SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Antibodies to Hepatitis B e antigen (Anti-HBe)

Device Trade Name: LIAISON® XL MUREX Anti-HBe
LIAISON® XL MUREX Control Anti-HBe

Device Procode: LOM

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180049

Date of FDA Notice of Approval: August 29, 2020

II. INDICATIONS FOR USE

LIAISON XL MUREX Anti-HBe
The LIAISON® XL MUREX Anti-HBe assay is an *in vitro* chemiluminescent immunoassay (CLIA) for the qualitative detection of total antibodies to hepatitis B e antigen (anti-HBe) in human adult and pediatric (2 to 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 Anti-HBe
The LIAISON® XL MUREX Control Anti-HBe (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON® XL MUREX Anti-HBe assay. The performance characteristics of LIAISON® XL MUREX Control Anti-HBe have not been established for any other assays or instrument platforms different from LIAISON®XL Analyzer.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

LIAISON XL MUREX Anti-HBe is a qualitative competitive 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, anti-HBe present in calibrators, samples or controls binds to a fixed amount of recombinant HBeAg thus forming an HBeAg-anti-HBe immune complex. During the second incubation, the antibody conjugate and the solid-phase antibody compete with anti-HBe present in the specimen for recombinant HBeAg that allows the conjugate to bind to the solid phase forming a sandwich. If all HBeAg added is sequestered in an HBeAg-anti-HBe immune complex during the first incubation, no sandwich is formed during the second incubation. After the second incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is induced. The light conjugate is measured by a photomultiplier as relative light units (RLU) and is inversely indicative of anti-HBe concentration present in calibrators, samples or controls.

Components of the LIAISON XL MUREX Anti-HBe assay

All reagents are supplied ready to use

The table below describes the components of the LIAISON XL MUREX Anti-HBe kit.

Table 1: Components of the LIAISON XL MUREX Anti-HBe

Magnetic Particles 1 vial – 1.3 mL	Magnetic particles coated with antibody to HBeAg (mouse monoclonal), BSA, phosphate buffer, < 0.1% sodium azide.
Calibrator 1 1 vial – 1.5 mL	Fetal calf serum containing high anti-HBe antibody levels (human), 0.2% ProClin® 300, preservatives.
Calibrator 2 1 vial – 1.5 mL	Human serum without anti-HBe antibodies, 0.2% ProClin® 300, preservatives, an inert blue dye.
Conjugate 1 vial – 8.0 mL	Antibody to HBeAg (mouse monoclonal) conjugated to an isoluminol derivative, fetal calf serum, phosphate buffer, 0.2% ProClin® 300, preservatives.
Neutralizing Solution (HBeAg) 1 vial – 8 mL	HBeAg obtained in E. coli by the recombinant DNA technology, human serum, non monoclonal), TRIS buffer, 0.2% ProClin® 300, preservatives, an inert red dye.
Number of tests	100

LIAISON XL MUREX Control Anti-HBe set consists of two 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 Anti-HBe assay.

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

NEGATIVE CONTROL 2 vials – 2.3 mL each	Human serum without anti-HBe antibodies with 0.2% ProClin® 300 and preservatives.
POSITIVE CONTROL 2 vials – 2.3 mL each	Human serum containing HBe antibodies (human), 0.2% ProClin® 300, preservatives, and an inert orange dye.

Interpretation of the Results (anti-HBe):

The interpretation of results for the LIAISON XL MUREX Anti-HBe is as follow:

Cutoff of 0.800 index value determines whether a sample has detectable levels of anti-HBe:

- **Non-Reactive:** Samples with anti-HBe levels equal to or above an index value of 0.800 are considered Non-Reactive and presumed negative for Anti-HBe
- **Reactive:** Samples with anti-HBe levels below an index value of 0.800 are considered Reactive and presumed positive for anti-HBe.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of total antibodies to hepatitis B e antigen (Anti-HBe). 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 conjunction 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 Anti-HBe assay (318160) and LIAISON® XL MUREX Control Anti-HBe (318161) are essentially the same as the CE-marked LIAISON® Anti-HBe assay (310160) and LIAISON® Control Anti-HBe (310161) with some minor modifications to raw material manufacturing processes.

The LIAISON® XL MUREX Anti-HBe assay (318160) and LIAISON® XL MUREX Control Anti-HBe (318161) have not been marketed in the U.S. or any foreign country.

