SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Assay, Enzyme Linked Immunosorbent, Hepatitis C Virus

Device Trade Name: LIAISON XL MUREX HCV Ab
LIAISON XL MUREX Control HCV Ab

Device Procode: MZO

Applicants Name and Address: DiaSorin Inc.
1951 Northwestern Avenue
Stillwater, MN 55082

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190011

Date of FDA Notice of Approval: October 18, 2019

II. INDICATIONS FOR USE

LIAISON XL MUREX HCV Ab assay
The LIAISON XL MUREX HCV Ab assay is an *in vitro* chemiluminescent immunoassay (CLIA) for the qualitative determination of specific antibodies to hepatitis C virus (anti-HCV) in human adult and pediatric (2 – 21 years) serum and plasma (lithium and sodium heparin, sodium citrate and di-potassium EDTA) samples including separator tubes, on the LIAISON XL Analyzer. It is intended to be used as an aid in the diagnosis of HCV infection. The assay may also be used as an aid in the diagnosis of HCV infection in pediatric subjects and in pregnant women. The test does not determine the state of infection or associated disease.

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

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

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LIAISON XL MUREX HCV Ab assay and LIAISON XL MUREX Control HCV Ab labeling.

V. DEVICE DESCRIPTION

Kit Components

Reagents: The LIAISON XL MUREX HCV Ab is an *in vitro* diagnostic device consisting of five (5) reagents provided in individual compartments within a plastic container called the Reagent Integral. The assay configuration allows performance of 100 tests.

The assay is comprised of the following components:

- One (1) vial of Magnetic particles coated with HCV core and NS4 recombinant antigens (produced in baculovirus and *E. coli* respectively), streptavidin-coated magnetic particles, bovine serum albumin (BSA), phosphate buffered saline (PBS) buffer, Ethylenediaminetetraacetic acid (EDTA) and preservatives.
- One (1) vial Calibrator containing diluted and inactivated serum/plasma containing low anti-HCV levels, BSA, PBS buffer, EDTA, 0.2% ProClin 300[1] and an inert yellow dye.
- One (1) vial Biotinylated HCV Nonstructural protein 3 (NS3) recombinant antigen (produced in *E. coli*), 2-(N-morpholino)ethanesulfonic acid (MES) buffer and preservatives.
- One (1) vial Specimen Diluent containing BSA, casein, non-specific recombinant protein (produced in *E. coli*), phosphate buffer, EDTA, preservatives and an inert blue dye.
- One (1) vial Conjugate containing Mouse monoclonal IgG to human IgG conjugated to an isoluminol derivative, foetal calf serum, phosphate buffer, 0.2% ProClin® 300, preservatives and an inert red dye.

Controls: LIAISON XL MUREX Control HCV Ab consists of two (2) levels (positive and negative) ready to use controls. Each control solution allows at least twenty (20) tests to be performed.

The control set is an additional material required to perform the test. The controls are comprised of the following components:

- Two (2) vials Negative control containing Human serum/plasma non-reactive for HCV antigens and antibodies, 0.2% ProClin® 300 and preservatives.
- Two (2) vials Positive control containing inactivated human serum/plasma reactive for HCV antibodies, 0.2% ProClin® 300 and preservatives.

In addition, the following ~~Analyzer and~~ accessories are required for performing the LIAISON XL MUREX HCV Ab and LIAISON XL MUREX Control HCV Ab:

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

Assay Principle

The method for qualitative determination of specific IgG to hepatitis C virus (HCV) is an indirect chemiluminescence immunoassay (CLIA). Two recombinant antigens (core and NS4) specific for HCV are used for coating magnetic particles (solid phase), while a third ready to use aqueous HCV antigen (biotinylated NS3) is also provided. During the first incubation, the biotinylated antigen is captured by streptavidin-coated magnetic particles, and HCV antibodies present in the calibrator, samples or controls bind to the solid phase through the recombinant HCV antigens. During the second incubation, a mouse monoclonal antibody to human IgG, linked to an isoluminol derivative (isoluminol-antibody conjugate), reacts with IgG to HCV already bound to the solid phase. After each incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of IgG to HCV presence in the calibrator, samples or controls.

