SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Detection of Hepatitis B e antigen (HBeAg)

Device Trade Name: LIAISON® XL MUREX HBeAg
LIAISON® XL MUREX Control HBeAg

Device Procode: LOM

Applicant's Name and Address: DiaSorin Inc.
1951 Northwestern Avenue
Stillwater, Minnesota 55082-0285

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180048

Date of FDA Notice of Approval: August 29, 2020

II. INDICATIONS FOR USE

LIAISON® XL MUREX HBeAg
The LIAISON® XL MUREX HBeAg assay is an *in vitro* chemiluminescent immunoassay (CLIA) for the qualitative detection of hepatitis B virus (HBV) e antigen (HBeAg) in human adult and pediatric (2-21 years) serum and plasma (lithium and sodium heparin, sodium citrate and K_2 EDTA), including separator tubes, on the LIAISON® XL Analyzer. Assay results in conjunction with other laboratory results and clinical information 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 virus (HBV) infection..

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

LIAISON® XL MUREX Control HBeAg
The LIAISON® XL MUREX Control HBeAg (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON® XL MUREX HBeAg assay. The performance characteristics of LIAISON® XL MUREX Control HBeAg have not been established for any other assays 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 HBeAg labeling.

V. DEVICE DESCRIPTION

LIAISON XL MUREX HBeAg is a qualitative direct sandwich chemiluminescent immunoassay (CLIA). Antibodies to HBeAg (mouse monoclonal) are used for coating magnetic particles (solid phase) and are linked to an isoluminol antibody conjugate. During the first incubation, the antibody conjugate reacts with HBeAg present in calibrators, samples, or controls and bind to the solid phase and form 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 conjugate, is measured by a photomultiplier as relative light units (RLU) and is inversely indicative of HBeAg concentration present in calibrators, samples, or controls.

Components of the LIAISON XL MUREX HBeAg assay

All reagents are supplied ready to use.

The table below describes the components of the LIAISON XL MUREX HBeAg kit.

Table 1: Components of the LIAISON XL MUREX HBeAg

Magnetic Particles 1 vial – 2.5 mL	Magnetic particles coated with antibody to HBeAg (mouse monoclonal), BSA, phosphate buffer, < 0.1% sodium azide.
Calibrator 1 1 vial – 1.5 mL	Human serum containing low HBeAg levels (obtained in E. coli by the recombinant DNA technology), 0.2% ProClin® 300, preservatives.
Calibrator 2 1 vial – 1.5 mL	Human serum containing high HBeAg levels (obtained in E. coli by the recombinant DNA technology), TRIS buffer, 0.2% ProClin® 300, preservatives, an inert blue dye.
Conjugate 1 vial – 13.0 mL	Antibodies to HBeAg (mouse monoclonal) conjugated to an isoluminol derivative, fetal calf serum, non-specific mouse IgG, phosphate buffer, 0.2% ProClin® 300, preservatives.
Number of tests	100

LIAISON® XL MUREX Control HBeAg set consists of two (2) controls (positive and negative) that are ready to use. Each control set contains enough solution to allow for at least 20 tests. The control set is an additional material required to perform the test. The controls are used for monitoring the performance of the LIAISON® XL MUREX HBeAg assay.

The control set is additional material required to perform the test.

NEGATIVE CONTROL 2 vials – 2.3 mL each	Human serum without HBeAg with 0.2% ProClin® 300 and preservatives.
POSITIVE CONTROL 2 vials – 2.3 mL each	Human serum containing HBeAg (obtained in E. coli by the recombinant DNA technology), 0.2% ProClin® 300, preservatives

Interpretation of the Results (HBeAg):

The interpretation of results for the LIAISON® XL MUREX HBeAg is as follow:

Cutoff of 0.800 index value determines whether a sample has detectable levels of HBeAg:

