS-1-U3	90	16.532	0.531	3.2%	1.198	7.2%	1.311	7.9%	0.892	5.4%	1.585	9.6%
AHBS-1-U4	90	25.670	1.265	4.9%	2.254	8.8%	2.585	10.1%	0.981	3.8%	2.765	10.8%
AHBS-1-U5	90	33.063	1.140	3.4%	2.018	6.1%	2.317	7.0%	1.000	3.0%	2.524	7.6%
AHBS-1-U6	90	72.782	2.392	3.3%	4.628	6.4%	5.210	7.2%	2.950	4.1%	5.987	8.2%
AHBS-1-U7	90	113.361	4.672	4.1%	8.672	7.7%	9.850	8.7%	8.769	7.7%	13.188	11.6%
AHBS-1-U8	90	282.244	8.281	2.9%	10.400	3.7%	13.294	4.7%	20.494	7.3%	24.429	8.7%

*Precision calculations are based on signal (RLU)

10. Pediatric and Adult Sample Equivalency

Pediatric samples were tested to determine if these types of samples provide equivalent results to adult human serum.

A total of thirty (30) negative pediatric patient samples were used for this study. The pediatric samples encompassed the age range of two (2) months to twenty-one (21) years. Ten (10) pediatric samples were spiked with an anti-HBs high positive sample to obtain high negative samples. Ten (10) pediatric samples were spiked with an IgG anti-HBs high positive sample to obtain low positive samples. Ten (10) pediatric samples were spiked with an anti-HBs high positive sample to obtain moderate positive samples. Adult negative pool samples were used as controls and were spiked with an anti-HBs high positive sample to achieve the same three (3) levels of samples: high negative, low positive and moderate positive samples.

The samples were tested in duplicate, with the LIAISON XL MUREX Anti-HBs assay. Percent (%) recovery of the analyte from the pediatric and adult blood was calculated for each sample.

All acceptance criteria were met demonstrating acceptable performance of pediatric samples. It can be concluded that pediatric samples react in the same way as the adult samples and are acceptable for use in the LIAISON XL MUREX Anti-HBs assay.

B. Animal Studies

Not Applicable.

C. Additional Studies

Not Applicable.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the detection and quantitation of antibodies to hepatitis-B surface antigen with the LIAISON XL MUREX Anti-HBs using samples that would routinely be tested for hepatitis in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

A multi-site clinical agreement study was conducted to evaluate the clinical performance of the LIAISON XL MUREX Anti-HBs assay on samples that would routinely be tested for hepatitis and samples that were selected from individuals that were diagnosed with acute or chronic Hepatitis B infection.

The clinical agreement study involved the testing of 3,082 samples on six (6) FDA approved reference assays, each detecting a unique serological marker (HBsAg, HBeAg, Anti-HBs, Anti-HBc, Anti-HBc IgM, and Anti-HBe) in order determine the HBV classification for each of the samples tested.

The samples were collected from 6 different countries: Russia, Colombia, Cameroon, Ghana, Nigeria, and the United States. The U.S. samples were from multiple states including Ohio, Pennsylvania, Indiana, Florida, California, Texas, New Jersey, Tennessee, Massachusetts, and Puerto Rico.

The prospective (unselected) subjects were defined as follows:

- Pediatric and adult male (38.2%), female (61.7%) and unknown gender (0.1%) subjects at risk for hepatitis due to medical conditions (dialysis, transplantation), occupation, lifestyle, behavior or a known exposure event.
- Subjects showing signs or symptoms and individuals living in an area with a higher probability of HBV infection.
- The demographic breakdown of the prospective population was as follows: American Indian/Alaskan Native (0.1%), Asian (0.8%), Black/African American (31.2%), Caucasian (62.5%), Other (5.2%), and Unknown (0.2%) with an age range of 2 - 98 years of age.