Patient results should be interpreted as follows:
- Samples with S/CO value of less than 0.80 are considered non-reactive for HCV antibodies.
- Samples with S/CO value equal to or greater than 1.00 are considered reactive for HCV antibodies..
- Samples with S/CO values greater than or equal to 0.80 and less than 1.00 are considered equivocal. Equivocal samples should be retested in duplicate in order to confirm the initial result. Samples having at least 2 out of the 3 results equal to or above S/CO value of 1.0 are considered reactive. Samples having at least 2 out of the 3 results less than S/CO value of 1.0 are considered non-reactive.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of antibodies to hepatitis C (HCV). There are currently several FDA approved *in vitro* diagnostic tests commercially available for serological markers of hepatitis C virus (HCV) infection which, when used in conjunction with a patient's medical history, clinical examination and other laboratory findings, may be used as an aid in the diagnosis of HCV infection in patients with symptoms of hepatitis or who may be at risk for hepatitis C (HCV) 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 HCV Ab assay (318240) and LIAISON XL MUREX Control HCV Ab (318241) are very similar to the CE-marked LIAISON XL MUREX HCV Ab assay (310240) and LIAISON XL MUREX Control HCV Ab (310241). Some modifications to the development of all reagents in a liquid solution and to raw material manufacturing processes have been introduced.

The LIAISON XL MUREX HCV Ab assay (318240) and LIAISON XL MUREX Control HCV Ab (318241) have not been marketed in the U.S. or any foreign country.

The CE marked LIAISON XL MUREX HCV Ab assay (310240) and LIAISON XL MUREX Control HCV Ab (310241) 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.

Table 1 includes a list all countries where the CE-marked versions have been marketed in the past year.

Table 1

Australia	Switzerland	Jordan
Austria	United Kingdom	Bahrain
Belgium	Colombia	Qatar
Brazil	Peru	Kuwait
China	Dominican Republic	Iraq
Czech	Guatemala	Greece
France	Panama	Russia
Germany	Paraguay	Cipro
Israel	Chile	Hungary
Italy	Argentina	Bulgaria
Mexico	Indonesia	Croatia
Netherlands	Pakistan	Lithuanian Republic
Nordic	Thailand	Romania
Poland	Morocco	South Africa Republic
Portugal	Tunisia	Turkey
Spain	Saudi Arabia	

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 HCV Ab is intended for *in vitro* diagnostic use, and as a result, there is no direct adverse effect on the patient. Standard good laboratory practices are considered sufficient to minimize risks to the end user.

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

A false negative (non-reactive) anti-HCV result in a diagnostic setting may lead to a patient with HCV going unidentified. Under these circumstances there is a safety concern for both the patient and public, since such individuals may be capable of transmitting HCV infection. However, if a patient is known to be at high risk of HCV infection, or is symptomatic, and the physician's suspicion of HCV infection is high, HCV RNA testing is often employed and is of diagnostic value, even after initial negative anti-HCV result.

A false positive (reactive) result is not considered a patient or public health risk because a reactive result in a clinical lab should be followed up with supplemental testing (e.g. immunoblot and/or PCR for detection of HCV RNA) to determine inactive or unresolved infection versus active HCV replication. Treatment of the patient with chronic HCV infection is initiated only after extensive clinical, laboratory and behavioral assessment of the patient (e.g. elevated ALT levels for six months, detectable serum HCV RNA, liver biopsy with portal fibrosis, and abstinence from drugs and alcohol).

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Cut-off Determination

   The cut-off was established internally at DiaSorin and verified by testing fifty (50) known negative samples and fifty (50) known HCV positive samples. A Receiver Operating Characteristics (ROC) analysis was performed on the results of the specimens tested. The assay's cut-off was evaluated with the observed results to demonstrate that its selection represents the best level of specificity, without compromising the sensitivity.

   The cut-off value with an S/CO value of 1.0 is within the optimal range determined by the ROC curve to discriminate between negative and positive results.

2. Sensitivity / Seroconversion panel studies

   The seroconversion sensitivity of the LIAISON XL MUREX HCV Ab assay has been demonstrated by testing 21 commercial seroconversion panels in comparison

to a reference anti-HCV immunoassay in terms of number of days from initial draw to first positive sample, as well as the difference between the last non-reactive results and the first reactive results.