- **Reactive:** Samples with HBeAg levels equal to or above an index value of 0.900 are considered Reactive and presumed positive for HBeAg.
- **Non-Reactive:** Samples with HBeAg levels below an index value of 0.700 are considered Non-reactive and presumed negative for HBeAg
- Samples with HBeAg levels ranging between an index value of 0.700 and 0.900 are considered initially equivocal. Initially equivocal samples must be retested in duplicate. Samples that are repeatedly equal to or above 0.800 (i.e. at least 2 out of 3 results) are considered Reactive and presumed positive for HBeAg. Samples that are repeatedly below 0.800 (i.e. at least 2 out of 3 results) are considered Non-reactive and presumed negative for HBeAg.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of HBeAg. There are currently several FDA approved in vitro diagnostic tests commercially available for serological markers of hepatitis B virus (HBV) infection which, when used in conjuction with a patient's medical history, clinical examination and other laboratory finding, 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 determining acute infection. 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 HBeAg assay (318150) and LIAISON® XL MUREX Control HBeAg (318151) are essentially the same as the CE-marked LIAISON® HBeAg assay (310150) and LIAISON® Control HBeAg (310111) with some minor modifications to raw material manufacturing processes.

The LIAISON® XL MUREX HBeAg assay (318150) and LIAISON® XL MUREX Control HBeAg (318151) have not been marketed in the U.S. or any foreign country. The LIAISON® HBeAg (310150) and the LIAISON® Control HBeAg (310151) 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 2: Countries Where CE-Marked Versions Have Been Marketed

Austria	Argentina	Australia
Netherlands Antilles	Bangladesh	Belgium
Bulgaria	Brunei	Brazil
Switzerland	Colombia	Czech Republic
Germany	Denmark	Dominican Republic
Algeria	Egypt	Spain
France	United Kingdom	Greece
Croatia	Israel	Iraq
Iran	Italy	South Korea
Kuwait	Lebanon	Sri Lanka
Luxembourg	Morocco	Mongolia
Mexico	Netherlands	Norway
Nepal	Peru	Poland
Portugal	Paraguay	Qatar
Romania	Saudi Arabia	Slovenia
Sweden	Thailand	Tunisia
Turkey	Vietnam	South Africa
China		

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The LIAISON® XL MUREX HBeAg 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.

The risks associated with the device, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the instrument.

Risks of a false positive test includes improper patient management, including missing the opportunity for treatment of hepatitis B with antiviral medication in a subset of patients with hepatitis B. In patients without cirrhosis, false positive tests will require a higher HBV DNA threshold (>20k units/mL) than would be required otherwise for a clinician to initiate treatment, resulting in the potential undertreatment of a patient who has hepatitis B infection and whose clinical picture would otherwise warrant antiviral

treatment. 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 tests would include improper patient management, including treatment of hepatitis B with antiviral medication. In patients without cirrhosis but with negative HBeAg and chronic hepatitis, normal liver enzymes, but HBV DNA levels >2k IU/mL, liver biopsy may be recommended with its associated risks of infection and bleeding. As the number of patients in this specific category is exceedingly small, this specific risk of a false negative HBeAg is likely minimal. In patients without cirrhosis, false negative tests will require a lower HBV DNA threshold (>2k units/mL) than would be required otherwise for a clinician to initiate treatment, resulting in treatment of a patient who has hepatitis B infection but whose clinical picture may not otherwise warrant antiviral treatment. 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.

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 106 samples (55 known negative and 51 known positive). A receiver Operating Characteristics (ROC) analysis was performed on the results of the specimens tested. The assay's cutoff 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 of 0.8 is within the optimal range determined by the ROC curve to discriminate between negative and positive results.

2. Sensitivity/Seroconversion Panels
   The seroconversion sensitivity of the LIAISON® XL MUREX HBeAg assay has been demonstrated by testing 14 commercial seroconversion panels in comparison to a reference HBeAg 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 HBeAg yielded a positive result sooner by one or more blood draws than the comparator assay in two (2) of the 14 panels and later than the reference HBeAg assay in one (1) panel.

3. Analytical Sensitivity/Dilution Study with Standard
   The sensitivity of the LIAISON® XL MUREX HBeAg was evaluated by preparing serial dilutions of the HBe Reference antigen 82 (HBeAg, Paul-Ehrlich-Institute Germany).

   Dilutions were tested in triplicate on three reagent lots, using one lot of kit controls, across four LIAISON® XL Analyzers.

   The cutoff concentration corresponds to 0.065 PEI U/mL.