The retrospective (selected/archived) samples were from male (69.5%), female (21.9%), and unknown gender (8.6%) subjects diagnosed with acute and/or chronic Hepatitis having an age range of 17 - 67 years of age from the following ethnicities: Asian (1.6%), Black/African American (23.8%), Caucasian (73%), other (1.2%) and 0.4% Unknown.

The distribution of LIAISON XL MUREX Anti-HBs reactive and non-reactive results by age and gender of the overall prospective population are presented below.

Table 7: Demographic Summary of the Prospective Population

Age Range	Gender	LIAISON XL MUREX				Total
		+		-		
		n	%	n	%	
0-9	F	5	100.0%	0	0.0%	5
	M	3	30.0%	7	70.0%	10
10-19	F	21	52.5%	19	47.5%	40
	M	8	53.3%	7	46.7%	15
20-29	F	251	64.5%	138	35.5%	389
	M	130	55.8%	103	44.2%	233
30-39	F	253	53.4%	221	46.6%	474
	M	111	49.6%	113	50.4%	224
40-49	F	121	41.7%	169	58.3%	290
	M	68	33.8%	133	66.2%	201
50-59	F	106	45.7%	126	54.3%	232
	M	70	37.8%	115	62.2%	185
60-69	F	62	39.2%	96	60.8%	158
	M	50	46.3%	58	53.7%	108

Age Range	Gender	LIAISON XL MUREX				
		+		-		Total
		n	%	n	%	
70-79	F	15	32.6%	31	67.4%	46
	M	16	41.0%	23	59.0%	39
80-89	F	8	57.1%	6	42.9%	14
	M	2	28.6%	5	71.4%	7
90-98	F	4	100.0%	0	0%	4
	M	0	0%	0	0%	0
Unk	F	1	100.0%	0	0%	1
	M	1	100.0%	0	0%	1
Total		**1306**	**48.8%**	**1370**	**51.2%**	**2676**

Hepatitis B Status Classification

Hepatitis B Status Classification was based on testing all the samples with FDA approved HBV assays for HBsAg, HBeAg, Anti-HBc, Anti-HBc IgM, Anti-HBe and Anti-HBs. HBV classification for the prospective and retrospective specimens is presented below.

Table 8: Hepatitis B Status Classification

HBV Classification	HBsAg	HBeAg	Total Anti-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
Acute	R	NR	NR	NR	NR	NR	12	97
Acute	R	R	NR	NR	NR	NR		
Acute	R	R	R	R	NR	NR		
Acute	R	R	R	R	R	NR		
Acute	R	R	R	R	EQV	NR		
Acute	R	NR	R	EQV	R	NR		
Acute	R	NR	R	R	EQV	NR		
Acute	R	EQV	R	R	R	NR		
Acute	R	NR	R	R	NR	NR		
Acute	R	R	R	EQV	NR	NR		
Acute	R	R	R	R	NR	R		
Acute	R	R	R	R	EQV	R		
Acute	R	R	R	R	R	EQV		
Late Acute	R	NR	R	R	R	NR	2	32
Late Acute	R	NR	R	R	R	R		
Chronic	R	NR	NR	NR	R	NR	76	68

HBV Classification	HBsAg	HBeAg	Total Anti-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
Chronic	R	NR	R	NR	NR	R		
Chronic	R	R	R	NR	NR	R		
Chronic	R	R	R	NR	NR	NR		
Chronic	R	EQV	R	NR	NR	NR		
Chronic	R	NR	R	NR	R	NR		
Chronic	R	NR	R	NR	NR	NR		
Chronic	R	NR	R	NR	R	R		
Chronic	R	EQV	R	NR	NR	NR		
Early Recovery	NR	NR	R	R	R	NR		
Early Recovery	NR	NR	R	EQV	R	R		
Early Recovery	NR	NR	R	R	NR	NR		
Early Recovery	NR	NR	R	NR	R	NR	48	9
Early Recovery	NR	NR	R	NR	NR	NR		
Early Recovery	NR	NR	R	R	NR	R		
Early Recovery	NR	NR	R	R	R	R		
Recovery	NR	NR	R	NR	R	R		
Recovery	NR	NR	NR	NR	R	R	131	36
Recovery	NR	NR	R	NR	EQV	R		
Immune Due to Natural Infection	NR	NR	R	NR	NR	R	104	3
Immune Due to Natural Infection	NR	NR	R	NR	NR	EQV		
HBV Vaccine Response	NR	NR	NR	NR	NR	R	1144	8
HBV Vaccine Response	NR	NR	NR	NR	NR	EQV		
Not Previously Infected	NR	NR	NR	NR	NR	NR	1302	1