The CE marked LIAISON® Anti-HBe and the LIAISON® Control Anti-HBe 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.

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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	Mexico
Netherlands	Norway	Panama
Peru	Poland	Portugal
Paraguay	Qatar	Romania
Serbia	Saudi Arabia	Slovenia
Sweden	Thailand	Tunisia
Turkey	South Africa	Vietnam
China		

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.

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 premature discontinuation of antiviral treatment should a clinician be falsely led to determine a patient has seroconverted. This risk is mitigated by the fact that this assay is usually repeated and is used as part of a panel. Repeatedly false positive results have the potential to lead to inappropriate treatment decisions, however anti-HBe is not used in isolation to determine seroconversion status. Because anti-HBe is sometimes included as part of a panel in clinical practice to diagnose hepatitis B but is more commonly utilized as part of a panel to determine chronicity of disease and immune-active versus chronic infection, the risk of a false positive will likely be somewhat mitigated as incongruous test results would lead a clinician to either retest the patient or further investigate the etiology of hepatitis. It is not clear that the comparator assay is necessarily clinical truth in its positive test. It may be that the DiaSorin assay is detecting true positives that the comparator is missing via higher sensitivity of this assay or a relatively lower limit of detection.

Risk of a false negative test includes improper patient management, including continued 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 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. Anti-HBe is not used in this same manner as HBeAg to guide treatment decisions, and thus confers less clinical risk to this subpopulation than a false negative or false positive HBeAg test. Anti-HBe is not used in isolation to determine seroconversion status. Because anti-HBe is sometimes included as part of a panel in clinical practice to diagnose hepatitis B but is more commonly utilized as part of a panel to determine chronicity of disease and immune-active v. chronic infection, the risk of a false negative will likely be mitigated as incongruous test results would lead a clinician to either retest the patient or further investigate the etiology of hepatitis.

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 110 samples (60 known negative and 50 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 Anti-HBe assay has been demonstrated by testing 6 commercial seroconversion panels in comparison to a reference anti-HBe 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-HBe yielded a positive result sooner by one or more blood draws or more than the comparator assay in 1 of the 6 panels.

3. Analytical Sensitivity/Dilution Study with Standard
   The sensitivity of the LIAISON XL MUREX Anti-HBe was evaluated by preparing serial dilutions of the HBe Reference material IgM 82 (IgG anti-HBe, 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 0.150 PEI U/mL.

4. Analytical Specificity (Cross-Reactivity)
   A study was conducted to evaluate the LIAISON XL MUREX Anti-HBe for cross-reactivity with specimens from individuals with 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 Anti-HBe and on a reference Anti-HBe assay.

   Of the 305 samples, no evidence of cross-reactivity 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 Anti HBe assay	LIAISON® XL MUREX Anti-HBe	
			Non-reactive	Reactive
Anti-nuclear antibodies (ANA)	10	Negative	10	0
Auto-immune hepatitis	10	Negative	10	0
C. trachomatis	11	Negative	11	0
CMV (IgG / IgM)	11	Negative	11	0
EBV (IgM)	11	Negative	11	0
Fatty liver disease	11	Negative	11	0
HAMA	11	Negative	11	0
Hemodialysis patient	11	Negative	11	0
Hepatitis A Virus (anti-HAV IgM)	11	Negative	11	0
Hepatitis C Virus (anti-HCV)	11	Negative	11	0
Hepatocellular carcinoma	11	Negative	11	0
HIV-1 (anti-HIV-1)	11	Negative	11	0
HIV-2 (anti-HIV-2)	11	Negative	11	0
HSV (IgG / IgM)	11	Negative	11	0
HTLV-1/2 (anti-HTLV)	11	Negative	11	0
IgG monoclonal gammopathy	11	Negative	11	0

Organism/Condition	N	Comparator Anti HBe assay	LIAISON® XL MUREX Anti-HBe	
			Non-reactive	Reactive
IgM monoclonal gammopathy	10	Negative	10	0
Influenza vaccine recipients	11	Negative	11	0
Multiparous pregnancies	11	Negative	11	0
Multiple myeloma	11	Negative	11	0
Multiple transfusion recipients	11	Negative	11	0
N. gonorrhoeae	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
T. pallidum	11	Negative	11	0
T. cruzi (anti-*T. cruzi*)	11	Negative	11	0

5. Endogenous Interference
   A study was conducted to evaluate the LIAISON XL MUREX Anti-HBe for endogenous interference. Ten negative samples or negative pools were spiked with an Anti-HBe high positive sample in order to achieve two levels of samples: high negative and low positive. The spiked sets were divided into two 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 twenty-six 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 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 Anti-HBe. Each sample was divided into three aliquots. Two sets of aliquots were spiked with an anti-HBe 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.