4. Analytical Specificity (Cross-Reactivity)
   A study was conducted for the LIAISON® XL MUREX HBeAg to evaluate potential interference from other conditions that may result from atypical immune system activity and for potential cross-reactivity with specimens from individuals with various medical conditions unrelated to HBV infection. A total of 305 samples from 28 unrelated medical conditions were tested in singlicate on one kit lot of LIAISON® XL MUREX HBeAg and on a reference HBeAg assay.

   Of the 305 samples, one (1) cross-reactivity with CMV antibodies was observed. The results of each potential cross reactant are shown in table below.

Table 3: Summary of Cross-Reactivity Study

Organism/Condition	**N**	**Comparator HBeAg assay**	**LIAISON® XL MUREX HBeAg**	
			Non-reactive	**Reactive**
Anti-nuclear antibodies (ANA)	10	Negative	10	0
Auto-immune hepatitis	10	Negative	10	0
HAMA	11	Negative	11	0
Hemodialysis patient	11	Negative	11	0
Multiparous pregnancies	11	Negative	11	0
Multiple transfusion recipients	11	Negative	11	0
Pregnancy 1st trimester	11	Negative	11	0
Pregnancy 2nd trimester	11	Negative	11	0
Pregnancy 3rd trimester	11	Negative	11	0
Rheumatoid Factor	11	Negative	11	0
Syphilis (*T. Pallidum*)	10	Negative	10	0
Toxoplasmosis (*Toxoplasma gondii*)	10	Negative	10	0
CMV (Cytomegalovirus)	10	Negative	9	1
EBV (Epstein-Barr virus)	10	Negative	10	0
HAV (Hepatitis A virus)	10	Negative	10	0
HIV (human immunodeficiency virus)	10	Negative	10	0
HSV (herpes simplex virus)	10	Negative	10	0
HTLV (Human T-Lymphotropic Virus)-1/2	10	Negative	10	0

Parvovirus B19	10	Negative	10	0
Rubella virus	10	Negative	10	0
Varicella-zoster virus	10	Negative	10	0
T. cruzi	10	Negative	10	0
Staphylococcus aureus	10	Negative	10	0
Pseudomonas aeruginosa	10	Negative	10	0
E. coli	10	Negative	10	0
Hepatitis C (HCV)	10	Negative	10	0
Chlamydia (*C.trachomatis*)	11	Negative	11	0

5. Endogenous Interference
   A study was conducted to evaluate the LIAISON® XL MUREX HBeAg for endogenous interference. Ten (10) negative samples or negative pools were spiked with an HBeAg high positive sample in order to achieve two (2) levels of samples: high negative and low positive. The spiked sets were divided into two (2) aliquots. The first aliquot was spiked with high concentration of potentially interfering substance. The second set of high negative and low positive aliquots (samples without any potentially interfering substances) were used as control samples for the study. Both samples with and without potentially interfering substance were tested in the same run, in 26 replicates each, on one lot of kit reagents and with one lot of kit controls. Biotin was not evaluated in this study because the assay does not employ biotin-streptavidin technology.

   No interference was observed at the concentration for each substance listed below.

Table 4: Interfering Substances

Substances	Tested Concentrations
Triglycerides	3000 mg/dL
Hemoglobin	1000 mg/dL
Unconjugated bilirubin	20 mg/dL
Conjugated bilirubin	20 mg/dL
Albumin	6000 mg/dL
Cholesterol	350 mg/dL

6. Sample Equivalence/Matrix Effect
   Twenty-five (25) paired sets of matched serum (with and without gel SST) and plasma (lithium heparin, sodium heparin, sodium citrate, and dipotassium EDTA) were tested to determine if these sample types provide equivalent results on the LIAISON® XL MUREX HBeAg. Each sample was divided into three (3) aliquots. Two (2) sets of aliquots were spiked with an HBeAg high positive sample to achieve two levels of samples: high negative and low positive samples. The third aliquot served as un-spiked control. 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), Lithium Heparin, Sodium Heparin, Sodium Citrate, and Dipotassium EDTA (K_2-

EDTA).

7. Carry-Over Study
   A carry-over study was performed to evaluate the extent of carry-over and the associated residual risk for signal carry-over in the instrument's measuring cell as a result of a high signal-generating sample. The study included on HBeAg negative serum sample, one (1) low positive serum sample and one (1) high positive sample. 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 significance amount of analyte is carried over from one sample reaction into the subsequent sample reactions.