HBV Classification	HBsAg	HBeAg	Total Anti-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
Not Interpretable	NR	NR	NR	NR	R	NR	7	2
Not Interpretable	NR	NR	NR	R	NR	NR		
Not Interpretable	NR	R	NR	NR	NR	NR		
Not Interpretable	NR	R	NR	NR	NR	R		
Not Interpretable	NR	R	R	R	NR	EQV		
Not Interpretable	NR	R	R	R	NR	R		
Not Interpretable	R	NR	NR	NR	NR	R		
Total							**2826**	**256**

Clinical Agreement Study Analysis

Comparison results of the LIAISON XL MUREX Anti-HBs to the reference anti-HBs assay are presented with Negative and Positive percent (%) agreement and 95% confidence intervals for combined prospective and retrospective specimens for each of the HBV Classification categories. In addition, Pediatric Cumulative (prospective and retrospective) Clinical Agreement results are presented below.

Table 9: Cumulative Clinical Agreement (Combined Prospective & Retrospective)

HBV Classification	Reference Anti-HBs assay						Total
	Reactive		Eqv		Non reactive		
	LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		
	Positive	Negative	Positive	Negative	Positive	Negative	
Acute	2	2	0	1	0	104	109
Late Acute	1	1	0	0	0	32	34
Chronic	3	1	0	0	1	139	144
Early Recovery	8	0	0	0	9	40	57
Recovery	163	4	0	0	0	0	167
Immune Due to Natural Infection	103	0	3	1	0	0	107

HBV Classification	Reference Anti-HBs assay						Total
	Reactive		Eqv		Non reactive		
	LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		
	Positive	Negative	Positive	Negative	Positive	Negative	
HBV Vaccine Response	1106	14	16	16	0	0	1152
Not Previously Infected	0	0	0	0	29	1274	1303
Not Interpretable	3	0	0	1	0	5	9
Total	**1389**	**22**	**19**	**19**	**39**	**1594**	**3082**

Table 10: Cumulative Clinical Agreement (Combined Prospective & Retrospective)

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	2/5 (40.0%) 95% CI: 11.8% to 76.9%	104/104 (100.0%) 95% CI: 96.4% to 100.0%
Late Acute	1/2 (50.0%) 95% CI: 9.5% to 90.5%	32/32 (100.0%) 95% CI: 89.3% to 100.0%
Chronic	3/4 (75.0%) 95% CI: 30.1% to 95.4%	139/140 (99.3%) 95% CI: 96.1% to 99.9%
Early Recovery	8/8 (100.0%) 95% CI: 67.6% to 100.0%	40/49 (81.6%) 95% CI: 68.6% to 90.0%
Recovery	163/167 (97.6%) 95% CI: 94.0% to 99.1%	N/A
Immune Due to Natural Infection	103/104 (99.0%) 95% CI: 94.8% to 99.8%	0/3 (0.0%) 95% CI: 0.0% to 56.2%
HBV Vaccine Response	1106/1136 (97.4%) 95% CI: 96.3% to 98.1%	0/16 (0.0%) 95% CI: 0.0% to 19.4%
Not Previously Infected	N/A	1274/1303 (97.8%) 95% CI: 96.8% to 98.4%
Not Interpretable	3/4 (75.0%) 95% CI: 30.1% to 95.4%	5/5 (100.0%) 95% CI: 56.6% to 100.0%
Total	1389/1430 (97.1%) 95% CI: 96.1% to 97.9%	1594/1652 (96.5%) 95% CI: 95.5% to 97.3%

Clinical Endpoints

With regard to safety, as an *in vitro* diagnostic test, the LIAISON XL MUREX Anti-HBs test involves taking a sample of plasma or serum from a patient. The test, therefore, presents

no more safety hazard to an individual being tested than other tests where blood samples are drawn. Safety issues regarding false positive and negative test results are discussed in section VIII.