The LIAISON XL MUREX HCV Ab was reactive in the same bleed as the reference assay in 17 of the 21 panels tested. The LIAISON XL MUREX HCV Ab was reactive earlier than the reference assay in 3 of the 21 panels tested. The reference assay was reactive earlier than the LIAISON XL MUREX HCV Ab assay in 1 of the 21 panels tested.

3. Genotype Detection

Testing was performed to evaluate the ability of the LIAISON XL MUREX HCV Ab assay to detect antibodies to various known HCV genotypes and subtypes. Thirty-one (31) specimens were available and consisted of the following genotypes, as determined by the specimen vendor with commercially available HCV RNA assays: 1, 2, 3, 4, 5 and 6. The specimens were tested with the LIAISON XL MUREX HCV Ab assay and all were found to be reactive.

4. Endogenous Interference

The LIAISON XL MUREX HCV Ab assay was tested for potential interference of high levels of endogenous substances and drugs including Triglycerides (3000 mg/dL), Hemoglobin (1000 mg/dL), Bilirubin (conjugated and unconjugated 40 mg/dL), Albumin (6000 mg/dL), Cholesterol (400 mg/dL), Biotin (100 ng/mL), Total Protein (150 g/L), Immunoglobulin G (6 g/L), Ribavirin (120 mg/dL), and Inteferon-alpha2α (6000 IE/mL). No interference was observed at the levels tested.

5. Analytical Specificity (Cross-Reactivity)

A study was conducted to evaluate the LIAISON XL MUREX HCV Ab assay for cross-reactivity with specimens from individuals with medical conditions unrelated to HCV infection. The study was performed by testing 393 samples from 27 potentially cross-reactive subgroups. All samples tested resulted Non-reactive by a comparator immunoassay. Only one sample (Fatty liver disease), out of a total of 393 samples tested resulted Reactive with the LIAISON XL MUREX HCV Ab assay. A comparison of the analytical specificity between the two assays is summarized in Table 2:

Table 2

Organism / Condition	**N**	**Comparator HCV Ab assay**	**LIAISON XL MUREX HCV Ab**	
			Non-reactive	**Reactive**
Anti-nuclear antibodies (ANA)	13	Non-reactive	13	0
Non-viral liver diseases (i.e. Auto-immune hepatitis)	14	Non-reactive	14	0

C. trachomatis (anti-*chlamidia* positive)	15	Non-reactive	15	0
CMV (anti-CMV positive)	13	Non-reactive	13	0
EBV (anti-EBV positive)	15	Non-reactive	15	0
HSV (anti-HSV positive)	15	Non-reactive	15	0
E.Coli (anti-*E.Coli* positive)	15	Non-reactive	15	0
Fatty liver disease	15	Non-reactive	14	1
HAMA	15	Non-reactive	15	0
Hemodialysis patient	14	Non-reactive	14	0
Hepatitis A Virus (anti-HAV positive)	12	Non-reactive	12	0
Hepatitis B Virus (anti-HBV positive)	14	Non-reactive	14	0
Hepatocellular carcinoma	12	Non-reactive	12	0
HIV-1 (anti-HIV-1 positive)	8	Non-reactive	8	0
HIV-2 (anti-HIV-2 positive)	12	Non-reactive	12	0
HTLV-1/2 (anti-HTLV positive)	15	Non-reactive	15	0
IgG monoclonal gammopathy	11	Non-reactive	11	0
IgM monoclonal gammopathy	5	Non-reactive	5	0
Influenza vaccine recipients	15	Non-reactive	15	0
Multiparous pregnancies	15	Non-reactive	15	0
Multiple myeloma	14	Non-reactive	14	0
Multiple transfusion recipients	12	Non-reactive	12	0
N. gonorrhoea (anti-*Neisseria* positive)	15	Non-reactive	15	0
Pregnancy 1st trimester	15	Non-reactive	15	0
Pregnancy 2nd trimester	15	Non-reactive	15	0
Pregnancy 3rd trimester	15	Non-reactive	15	0
Rheumatoid Factor	14	Non-reactive	14	0
T. pallidum (anti-*treponema* positive)	15	Non-reactive	15	0
T.cruzi (anti-*T. cruzi* positive)	15	Non-reactive	15	0