8. High Dose Hook Effect
   Testing was performed to assess the saturation effect that may appear when testing samples containing extremely high levels of analyte resulting in a reported result that is lower than the actual analyte concentration. Three (3) samples with analyte level above the upper end of the assay were tested neat and after serial dilution in human serum. Testing was performed in triplicate with one (1) reagent lot. The signal (RLU) obtained was plotted versus the analyte concentration (Index value). No high dose hook effect (decrease in signal) was observed at HBeAg RLU values up to 2,902,720 RLUs (high positive).

9. 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 HBeAg 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 4, 14, 24, 28, 43, 48, and 52 hours of storage at RT.
   - -20 °C study – samples were tested unstressed (T=0) and stored at -20 °C or lower for 1, 3, 4, and 5 months.
   - Freeze/Thaw (F/T) study – samples were tested unstressed (T=0) and after 1, 2, 3, 4, 5, 6, 7, 8, and 9 F/T cycles. Samples were frozen for 12-24 hours at -20°C or lower and thawed at room temperature.

Table 5: Sample Stability Claims in Serum and Plasma

	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 and plasma	8	7 days	3 months	24 hours

Reagent Stability-Real-Time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON® XL MUREX HBeAg. Three (3) lots of LIAISON® XL MUREX HBeAg were stored at the recommended storage temperature of 2-8ºC throughout the study. Performance was assessed against clinically relevant acceptance criteria using three (3) lots of LIAISON® XL MUREX Control HBeAg (positive and negative) and an internal stability panel consisting of 11 samples. Study demonstrated that reagents are stable and continue to meet acceptance criteria 20 months after date of manufacture.

Reagent Stability- Reagent On-Board

Stability studies were conducted to determine the length of time the LIAISON® XL MUREX HBeAg Reagent Integral can be stored on-board the LIAISON® XL Analyzer in the refrigerated area once open. One lot of LIAISON® XL MUREX HBeAg and LIAISON® XL MUREX Control HBeAg (negative and positive) along with the internal stability panel were tested in duplicate at one (1) week intervals up to 13 weeks. The LIAISON® XL MUREX HBeAg is stable on-board the LIAISON® XL Analyzer for 12 weeks.

Reagent Stability- Open Use

The aim of this study was to assess the open use stability of the LIAISON® XL MUREX HBeAg kit reagents by stimulating normal conditions of use as specified in the instructions for use. Testing of samples was performed in duplicate, on one lot of LIAISON® XL MUREX HBeAg and one lot of LIAISON® XL MUREX Control HBeAg Results were calculated using the initial (time zero) assay calibration. The opened Reagent Integral was then removed from the XL Analyzer and stored at 2-8ºC. Kit performance using the opened Reagent Integral was evaluated weekly up to 13 weeks. The Reagent Integral is stable after opening for 12 weeks when stored at 2-8ºC.

Reagent Stability-Calibrator stability

The LIAISON® XL MUREX HBeAg calibrators are included on the Reagent Integral. All studies for the Reagent Integral are applicable to the calibrators provided.

Control Stability-Real Time Shelf-Life

Studies were performed to establish the shelf-life for the LIAISON® XL MUREX Control HBeAg. Three lots of LIAISON® XL MUREX Control HBeAg were stored at the recommended storage temperature of 2-8ºC throughout the study. Results demonstrate that the positive and negative controls are stable and continue to meet acceptance criteria at 22 months when stored at 2-8ºC.

Control Stability-Open Use

The aim of this study was to assess stability of opened Control vials by simulating normal conditions of use, as specified in the instructions for use. Testing was performed in duplicate on one lot of LIAISON® XL MUREX Control HBeAg. LIAISON® XL MUREX Control HBeAg was within the established range. The LIAISON® XL MUREX Control HBeAg is stable for 12 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 reagents maintain their properties during the shipment and delivery conditions to the customer. After being subjected to simulates stress conditions, testing was performed on three (3) lots of kit reagents and three (3) lots of kit controls, with a fresh calibration at each test time point. All testing performed met acceptance criteria under various simulated transport conditions.

10. Precision

Internal Twenty (20) Days

A precision/reproducibility study was carried out over a period of 20 days on the LIAISON® XL MUREX HBeAg 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 10 serum-based samples and controls were tested in two (2) replicates per run, in two (2) runs per day, by multiple operators, using three (3) reagent kit lots and three (3) Controls lots, over a period of 20 days. The testing days were within one calibration cycle.