7. Carry-Over Study

   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 a result of a high signal-generating sample. The study included one anti-HBe negative serum sample, one low positive serum sample and one 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. 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.

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	6	7 days	3 months	4 day

Reagent Stability-Real-Time (Shelf-Life)
Studies were performed to establish the shelf-life for the LIAISON XL MUREX Anti-HBe. Three lots of LIAISON XL MUREX Anti-HBe were stored at the recommended storage temperature of 2-8ºC throughout the study. Performance was assessed against clinically relevant acceptance criteria using three lots of LIAISON XL MUREX Control Anti-HBe (positive and negative) and an internal stability panel consisting of eleven samples. Study demonstrated that reagents are stable and continue to meet acceptance criteria 19 months after date of manufacture.

Reagent Stability- Reagent On-Board
Stability studies were conducted to determine the length of time the LIAISON XL MUREX Anti-HBe Reagent Integral can be stored on-board the LIAISON XL Analyzer in the refrigerated area once open. One lot of LIAISON XL MUREX Anti-HBe and LIAISON XL MUREX Control Anti-HBe (negative and positive) along with the internal stability panel were tested in duplicate at one week intervals up to 13 weeks. The LIAISON XL MUREX Anti-HBe 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 Anti-HBe 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 Anti-HBe and one lot of LIAISON XL MUREX Control Anti-HBe 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 Anti-HBe 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 Anti-HBe. Three lots of LIAISON XL MUREX Control Anti-HBe 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 19 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 Anti-HBe. LIAISON XL MUREX Control Anti-HBe was within the established range. The LIAISON XL MUREX Control Anti-HBe is stable for 12 weeks after opening when stored at 2-8ºC 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 3 lots of kit reagents and 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.

9. Precision

Internal 20 Days

A precision/reproducibility study was carried out over a period of 20 days on the LIAISON XL MUREX Anti-HBe 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 2 replicates per run, in 2 runs per day, by multiple operators, using 3 reagent kit lots and 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 Anti-HBe Assay All 3 Lots Combined											
Sample ID	**N**	**Mean**	**Repeatability**		**Between-Run**		**Between-Day**		**Between-Lot**		**Within Laboratory**	
		Index/RLU	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Ctrl Neg #RS-729	240	257154.2*	4124.7	1.6%	3667.4	1.4%	2337.9	0.90%	47992.8	18.7%	48365.6	18.8%
Ctrl Neg #RS-730	240	254826.1*	3898.9	1.5%	3817.6	1.5%	3325.6	1.3%	47345.5	18.6%	47774.8	18.7%
Ctrl Neg #RS-731	240	257123.9*	3727.7	1.4%	4371	1.7%	3472.4	1.4%	46563.6	18.1%	47044.9	18.3%
Ctrl Pos #RS-732	240	0.55	0.007	1.3%	0.014	2.6%	0.005	0.9%	0.024	4.4%	0.029	5.3%
Ctrl Pos #RS-73	240	0.53	0.009	1.7%	0.013	2.4%	0.006	1.1%	0.019	3.6%	0.025	4.8%
Ctrl Pos #RS-734	240	0.53	0.008	1.4%	0.011	2.1%	0.009	1.7%	0.02	3.7%	0.025	4.8%
AHBE-2-U2	240	1.6	0.023	1.4%	0.043	2.7%	0.048	3.0%	0.028	1.8%	0.074	4.6%
AHBE-1-U2	240	1.86	0.035	1.9%	0.023	1.2%	0.033	1.7%	0.072	3.9%	0.089	4.8%
AHBE-1-U3	240	1.86	0.031	1.6%	0.029	1.5%	0.027	1.5%	0.065	3.5%	0.082	4.4%
AHBE-2-U4	240	1.63	0.022	1.4%	0.037	2.3%	0.045	2.7%	0.032	2.0%	0.07	4.3%
AHBE-1-U5	240	0.73	0.012	1.6%	0.013	1.7%	0.01	1.4%	0.01	1.3%	0.022	3.0%
AHBE-1-U6	240	0.81	0.012	1.5%	0.014	1.7%	0.011	1.3%	0.025	3.1%	0.033	4.0%
AHBE-1-U7	240	0.71	0.011	1.6%	0.016	2.3%	0.011	1.6%	0.014	1.9%	0.027	3.7%
AHBE-1-U8	240	0.24	0.004	1.7%	0.007	2.7%	0.003	1.4%	0.012	5.1%	0.015	6.2%
AHBE-1-U9	240	0.21	0.004	1.7%	0.006	3.1%	0.005	2.4%	0.006	3.0%	0.011	5.2%
AHBE-1-U10	240	0.18	0.003	1.7%	0.004	2.3%	0.005	2.6%	0.007	4.0%	0.01	5.6%