With regard to effectiveness, the clinical performance of the LIAISON XL MUREX Anti-HBs was evaluated versus a FDA approved anti-HBs test for patients at risk for infection with hepatitis B and for patients with signs and symptoms of hepatitis.

With regard to success/failure criteria, the assay performed well with a positive percent agreement (PPA) of 97.1% a negative percent agreement (NPA) of 96.5% among subjects in various stages of HBV infection, a PPA of 97.4% in HBV-vaccinated subjects, a PPA of 99.0% in subjects immune due to natural infection, and an NPA of 97.8% among subjects not previously infected with HBV.

B. Accountability of PMA Cohort

The clinical agreement study involved the testing of 3,082 samples on six (6) FDA approved reference assays, each detecting a unique serological marker (HBsAg, HBeAg, Anti-HBs, Anti-HBc, Anti-HBc IgM, and Anti-HBe in order determine the HBV classification for each of the samples tested.

The samples were collected from 6 different countries: Russia, Colombia, Cameroon, Ghana, Nigeria, and the United States. The U.S. samples were from multiple states including Ohio, Pennsylvania, Indiana, Florida, California, Texas, New Jersey, Tennessee, Massachusetts, and Puerto Rico.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an anti-HBs detection study performed in the US.

The prospective (unselected) subjects were defined as follows:

- Pediatric and adult male (38.2%), female (61.6%) and unknown gender (0.2%) subjects at risk for hepatitis due to medical conditions (dialysis, transplantation), occupation, lifestyle, behavior or a known exposure event.
- Subjects showing signs or symptoms and individuals living in an area with a higher probability of HBV infection.
- The demographic breakdown of the prospective population was as follows: American Indian/Alaskan Native (0.1%), Asian (0.8%), Black/African American (31.2%), Caucasian (62.5%), Other (5.2%), and Unknown (0.2%) with an age range of 2 - 98 years of age.

The retrospective (selected/archived) samples were from male (69.5%), female (21.9%), and unknown gender (8.6%) subjects diagnosed with Acute and/or Chronic Hepatitis having an age range of 17 - 67 years of age from the following ethnicities: Asian (1.6%),

Black/African American (23.8%), Caucasian (73%), other (1.2%) and 0.4% Unknown. The table below shows the demographic distribution of the cohort.

Table11: Prospective and Retrospective Demographic Summary

	Adult				Pediatric (2-21)				Unknown Age			
	Prospective		Retrospective		Prospective		Retrospective		Prospective		Retrospective	
Race	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
American Indian/ Alaskan Native	2	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Asian	21	0.8%	4	1.9%	3	1.9%	0	0.0%	0	0.0%	0	0.0%
Black/ African American	832	31.2%	57	27.7%	64	39.8%	4	13.8%	0	0.0%	0	0.0%
Native Hawaiian or Other Pacific Islander	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
White	1664	62.5%	141	68.4%	89	55.3%	25	86.2%	2	100.0%	21	100.0%
Unknown	6	0.2%	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other	138	5.2%	3	1.5%	5	3.1%	0	0.0%	0	0.0%	0	0.0%
Total	**2663**	**100.0%**	**206**	**100.0%**	**161**	**100.0%**	**29**	**100.0%**	**2**	**100.0%**	**21**	**100.0%**

D. Safety and Effectiveness Results

1. Safety Results

With regard to safety, as an *in vitro* diagnostic test, the LIAISON XL MUREX Anti-HBs test involves taking a sample of plasma or serum from a patient. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood samples are drawn.