The results are shown in the following table.

Table 6: Summary of 20-Day Precision Study

	LIAISON® XL MUREX HBeAg Assay All 3 Lots Combined											
Sample ID	**N**	**Mean**	**Repeatability (Within Precision)**		**Between Runs**		**Between Days**		**Between Lots**		**Within Laboratory**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Ctrl Neg #RS-746	240	487.35*	21.603	4.4%	0	0.00%	15.631	3.2%	4.63	1.0	26.789	5.5
Ctrl Neg #RS-747	240	493.69*	21.996	4.5%	4.016	0.8%	13.786	2.8%	7.167	1.5	27.228	5.5
Ctrl Neg #RS-748	240	488.44*	21.319	4.4%	9.147	1.9%	11.963	2.4%	0.00	0	26.077	5.3
Ctrl Pos #RS-749	240	5.91	0.069	1.2%	0.083	1.4%	0.097	1.6%	0.04	0.7	0.15	2.5
Ctrl Pos #RS-750	240	6.92	0.099	1.4%	0.112	1.6%	0.111	1.6%	0.063	0.9	0.197	2.8
Ctrl Pos #RS-751	240	6.01	0.072	1.2%	0.073	1.2%	0.107	1.8%	0.045	0.7	0.155	2.6
HBEA-1-U1	240	*484.90	19.696	4.1%	9.941	2.1%	10.938	2.3%	0.00	0	24.553	5.1
HBEA-1-U2	240	0.77	0.027	3.5%	0.025	3.2%	0.017	2.2%	0.032	4.1	0.052	6.7
HBEA-1-U3	240	0.87	0.027	3.1%	0.011	1.3%	0.031	3.6%	0.033	3.8	0.054	6.2

HBEA-1-U4	240	0.78	0.026	3.3%	0.04	5.1%	0.04	5.1%	0.026	3.3	0.067	8.6
HBEA-1-U5	240	2.56	0.037	1.4%	0.031	1.2%	0.046	1.8%	0.037	1.4	0.076	3.0
HBEA-1-U6	240	2.5	0.032	1.3%	0.024	1.0%	0.041	1.7%	0.038	1.5	0.069	2.8
HBEA-1-U7	240	2.31	0.036	1.6%	0.044	1.9%	0.057	2.5%	0.051	2.2	0.095	4.1
HBEA-1-U8	240	29.12	0.282	1.0%	0.585	2.0%	0.519	1.8%	0.134	0.5	0.842	2.9
HBEA-1-U9	240	27.64	0.255	0.9%	0.669	2.4%	0.682	2.5%	0.00	0	0.982	3.6
HBEA-1-U10	240	40.31	0.439	1.1%	1.498	3.7%	0.426	1.1%	0.047	0.1	1.618	4.0

*Samples below the reading range of the assay, precision calculations are based on signal (RLU)

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 HBeAg. The CLSI document EP15-A3 was consulted in the preparation of the testing protocol. The coded panel comprised 10 serum-based 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) days with multiple technicians performing the testing.

The following table shows the results.

Table 7: Summary of 5-Day Precision Study

Sample ID	N	mean	Repeatability (Within run)		Between Days/Runs		Within Laboratory		Between Sites/ Lots		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Neg (all 3 lots)	90	432.244*	21.493	5.0%	17.445	4.0%	27.682	6.4%	40.55	9.4%	49.098	11.4%
Ctrl Pos (all 3 lots)	90	5.992	0.125	2.1%	0.055	0.9%	0.136	2.3%	0.803	13.4%	0.814	13.6%
HBEA-1-U1	90	427.622*	21.315	5.0%	13.391	3.1%	25.172	5.9%	52.978	12.4%	58.654	13.7%
HBEA-1-U2	90	0.784	0.041	5.2%	0.032	4.1%	0.052	6.6%	0.083	10.5%	0.098	12.4%
HBEA-1-U3	90	0.838	0.027	3.2%	0.025	3.0%	0.036	4.3%	0.08	9.6%	0.088	10.5%
HBEA-1-U4	90	0.762	0.035	4.5%	0.061	8.0%	0.07	9.2%	0.097	12.7%	0.120	15.7%
HBEA-1-U5	90	2.605	0.07	2.7%	0.039	1.5%	0.08	3.1%	0.215	8.2%	0.229	8.8%
HBEA-1-U6	90	2.387	0.063	2.7%	0.134	5.6%	0.148	6.2%	0.102	4.3%	0.180	7.5%
HBEA-1-U7	90	2.319	0.059	2.6%	0.086	3.7%	0.105	4.5%	0.171	7.4%	0.200	8.6%
HBEA-1-U8	90	28.141	0.641	2.3%	0.716	2.5%	0.961	3.4%	1.752	6.2%	1.998	7.1%
HBEA-1-U9	90	27.154	0.488	1.8%	1.204	4.4%	1.299	4.8%	2.181	8.0%	2.538	9.3%
HBEA-1-U10	90	40.012	0.825	2.1%	1.317	3.3%	1.554	3.9%	2.74	6.8%	3.15	7.9%