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

External Precision 5-day Study

A 5 day precision/reproducibility study was conducted at 2 external laboratories and at DiaSorin Inc. to verify the precision of the LIAISON XL MUREX Anti-HBe. 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 3 sites on the LIAISON XL Analyzer using 6 replicates per run in 1 run per day for five 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		Between-Day/Run		Within Laboratory Precision		Between-Site/lots		Total Reproducibility	
		Index/ RLU	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Neg	90	192896.4*	4442.1	2.3%	7554.3	3.9%	8763.6	4.5%	43958.1	22.8%	44688.3	23.2%
Ctrl Pos	90	0.518	0.011	2.2%	0.014	2.8%	0.018	3.5%	0.046	8.8%	0.049	9.4%
AHBE-2-U2	90	1.698	0.047	2.7%	0.025	1.5%	0.053	3.1%	0.023	1.4%	0.056	3.3%
AHBE-1-U2	90	1.862	0.056	3.0%	0.087	4.7%	0.103	5.6%	0.196	10.5%	0.217	11.7%
AHBE-1-U3	90	1.841	0.051	2.8%	0.081	4.4%	0.096	5.2%	0.181	9.8%	0.202	11.0%
AHBE-2-U4	90	1.729	0.032	1.8%	0.03	1.7%	0.044	2.5%	0.035	2.0%	0.054	3.1%
AHBE-1-U5	90	0.762	0.025	3.3%	0.053	6.9%	0.059	7.7%	0.119	15.7%	0.131	17.2%
AHBE-1-U6	90	0.834	0.026	3.1%	0.048	5.8%	0.055	6.6%	0.092	11.0%	0.105	12.6%
AHBE-1-U7	90	0.733	0.028	3.9%	0.049	6.7%	0.057	7.8%	0.106	14.5%	0.119	16.2%
AHBE-1-U8	90	0.252	0.01	3.9%	0.013	5.2%	0.016	6.5%	0.046	18.3%	0.049	19.2%
AHBE-1-U9	90	0.227	0.009	4.1%	0.025	11.2%	0.027	11.9%	0.045	19.7%	0.051	22.4%
AHBE-1-U10	90	0.208	0.014	6.6%	0.022	10.6%	0.026	12.5%	0.062	29.9%	0.067	32.0%

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

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 2 months to 21 years. Ten (10) pediatric samples were spiked with an anti-HBe high positive sample to obtain high negative samples. Ten (10) pediatric samples were spiked with an IgG anti-HBe high positive sample to obtain low positive samples. Ten (10) pediatric samples were spiked with an anti-HBe high positive sample to obtain moderate positive samples. Adult negative pool samples were used as controls and were spiked with an anti-HBe high positive sample to achieve the same 3 levels of samples: high negative, low positive and moderate positive samples.

The samples were tested in duplicate, with the LIAISON XL MUREX Anti-HBe. 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-HBe.

B. Animal Studies

Not Applicable

C. Additional Studies

Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the detection of antibodies to hepatitis-B e antigen with the LIAISON XL MUREX Anti-HBe 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-HBe 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 2939 samples (2812 were collected prospectively) 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.