There were no adverse effects that occurred in the PMA clinical study.

2. Effectiveness Results

The analysis of effectiveness was based on the 3,082 evaluable patients. Key effectiveness outcomes are presented in the tables below.

Table 12: Clinical Comparison for Prospectively Collected Samples

HBV Classification	Roche Anti-HBs						Total
	+		Eqv		-		
	LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		
	+	-	+	-	+	-	
Acute	0	0	0	0	0	12	12
Late Acute	0	0	0	0	0	2	2
Chronic	3	1	0	0	1	71	76
Early Recovery	5	0	0	0	8	35	48
Recovery	127	4	0	0	0	0	131
Immune Due to Natural Infection	100	0	3	1	0	0	104
HBV Vaccine Response	1099	13	16	16	0	0	1144
Not Previously Infected	0	0	0	0	29	1273	1302
Not Interpretable	1	0	0	1	0	5	7
Total	**1335**	**18**	**19**	**18**	**38**	**1398**	**2826**

Table 13: Percent Agreement for Prospectively Collected Samples

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	N/A	12/12 (100.0%) 95% CI: 75.7% to 100.0%
Late Acute	N/A	2/2 (100.0%) 95% CI: 34.2% to 100.0%
Chronic	3/4 (75.0%) 95% CI: 30.1% to 95.4%	71/72 (98.6%) 95% CI: 92.5% to 99.8%
Early Recovery	5/5 (100.0%) 95% CI: 56.6% to 100.0%	35/43 (81.4%) 95% CI: 67.4% to 90.3%
Recovery	127/131 (96.9%) 95% CI: 92.4% to 98.8%	N/A
Immune Due to Natural Infection	100/101 (99.0%) 95% CI: 94.6% to 99.8%	0/3 (0.0%) 95% CI: 0.0% to 56.2%
HBV Vaccine Response	1099/1128 (97.4%) 95% CI: 96.3% to 98.1%	0/16 (0.0%) 95% CI: 0.0% to 19.4%
Not Previously Infected	N/A	1273/1302 (97.8%) 95% CI: 96.8% to 98.4%
Not Interpretable	1/2 (50.0%) 95% CI: 9.5% to 90.5%	5/5 (100.0%) 95% CI: 56.6% to 100.0%
Total	1335/1371 (97.4%) 95% CI: 96.4% to 98.1%	1398/1455 (96.1%) 95% CI: 95.0% to 97.0%

Table 14: Clinical Comparison for Retrospectively Collected Samples

HBV Classification	Roche Anti-HBs						Total
	+		Eqv		-		
	LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		LIAISON XL MUREX Anti-HBs		
	+	-	+	-	+	-	
Acute	2	2	0	1	0	92	97
Late Acute	1	1	0	0	0	30	32
Chronic	0	0	0	0	0	68	68
Early Recovery	3	0	0	0	1	5	9
Recovery	36	0	0	0	0	0	36
Immune Due to Natural Infection	3	0	0	0	0	0	3
HBV Vaccine Response	7	1	0	0	0	0	8
Not Previously Infected	0	0	0	0	0	1	1
Not Interpretable	2	0	0	0	0	0	2
Total	**54**	**4**	**0**	**1**	**1**	**196**	**256**