*Precision calculations are based on signal (RLU) for the negative control.

11. 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 30 negative pediatric patient samples were used for this study. The pediatric samples encompassed the age range of two (2) months to 21 years. Ten (10) pediatric samples were spiked with an HBeAg high positive sample to obtain high negative samples. Ten (10) pediatric samples were spiked with an IgG HbeAg high positive sample to obtain low positive samples. Ten (10) pediatric samples were spiked with an HbeAg high positive sample to obtain moderate positive samples. Adult negative pool samples were used as controls and were spiked with an HbeAg 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 HbeAg. 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 HbeAg.

B. **Animal Studies**

Not Applicable

C. **Additional Studies**

Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant's primary clinmcial study was designed to establish a reasonable assurance of safety and effectiveness for the detection of hepatitis-Be antigen with the LIAISON® XL MUREX HbeAg 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 HbeAg 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 3082 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 locations including Ohio, Pennsylvania, Indiana, Florida, California, Texas, New Jersey, Tennessee, Massachusetts, and Puerto Rico.

Prospective (unselected) subjects were 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 distribution of LIAISON® XL MUREX HBeAg reactive and non-reactive results by age and gender of the overall prospective population are presented below.

Table 8: Demographic Summary of Prospective Population

Age Range	Gender	LIAISON® XL MUREX HBeAg				Total
		+		-		
		n	%	n	%	
0-9	F	0	0.0%	5	100.0%	5
	M	0	0.0%	10	100.0%	10
10-19	F	0	0.0%	40	100.0%	40
	M	0	0.0%	15	100.0%	15
20-29	F	9	2.3%	380	97.7%	389
	M	14	6.0%	219	94.0%	233
30-39	F	3	0.6%	471	99.4%	474
	M	11	4.9%	213	95.1%	224
40-49	F	1	0.3%	289	99.7%	290
	M	6	3.0%	195	97.0%	201
50-59	F	3	1.3%	229	98.7%	232
	M	0	0.0%	185	100.0%	185
60-69	F	0	0.0%	158	100.0%	158
	M	0	0.0%	108	100.0%	108

Age Range	Gender	LIAISON® XL MUREX HBeAg				
		+		-		Total
		n	%	n	%	
70-79	F	0	0.0%	46	100.0%	46
	M	0	0.0%	39	100.0%	39
80-89	F	0	0.0%	14	100.0%	14
	M	0	0.0%	7	100.0%	7
90-98	F	0	0.0%	4	100.0%	4
	M	0	N/A	0	N/A	0
Unk	F	0	0.0%	1	100.0%	1
	M	0	0.0%	1	100.0%	1
Total		47	1.8%	2629	98.2%	2676

Hepatitis B status classification was based on testing all 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 9: Serological Classification by FDA-Approved HBV Panel

HBV Classification	HBsAg	HBeAg	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
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	48	9
Early Recovery	NR	NR	R	EQV	R	R		
Early Recovery	NR	NR	R	R	NR	NR		
Early Recovery	NR	NR	R	NR	R	NR		
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	131	36
Recovery	NR	NR	NR	NR	R	R		
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
Not Interpretable	NR	NR	NR	R	NR	NR	7	2
Not Interpretable	NR	R	NR	NR	NR	NR		

Clinical Agreement Study Analysis

Based on the HBV classifications, the LIAISON® XL MUREX HBeAg results for the 2826 prospective and 256 retrospective specimens were compared to a reference HBeAg assay. The following tables show this comparison and percent agreement with 95% confidence intervals with the reference HBeAg assay results.