The prospective (unselected) subjects were defined as follows:

- Pediatric and adult male (38.2%), female (61.8%) 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-HBe 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 Anti-HBe				
		+		-		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	3	0.8%	386	99.2%	389
	M	2	0.9%	231	99.1%	233
30-39	F	14	3.0%	460	97.0%	474
	M	6	2.7%	218	97.3%	224
40-49	F	19	6.6%	271	93.4%	290
	M	12	6.0%	189	94.0%	201
50-59	F	21	9.1%	211	90.9%	232
	M	19	10.3%	166	89.7%	185
60-69	F	13	8.2%	145	91.8%	158
	M	12	11.1%	96	88.9%	108
70-79	F	3	6.5%	43	93.5%	46
	M	1	2.6%	38	97.4%	39
80-89	F	4	28.6%	10	71.4%	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		129	4.8%	2547	95.2%	2676

Hepatitis B Status Classification

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	Total A-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
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	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							2812	127

Clinical Endpoints

As an in vitro diagnostic test, the LIAISON XL MUREX Anti-HBe 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 regards to effectiveness, the clinical performance of the LIAISON XL MUREX Anti-HBe was evaluated versus an FDA approved anti-HBe 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 98.0% and a negative percent agreement (NPA) of 99.1% among subjects in various states of HBV infection.

B. Accountability of PMA Cohort

The clinical agreement study involved the testing of 2939 samples (2812 were collected prospectively) 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 anti-HBe detection study performed in the US.

The prospective (unselected) subjects were defined as follows:

- Pediatric male (37.9%) and adult male (38.1%), pediatric female (60.9%) and adult female (61.8%), pediatric unknown gender (1.2%) and adult 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 tables below show the demographic distribution of the cohort.

Table 10: Demographics of Clinical Samples by Gender

	Adult				Pediatric (2-21)				Unknown Age			
	Prospective		Retrospective		Prospective		Retrospective		Prospective		Retrospective	
Gender	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	1637	61.8%	29	23.6%	98	60.9%	1	25.0%	1	50.0%	0	NA
Male	1009	38.1%	93	75.6%	61	37.9%	3	75.0%	1	50.0%	0	NA
Unknown	3	0.1%	1	0.8%	2	1.2%	0	0.0%	0	0.0%	0	NA
Total	2649	100.0%	123	100.0%	161	100.0%	4	100.0%	2	100.0%	0	NA

Table 11: 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	NA
Asian	21	0.8%	3	2.4%	3	1.9%	0	0.0%	0	0.0%	0	NA
Black/African American	827	31.2%	38	30.9%	64	39.8%	2	50.0%	0	0.0%	0	NA
Native Hawaiian or Other Pacific Islander	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	NA
White	1655	62.5%	79	64.2%	89	55.3%	2	50.0%	2	100.0%	0	NA
Unknown	6	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	NA
Other	138	5.2%	3	2.4%	5	3.1%	0	0.0%	0	0.0%	0	NA
Total	2649	100.0%	123	100.0%	161	100.0%	4	100.0%	2	100.0%	0	NA

D. Safety and Effectiveness Results

1. Safety Results

   With regard to safety, as an in vitro diagnostic test, the LIAISON XL MUREX Anti-HBe 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 below.

Clinical Agreement Study Analysis

Comparison results of the LIAISON XL MUREX Anti-HBe to the reference anti-HBe 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 12: Cumulative Clinical Agreement Adult and Pediatric (Combined Prospective and Retrospective) LIAISON XL Anti-HBe vs Reference Assay by Characterization

HBV Classification	Reference Anti-HBe assay						Total
	Reactive		Equivocal		Non-reactive		
	LIAISON® XL MUREX Anti-HBe		LIAISON® XL MUREX Anti-HBe		LIAISON® XL MUREX Anti-HBe		
	Reactive	Non-reactive	Reactive	Non-reactive	Reactive	Non-reactive	
Chronic	65	0	0	1	1	77	144
Early Recovery	23	1	0	0	3	30	57
Recovery	157	3	6	1	0	0	167
Immune Due to Natural Infection	0	0	0	0	11	96	107
HBV Vaccine Response	0	0	0	0	0	1152	1152
Not Previously Infected	0	0	0	0	2	1301	1303
Not Interpretable	2	0	0	0	2	5	9
Total	247	4	6	2	19	2661	2939