Table 15: Percent Agreement for Retrospectively Collected Samples

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	2/5 (40.0%) 95% CI: 11.8% to 76.9%	92/92 (100.0%) 95% CI: 96% to 100.0%
Late Acute	1/2 (50.0%) 95% CI: 9.5% to 90.5%	30/30 (100.0%) 95% CI: 88.6% to 100.0%
Chronic	N/A	68/68 (100.0%) 95% CI: 94.7% to 100.0%
Early Recovery	3/3 (100.0%) 95% CI: 43.8% to 100.0%	5/6 (83.3%) 95% CI: 43.6% to 97.0%
Recovery	36/36 (100.0%) 95% CI: 90.4% to 100.0%	N/A
Immune Due to Natural Infection	3/3 (100.0%) 95% CI: 43.8% to 100.0%	N/A
HBV Vaccine Response	7/8 (87.5%) 95% CI: 52.9% to 97.8%	N/A
Not Previously Infected	N/A	1/1 (100.0%) 95% CI: 20.7% to 100.0%
Not Interpretable	2/2 (100.0%) 95% CI: 34.2% to 100.0%	N/A
Total	54/59 (91.5%) 95% CI: 81.6% to 96.8%	196/197 (99.5%) 95% CI: 97.8% to 99.9%

Table 16: Pediatric- Percent Agreement for Prospectively Collected Samples

HBV Classification	Prospective Age in Years	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
Late Acute	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
Chronic	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	4/5 (80.0%) 37.6%-96.4%
Early Recovery	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
Recovery	2-12	NA	NA
	13-18	NA	NA
	19-21	4/5 (80.0%) 37.6%-96.4%	NA
Immune Due to Natural Infection	2-12	NA	NA
	13-18	2/2 (100.0%) 34.2%-100.0%	NA
	19-21	1/1 (100.0%) 20.7%-100.0%	NA
HBV Vaccine Response	2-12	16/16 (100.0%) 80.6%-100.0%	0/1 (0.0%) 0.0%-79.3%
	13-18	14/16 (87.5%) 64.0%-96.5%	NA
	19-21	26/27 (96.3%) 81.7%-99.3%	0/2 (0.0%) 0.0%-65.8%
Not Previously Infected	2-12	NA	12/12 (100.0%) 75.7%-100.0%
	13-18	NA	11/13 (84.6%) 57.8%-95.7%
	19-21	NA	55/59 (93.2%) 83.8%-97.3%
Not Interpretable	2-12	NA	1/1 (100.0%) 20.7%-100.0%
	13-18	NA	NA
	19-21	NA	1/1 (100.0%) 20.7%-100.0%

Table 17: Pediatric- Percent Agreement for Retrospectively Collected Samples

HBV Classification	Retrospective Age in Years	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	2-12	NA	NA
	13-18	NA	6/6 (100.0%) 61.0%-100.0%
	19-21	NA	14/14 (100.0%) 78.5%-100.0%
Late Acute	2-12	NA	NA
	13-18	NA	3/3 (100.0%) 43.8%-100.0%
	19-21	NA	4/4 (100.0%) 51.0%-100.0%
Chronic	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	2/2 (100.0%) 34.2%-100.0%
Early Recovery	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	1/1 (100.0%) 20.7%-100.0%
Recovery	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
Immune Due to Natural Infection	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
HBV Vaccine Response	2-12	NA	NA
	13-18	NA	NA
	19-21	1/1 (100.0%) 20.7%-100.0%	NA
Not Previously Infected	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA
Not Interpretable	2-12	NA	NA
	13-18	NA	NA
	19-21	NA	NA

3. Subgroup Analyses

The study design enabled an assessment of assay performance by subgroup as depicted in tables above which show subjects stratified by stage of HBV infection and HBV vaccine response.

4. Pediatric Extrapolation

In this premarket application, existing clinical data from adult subjects was not leveraged to support approval of a pediatric patient population.
Samples from pediatric patients were tested in the clinical study in order to support a pediatric claim.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 3 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the LIAISON XL MUREX Anti-HBs test for the qualitative and quantitative determination of antibodies to hepatitis-B surface antigen in human serum and plasma (lithium and sodium heparin and K2 EDTA) samples including separator tubes, on the LIAISON XL Analyzer has been demonstrated in the following patient populations: adults and pediatric patients (2 – 21 years). The results of this test may be used as an aid in the diagnosis of hepatitis B virus (HBV) infection in patients with symptoms of hepatitis or who may be at risk for hepatitis B infection. The results of this test may be used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown. The positive agreement of the assay is 97.1% with a two-sided 95%