Table 9: Cumulative Clinical Agreement Adult and Pediatric (Combined Prospective and Retrospective) LIAISON XL® MUREX HBeAg vs Reference Assay Characterization

HBV Classification	Reference HBeAg assay						Total
	Reactive		Equivocal		Nonreactive		
	LIAISON® XL MUREX HBeAg		LIAISON® XL MUREX HBeAg		LIAISON® XL MUREX HBeAg		
	Reactive	NonReactive	Reactive	NonReactive	Reactive	NonReactive	
Acute	98	0	1	0	2	8	109
Late Acute	0	0	0	0	1	33	34
Chronic	55	1	6	1	1	80	144
Early Recovery	0	0	0	0	1	56	57
Recovery	0	0	0	0	0	167	167

Immune due to Natural Infection	0	0	0	0	0	107	107
HBV Vaccine Response	0	0	0	0	0	1152	1152
Not Previously Infected	0	0	0	0	1	1302	1303
Not Interpretable	2	3	0	0	0	4	9
Total	155	4	7	1	6	2909	3082

Comparison results of the LIAISON® XL MUREX HBeAg to the reference HBeAg assay are presented with negative and positive percent agreement (NPA and PPA, respectively) with the 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 10: Cumulative Clinical Agreement Adult and Pediatric (Combined Prospective and Retrospective) LIAISON® XL HBeAg vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	98/98 (100%) 95% CI: 96.3% to 100.0%	8/11 (72.7%) 95% CI: 43.4% to 90.3%
Late Acute	N/A	33/34 (97.1%) 95% CI: 85.1% to 99.5%
Chronic	55/57 (96.5%) 95% CI: 88.1% to 99.0%	80/87 (92.0%) 95% CI: 84.3% to 96.1%
Early Recovery	N/A	56/57 (98.2%) 95% CI 90.1% to 99.7%:
Recovery	N/A	167/167 (100%) 95% CI: 97.7% to 100.0%
Immune Due to Natural Infection	N/A	107/107 (100%) 95% CI: 96.5% to 100.0%
HBV Vaccine Response	N/A	1152/1152 (100%) 95% CI:99.7% to 100.0%
Not Previously Infected	N/A	1302/1303 (99.9%) 95% CI: 99.6% to 100.0%
Not Interpretable	2/5 (40.0%) 95% CI: 11.8% to 76.9%	4/4 (100%) 95% CI: 51.0% to 100.0%
Total	155/160 (96.9%) 95% CI: 92.9% to 98.7%	2909/2922 (99.6%) 95% CI: 99.6% to 99.7%

The following table shows the combined prospective and retrospective pediatric clinical agreement.

Table 11: Cumulative Pediatric Clinical Agreement (Combined Prospective and Retrospective) LIAISON® XL MUREX HBc IgM vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	98/98 (100%) 95% CI: 96.3% to 100.0%	8/11 (72.7%) 95% CI: 43.4% to 90.3%
Late Acute	N/A	33/34 (97.1%) 95% CI: 85.1% to 99.5%
Chronic	55/57 (96.5%) 95% CI: 88.1% to 99.0%	80/87 (92.0%) 95% CI: 84.3% to 96.1%
Early Recovery	N/A	56/57 (98.2%) 95% CI 90.1% to 99.7%:
Recovery	N/A	167/167 (100%) 95% CI: 97.7% to 100.0%
Immune Due to Natural Infection	N/A	107/107 (100%) 95% CI: 96.5% to 100.0%
HBV Vaccine Response	N/A	1152/1152 (100%) 95% CI:99.7% to 100.0%
Not Previously Infected	N/A	1302/1303 (99.9%) 95% CI: 99.6% to 100.0%
Not Interpretable	2/5 (40.0%) 95% CI: 11.8% to 76.9%	4/4 (100%) 95% CI: 51.0% to 100.0%
Total	155/160 (96.9%) 95% CI: 92.9% to 98.7%	2909/2922 (99.6%) 95% CI: 99.6% to 99.7%

Clinical Endpoints

As an in vitro diagnostic test, the LIAISON® XL MUREX HBeAg 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.