6. Sample Equivalence/Matrix Effect

Thirty-two (32) paired sets of matched serum (with and without gel SST) and plasma (lithium and sodium heparin, sodium citrate and K_2EDTA) were tested to determine if these sample types provide equivalent results on the LIAISON XL MUREX HCV Ab assay. Each sample was divided into three aliquots. Two sets of aliquots were spiked with an anti-HCV high positive sample to achieve two (2) levels of samples: high negative and low positive samples. The third set of aliquots was un-spiked to serve as control samples. Where possible, native samples identified as high negative and low positive were used instead of spiking these samples. The results of the negative and low positive samples did not change the classification of the expected result. The results indicated that there is

equivalence among serum (with and without gel SST), K_2EDTA, lithium heparin, sodium heparin, and sodium citrate plasma.

7. Carry Over study

The LIAISON XL Analyzer uses disposable tips for sample pipetting which excludes risk of carryover by design. A carry-over study was performed to evaluate whether any significant amount of analyte is carried over from one sample reaction cuvette into the subsequent sample reaction cuvettes. A negative anti-HCV sample was analyzed in multiple runs alternately with a positive sample containing high levels of anti-HCV. The percentage of negative results for the negative sample was 100% and the percentage difference between the mean signal (RLU) values of all aliquots does not have an impact on clinical performance. All acceptance criteria were met, demonstrating that no significant amount of analyte is carried over from one sample reaction into the subsequent sample reactions.

8. Stability Studies

Sample stability

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-HCV 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, 2, 3, and 4 months.
- Freeze/Thaw (F/T) study – samples were tested unstressed (T=0) and after 1, 2, 3, 4, 5, 6, 7 and 8 F/T cycles. Samples were frozen for 12-24 hours at -20°C or lower and thawed at room temperature.

The studies indicate serum and plasma samples are stable for:

- Seven (7) days at 2-8°C
- Four (4) days at room temperature
- Three (3) months at -20°C
- Seven (7) Freeze/Thaw cycles.

Reagent Stability

Real-Time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON XL MUREX HCV Ab assay. Three (3) lots of LIAISON XL MUREX HCV Ab assay were stored at the recommended storage temperature of 2-8°C throughout the study. Performance was assessed against clinically relevant acceptance criteria using three (3) lots LIAISON XL MUREX Control HCV Ab (positive and negative) and an internal stability panel consisting of ten (10) samples. Testing was performed through thirteen (13) months from the date of manufacture and will continue through 18 months from date of manufacture.

Current results demonstrate that reagents are stable and continue to meet acceptance criteria thirteen months after the date of manufacture for the LIAISON XL MUREX HCV Ab and 12 months for the LIAISON XL MUREX Control HCV Ab.

Reagent Open Use

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

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

Kit performance using the opened Reagent Integral was evaluated weekly up to 13 weeks. After testing, kits were removed from the XL Analyzer stored in the refrigerator at 2-8 °C until the next testing point. Performance was assessed against clinically relevant acceptance criteria by testing the LIAISON XL MUREX Control HCV Ab (negative and positive) along with an internal stability panel at one (1) week intervals up to 13 weeks.

The LIAISON XL MUREX HCV Ab is stable after opening for 12 weeks when stored at 2-8 °C.

Reagent On-Board

Stability studies were conducted to determine the length of time the LIAISON XL MUREX HCV Ab Reagent Integral can be stored on-board the LIAISON XL Analyzer once opened. One (1) lot of the LIAISON XL MUREX HCV Ab Reagent Integral was stored on-board the LIAISON XL Analyzer throughout the 13 weeks of the study. Performance was assessed against clinically relevant acceptance criteria by testing the LIAISON XL MUREX Control HCV Ab (negative and positive) along with an internal stability panel at one (1) week intervals up to 13 weeks.

The LIAISON XL MUREX HCV Ab Reagent Integral is stable on-board the LIAISON XL Analyzer for 12 weeks.

Calibrator Stability

The LIAISON XL MUREX HCV Ab calibrator is included on the Reagent Integral. All studies for the Reagent Integral are applicable to the calibrator provided.

Calibration Interval Stability

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

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

Results demonstrate that the LIAISON XL MUREX HCV Ab calibration is stable for eight (8) weeks.