confidence interval (CI) of 96.1% - 97.1% and the negative percent agreement is 96.5% with a two-sided 95% CI of 95.5 – 97.3%.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above. Based on the results of these studies the LIAISON XL MUREX Anti-HBs assay when used according to the manufacturer's instructions can aid the physician in the diagnosis of HBV infection and in the determination of susceptibility to HBV infection. The positive agreement of the assay is 97.1% with a two-sided 95% confidence interval (CI) of 96.1% - 97.1% and the negative percent agreement is 96.5% with a two-sided 95% CI of 95.5 – 97.3%.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the assay are the determination of susceptibility to hepatitis B virus infection before or following vaccination, or as part of a hepatitis B panel, the appropriate diagnosis and treatment of hepatitis B infection. Treatment or vaccination for appropriate patients can mitigate the sequelae of hepatitis B infection and may result in improved morbidity and mortality in these patients. Known sequelae of hepatitis B infection include continued symptoms, increases in all-cause mortality, liver disease-related complications and death, hepato-cellular carcinoma rates, and need for liver transplantation. Additionally, diagnosis and appropriate treatment or appropriate vaccination for hepatitis B infection can potentially decrease transmission and disease burden in the general population and particularly in populations at high risk for hepatitis B infection. While the performance of the LIAISON XL MUREX Anti-HBs assay in the clinical study suggests that patients will benefit from the assay, low prevalence of certain HBV classifications (namely acute infection, chronic infection, and early recovery) is a source of potential uncertainty when analyzing the prospective and retrospective samples. The wide confidence intervals for those subgroups is expected due to the biology of hepatitis B infection and is acceptable.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Risks of false positive results when the device is used as an aid in the diagnosis of hepatitis B virus (HBV)
infection in patients with symptoms of hepatitis or who may be at risk for HBV infection include improper patient management, including treatment for hepatitis B with antiviral medication. Antiviral medication has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are coinfected

but undiagnosed with other viruses that are treated with the same antiviral medication, such as HIV, can lead to viral resistance, however the chance of an undiagnosed coinfection in a patient treated for hepatitis B is unlikely.

Risks of false positive results when the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown includes leading a provider to falsely believe that a patient has been vaccinated in the past and/or has current immunity when the patient, in fact, does not. This could lead to a patient inappropriately missing a vaccination.

Risks of false negative results when the device is used as an aid in the diagnosis of HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection include potentially missing and undertreating a patient who has hepatitis B infection. Missing and under-treating a patient with hepatitis B infection whose clinical picture warrants antiviral treatment could result in the known sequelae of HBV infection and may result in high morbidity and mortality in these patients. Additionally, missing a diagnosis of hepatitis B infection will not allow for clinicians to potentially decrease transmission and disease burden in the general population, particularly in populations at high risk for hepatitis B infection.

Risks of false negative results when the device is used as an aid in the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown include unnecessary repeated vaccination for hepatitis B. Although vaccination has risks such as local reactions, administrations of extra doses of single-antigen hepatitis B vaccine is not inherently harmful. In fact, it is common practice to administer higher dose vaccinations in an accelerated schedule for patients undergoing organ transplantation, for example.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support the claimed intended use, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The probable clinical benefits outweigh the potential risks for the proposed assay considering the performance of the device in the clinical trial and the low risk and associated risk mitigations in clinical practice. The proposed assay labelling will facilitate accurate assay implementation and interpretation of results. The clinical performance observed in the prospective and retrospective clinical trial suggests that errors will be uncommon and that the assay may provide substantial benefits to

patients as an accurate and sensitive aid in the diagnosis of HBV infection when used in conjunction with other laboratory results and clinical information or for the determination of susceptibility to HBV infection in individuals prior to or following HBV vaccination or where vaccination status is unknown.

XIII. CDRH DECISION

CDRH issued an approval order on February 21, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.