For effectiveness, clinical performance of the LIAISON® XL MUREX HBeAg was evaluated versus an FDA approved HBeAg test for patients at risk of 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 96.9% and a negative percent agreement (NPA) of 99.6% among subjects in various states of HBV infection.

B. **Accountability of PMA Cohort**

The clinical agreement study involved the testing of 3082 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 locations 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 HBeAg detection study performed in the U.S.

The prospective (unselected) subjects were 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 tables below show the demographic distribution of the cohort.

Table 12: Demographics of Clinical Study Samples by Gender

	Adult				**Pediatric (2-21)**				**Unknown Age**			
	Prospective		**Retrospective**		**Prospective**		**Retrospective**		**Prospective**		**Retrospective**	
Gender	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	1643	61.7%	54	26.2%	98	60.9%	2	6.5%	1	50.0%	0	0.0%
Male	1017	38.2%	151	73.3%	61	37.9%	29	93.5%	1	50.0%	0	0.0%
Unknown	3	0.1%	1	0.5%	2	1.2%	0	0.0%	0	0.0%	21	100.0%
Total	2663	100.0%	206	100.0%	161	100.0%	31	100.0%	2	100.0%	21	100.0%

Table 13: Demographics of Clinical Study Samples by Race

	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	12.9%	0	0.0%	0	0.0%
Native Hawaiian or Other Pacific	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%	27	87.1%	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%	31	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 HBeAg test involves taking a sample of plasma or serum for 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 3082 evaluable patients. Key effectiveness outcomes are presented in Tables 10-12 above.

3. Subgroup Analyses

   The study design enabled an assessment of assay performance by subgroup as depicted in table above which show subjects stratified by state of HBV infection.

4. Pediatric Extrapolation

   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 HBeAg test for the qualitative detection of hepatitis-B e antigen in human serum and plasma (lithium and sodium heparin, sodium citrate and K_2 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. The PPA of the assay is 96.9% with a two-sided 95% confidence interval (CI) of 92.9%-98.7% and the NPA of 99.6% with a two-sided 95% CI of 99.6%-99.7%.

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 HBeAg when used according to the manufacturer's instructions can aid the physician in the diagnosis of HBV infection. The PPA of the assay is 96.9% with a two-sided 95% confidence interval (CI) of 92.9%-98.7% and the NPA of 99.6% with a two-sided 95% CI of 99.6%-99.7%.

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

as part of a hepatitis B panel, the appropriate diagnosis and treatment of hepatitis B infection. Treatment 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 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 device in the clinical study suggests that patients will benefit from the assay, low prevalence of certain HBV classifications is a source of potential uncertainty when analyzing the samples. The wide confidence intervals for those subgroups is expected due to the biology of hepatitis B infection and is acceptable.

The risks associated with the device, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results and failure to correctly operate the instrument.

Risks of a false positive test includes improper patient management, including missing the opportunity for treatment of hepatitis B with antiviral medication in a subset of patients with hepatitis B. In patients without cirrhosis, false positive tests will require a higher HBV DNA threshold (>20k units/mL) than would be required otherwise for a clinician to initiate treatment, resulting in the potential undertreatment of a patient who has hepatitis B infection and whose clinical picture would otherwise warrant antiviral treatment. 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 tests would include improper patient management, including treatment of hepatitis B with antiviral medication. In patients without cirrhosis but with negative HBeAg and chronic hepatitis, normal liver enzymes, but HBV DNA levels >2k IU/mL, liver biopsy may be recommended with its associated risks of infection and bleeding. As the number of patients in this specific category is exceedingly small, this specific risk of a false negative HBeAg is likely minimal. In patients without cirrhosis, false negative tests will require a lower HBV DNA threshold (>2k units/mL) than would be required otherwise for a clinician to initiate treatment, resulting in treatment of a patient who has hepatitis B infection but whose clinical picture may not otherwise warrant antiviral treatment. 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.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support the claimed intended use and that 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 probable risks for the proposed assay considering the performance of the device in the clinical study and the low risk and associated risk mitigations in clinical practice. The proposed assay labeling will facilitate accurate assay implement 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.

XIII. CDRH DECISION

CDRH issued an approval order on August 29, 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.