Control stability

Real-time (Shelf-Life)

Studies were performed to establish the shelf-life for the LIAISON XL MUREX Control HCV Ab. Three lots of LIAISON XL MUREX Control HCV Ab were stored at the recommended storage temperature of 2-8°C throughout the study. Testing was performed through twelve months from the date of manufacture and will continue through 18 months from date of manufacture.

To establish the real time (2-8°C) shelf-life the kit controls must be within their established acceptance ranges throughout the study and are assessed against clinically relevant acceptance criteria.

Current results demonstrate that the positive and negative controls are stable and continue to meet acceptance criteria twelve (12) months after the date of manufacture for the LIAISON XL MUREX Control HCV Ab.

Open Use

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

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

The LIAISON XL MUREX Control HCV Ab (negative and positive) are stable for 12 weeks after opening when stored at 2-8 °C between uses.

9. Precision

Internal 20 days

A precision/reproducibility study was carried out over a period of twenty (20) days on the LIAISON XL MUREX HCV Ab assay using the LIAISON XL Analyzer. The CLSI document EP5-A3 was consulted in the preparation of the testing protocol. The testing was performed internally at DiaSorin S.p.A.

A coded panel of eleven (11) samples (Negative, three (3) High Negative, four (4) Low Positive, and three (3) Moderate Positive) and three (3) lots of the LIAISON XL MUREX Control HCV Ab (negative and positive) were tested in two (2) replicates per run, two (2) runs per day for 20 days using three (3) different lots of LIAISON XL MUREX HCV Ab reagents.

The Intra-Run precision of the combined three (3) lots of LIAISON XL MUREX HCV Ab ranged from 1.8 % to 10.5%. The Overall %CV of the combined 3 lots of LIAISON XL MUREX HCV Ab ranged from 8.4% to 29.5%. Table 3 shows the results:

Table 3

			LIAISON XL MUREX HCV Ab Assay All 3 Lots Combined									
Sample ID	**N**	**Mean**	**Intra-Run**		**Run-to-Run**		**Day-to-Day**		**Lot-to-Lot**		**Overall**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Kit Ctrl Neg lot 1	240	0.08	0.01	10.5%	0.006	7.6%	0.004	5.1%	0.013	15.2%	0.017	20.6%
		5898*	677.2	11.5%	472.1	8.0%	421.4	7.1%	973.8	16.5%	1344	22.8%
Kit Ctrl Neg lot 2	240	0.10	0.009	8.8%	0.005	4.8%	0.007	7.4%	0.008	8.5%	0.015	15.1%
		7085*	646.8	9.1%	382.3	5.4%	528.8	7.5%	758.0	10.7%	1191	16.8%
Kit Ctrl Neg lot 3	240	0.09	0.005	6.0%	0.005	5.8%	0.006	7.1%	0.018	19.4%	0.020	22.3%
		6440*	390.4	6.1%	438.0	6.8%	474.7	7.4%	1374	21.3%	1567	24.3%
Kit Ctrl Pos lot 1	240	3.19	0.059	1.9%	0.103	3.2%	0.151	4.7%	0.208	6.5%	0.283	8.9%
Kit Ctrl Pos lot 2	240	2.92	0.062	2.1%	0.097	3.3%	0.139	4.7%	0.180	6.2%	0.255	8.7%
Kit Ctrl Pos lot 3	240	2.77	0.059	2.1%	0.083	3.0%	0.161	5.8%	0.194	7.0%	0.272	9.8%
HCV1U10	240	0.11	0.009	7.7%	0.010	9.1%	0.010	9.2%	0.028	25.4%	0.033	29.5%
		8065*	597.6	7.4%	717.2	8.9%	790.6	9.8%	2211	27.4%	2527	31.3%
HCV1U11	240	0.82	0.019	2.3%	0.033	4.0%	0.048	5.9%	0.064	7.8%	0.089	10.8%
HCV1U12	240	0.82	0.020	2.4%	0.033	4.1%	0.043	5.2%	0.066	8.1%	0.087	10.7%
HCV1U13	240	0.82	0.019	2.3%	0.029	3.5%	0.048	5.9%	0.065	7.9%	0.088	10.7%
HCV1U14	240	1.5	0.036	2.3%	0.063	4.1%	0.077	5.0%	0.142	9.3%	0.177	11.6%
HCV1U15	240	1.38	0.036	2.6%	0.050	3.6%	0.069	5.0%	0.109	7.9%	0.143	10.3%
HCV1U16	240	1.4	0.037	2.6%	0.051	3.5%	0.066	4.5%	0.109	7.5%	0.142	9.8%
HCV1U17	240	1.1	0.033	3.0%	0.032	2.9%	0.043	3.9%	0.108	9.8%	0.125	11.4%
HCV1U18	240	3.2	0.064	2.0%	0.108	3.3%	0.148	4.6%	0.212	6.6%	0.287	8.9%
HCV1U19	240	3.2	0.060	1.8%	0.098	3.0%	0.157	4.9%	0.216	6.7%	0.291	9.0%
HCV1U20	240	3.2	0.071	2.2%	0.092	2.8%	0.148	4.6%	0.196	6.0%	0.271	8.4%