Table 13: Cumulative Comparison Adult and Pediatric (Combined Prospective and Retrospective) LIAISON XL MUREX Anti-HBe vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Chronic	65/66 (98.5%) 95% CI: 91.9% to 99.7%	77/78 (98.7%) 95% CI: 93.1% to 99.8%
Early Recovery	23/24 (95.8%) 95% CI: 79.8% to 99.3%	31/33 (93.9%) 95% CI: 80.4% to 98.3%
Recovery	157/160 (98.1%) 95% CI: 94.6% to 99.4%	0/7 (0.0%) 0.0% to 35.4%
Immune Due to Natural Infection	N/A	98/107 (91.6%) 95% CI: 84.8% to 95.5%
HBV Vaccine Response	N/A	1151/1152 (99.9%) 95% CI: 99.5% to 100.0%
Not Previously Infected	N/A	1302/1303 (99.9%) 95% CI: 99.6% to 100.0%
Not Interpretable	2/2 (100.0%) 95% CI: 34.2% to 100.0%	5/7 (71.4%) 95% CI: 35.9% to 91.8%

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Total	247/252 (98.0%) 95% CI: 94.5% to 99.1%	2664/2687(99.1%) 95% CI: 98.7% to 99.4%

Table 14:Cumulative Pediatric Clinical Agreement (Combined Prospective and Retrospective) LIAISON XL MUREX Anti-HBe vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Chronic	4/4 (100%) 95% CI: 51.0% to 100.0%	3/3 (100%) 95%CI: 43.8% to 100.0%
Early Recovery	1/1 (100%) 95% CI: 20.7% to 100.0%	N/A
Recovery	5/5 (100%) 95% CI:56.6% to 100.0%	N/A
Immune Due to Natural Infection	N/A	3/3 (100%) 95%CI: 43.8% to 100.0%
HBV Vaccine Response	N/A	63/63 (100%) 95%CI: 94.3% to 100.0%
Not Previously Infected	N/A	84/84 (100%) 95%CI: 95.6% to 100.0%
Not Interpretable	N/A	2/2 (100% 95%CI: 34.2% to 100.0%
Total	10/10 (100%) 95%CI: 72.3% to 100.0%	155/155 (100%) 95%CI: 97.6% to 100.0%

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 Anti-HBe test for the qualitative detection of antibodies to hepatitis-B e antigen in human serum and plasma (lithium heparin, sodium heparin, sodium citrate, and dipotassium 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 98.0% with a two-sided 95% confidence interval (CI) of 94.5%-99.1% and the NPA of 99.1% with a two-sided 95% CI of 98.7%-99.4%.

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-HBe when used according to the manufacturer's instructions can aid the physician in the diagnosis of HBV infection. The PPA of the assay is 98.0% with a two-sided 95% confidence interval (CI) of 94.5%-99.1% and the NPA of 99.1% with a two-sided 95% CI of 98.7%-99.4%.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the 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 premature discontinuation of antiviral treatment should a clinician be falsely led to determine a patient has seroconverted. This risk is mitigated by the fact that this assay is usually repeated and is used as part of a panel. Repeatedly false positive results have the potential to lead to inappropriate treatment decisions, however anti-HBe is not used in isolation to determine seroconversion status. Because anti-HBe is sometimes included as part of a panel in clinical practice to diagnose hepatitis B but is more commonly utilized as part of a panel to determine chronicity of disease and immune-active v. chronic infection, the risk of a false positive will likely be somewhat mitigated as incongruous test results that would lead a clinician to either retest the patient or further investigate the etiology of hepatitis. It is not clear that the comparator assay is necessarily clinical truth in its positive test. It may be that the DiaSorin assay is detecting true positives that the comparator is missing via higher sensitivity of this assay or a relatively lower limit of detection.

Risk of a false negative test includes improper patient management, including continued 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 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. Anti-HBe is not used in this same manner as HBeAg to guide treatment decisions, and thus confers less clinical risk to this subpopulation than a false negative or false positive HBeAg test. Anti-HBe is not used in isolation to determine seroconversion status. The risk of a false negative result will likely be mitigated as anti-HBe is almost always included as part of a panel in clinical practice, and incongruous panel test results would lead a clinician to either retest the patient or further investigate the etiology of hepatitis.

The clinical benefits outweigh the risks for the proposed assay considering the performance of the device in the clinical trial and the low risk and associated risk mitigations afforded by the premarket application. The proposed assay labelling will facilitate accurate assay implementation and interpretation of results. The clinical performance observed in the analytical and clinical studies suggests that errors will be uncommon and that the assay may provide substantial benefits to patients when used with other laboratory results and clinical information as an aid in the diagnosis of hepatitis B virus (HBV) infection.

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~~y~~ clinical benefits outweigh the potential 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 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.

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.