*precision calculations based on signal (RLU).

External Precision 5 day Study;
A five (5) day precision/reproducibility study was conducted at two (2) external laboratories and one internal site at DiaSorin Inc. to verify the precision of the LIAISON XL MUREX HCV ab assay. The CLSI document EP15-A3 was consulted in the preparation of the testing protocol.

The coded panel, comprised of eleven (11) samples was the same panel used in the 20 day precision study. The precision panel was tested at all three (3) sites on the LIAISON XL Analyzer using six (6) replicates per run in one (1) run per day for five (5) operating days with multiple technicians performing the testing. Table 4 shows the results of the five day multi-site/lot precision:

Table 4

			LIAISON XL MUREX HCV Ab Assay 5 Day Multi-Site / Multi-Lot									
Sample ID	**N**	**Mean (S/CO)**	**Intra-Run**		**Between-Day**		**Total within site/lot**		**Site/lot to site/lot**		**Total**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Kit Control Neg	90	0.074	0.002	2.8%	0.002	3.0%	0.003	4.0%	0.022	29.6%	0.022	29.9%
		4482*	131.4	2.9%	137.2	3.1%	182.3	4.1%	1134	25.3%	1149	25.6%
Kit Control Pos	90	2.9	0.136	4.7%	0.118	4.1%	0.172	5.9%	0.085	2.9%	0.192	6.6%
HCV1U10	90	0.100	0.004	4.2%	0.005	5.2%	0.006	6.4%	0.036	36.1%	0.037	36.7%
		6190*	160.7	2.6%	265.2	4.3%	303.1	4.9%	2210	35.7%	2231	36.0%
HCV1U11	90	0.818	0.028	3.4%	0.033	4.1%	0.042	5.1%	0.103	12.5%	0.111	13.5%
HCV1U12	90	0.810	0.026	3.2%	0.024	3.0%	0.034	4.2%	0.097	12.0%	0.103	12.7%
HCV1U13	90	0.818	0.026	3.1%	0.029	3.5%	0.037	4.5%	0.108	13.3%	0.115	14.0%
HCV1U14	90	1.5	0.058	3.8%	0.060	3.9%	0.080	5.2%	0.202	13.2%	0.217	14.2%
HCV1U15	90	1.4	0.045	3.2%	0.062	4.5%	0.075	5.3%	0.162	11.5%	0.178	12.7%
HCV1U16	90	1.5	0.064	4.4%	0.071	4.9%	0.091	6.3%	0.179	12.3%	0.201	13.8%
HCV1U17	90	1.1	0.037	3.3%	0.041	3.7%	0.053	4.7%	0.155	14.0%	0.163	14.7%
HCV1U18	90	3.3	0.101	3.1%	0.106	3.2%	0.140	4.3%	0.316	9.7%	0.346	10.6%
HCV1U19	90	3.2	0.095	2.9%	0.096	3.0%	0.130	4.0%	0.300	9.3%	0.327	10.1%
HCV1U20	90	3.3	0.113	3.5%	0.082	2.5%	0.132	4.0%	0.328	10.0%	0.354	10.8%

*precision calculations based on signal (RLU).

10. Pediatric and Adult Sample Equivalency

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

A total of thirty (30) negative pediatric patient samples were used for this study. The pediatric samples encompassed the age range of two (2) months to twenty-one (21) years. Ten (10) pediatric samples were spiked with anti-HCV high positive sample to obtain high negative samples. Ten (10) pediatric samples were spiked with anti-HCV high positive sample to obtain low positive samples. Ten (10) pediatric samples were spiked with anti-HCV high positive sample to obtain moderate positive samples.

The samples were tested with the LIAISON XL MUREX HCV Ab. Averaged result for each pediatric sample were compared to results obtained on adult samples. No significant difference was observed between the performance of pediatric and adult 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 HCV Ab assay.

B. Animal Studies

Not Applicable

C. Additional Studies

Not applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the detection of antibodies to HCV with the LIAISON XL MUREX HCV Ab 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 HCV Ab assay on samples that would routinely be tested for hepatitis.

The clinical agreement study involved the testing of 3,649 samples on FDA approved reference assays, in order determine the HCV infection status for each of the samples tested. The samples were collected from six (6) different countries: Russia (n=1; <0.1%), Germany (n=4; 0.1%), Italy (n=5; 0.1%), Vietnam (n=37; 1.0%), Colombia (n=227; 6.2%), and the United States (n=3380; 92.5%). The U.S. samples were from multiple states including California, Florida, Maryland, Massachusetts, Michigan, New York, Pennsylvania, Tennessee, Texas, and Virginia.

The Prospective (unselected) subjects were defined as follows:

- Pediatric and adult subjects at risk for hepatitis infection due to medical conditions, occupation, lifestyle, behavior, or known exposure event and individuals with signs and symptoms of hepatitis infection. The adult subject's ages 22 - 98 years were of American Indian/Alaskan Native (< 0.1%), Asian (2.1%), Black/African American (27.9%), Caucasian/White (58.1%), Native Hawaiian or Pacific Islander (0.1%), Other (11.4%), and Unknown (0.3%) and included 2049 subjects. The pediatric population

ages 2 – 21 years were of Asian (0.5%), Black/African American (16.4%), Caucasian (37.8%), Other (43.8%), and Unknown (1.5%) ethnicities and included 201 subjects.

- Subjects currently undergoing dialysis treatment. The dialysis population ages 22 – 91 years consisted of 200 samples of Asian (2.0%), Black/African American (20.0%), Caucasian/White (76.0%), or Unknown (2.0%) ethnicities.
- Pregnant women with no known risk factor for hepatitis C infection. The 804 subjects ages 15-45 years were of Asian (0.6%), Black/African American (25.1%), Caucasian/White (23.5%), American Indian or Alaska Native (0.4%), Native Hawaiian or Pacific Islander (<1.0%) and Unknown (50.1%) ethnicities.

The retrospective (selected/archived) populations were from individuals (ages 18 – 80) either diagnosed with a current HCV Infection or negative for HCV antibodies. The samples were of Caucasian/White (65.25%), Black/African American (30.75%), Unknown (2.50%), and Other (1.50%) ethnicities and included 400 specimens.

The distribution of LIAISON XL MUREX HCV Ab reactive and non-reactive results by age and gender of the overall prospective population are presented in Table 4 below.

Table 4

Age Range (years)	**Gender**	**LIAISON XL MUREX HCV Ab**				
		+ (reactive)		**- (non-reactive)**		**Total**
		n	**%**	**n**	**%**	
2-12	F	0	0.0	14	100.0	14
	M	0	0.0	18	100.0	18
13-18	F	0	0.0	60	100.0	60
	M	0	0.0	44	100.0	44
19-21	F	0	0.0	119	100.0	119
	M	0	0.0	74	100.0	74
22-29	F	10	1.6	624	98.4	634
	M	6	3.0	197	97.0	203
30-39	F	17	2.6	640	97.4	657
	M	21	9.2	207	90.8	228
40-49	F	18	7.5	221	92.5	239
	M	20	12.6	139	87.4	159
50-59	F	22	10.5	187	89.5	209
	M	33	17.5	156	82.5	189
60-69	F	13	9.2	129	90.8	142
	M	14	12.0	103	88.0	117
70-79	F	3	5.0	57	95.0	60
	M	4	7.5	49	92.5	53
80-89	F	0	0.0	14	100.0	14
	M	2	16.7	10	83.3	12
90-98	F	0	0.0	4	100.0	4
	M	0	NA	0	NA	0

Age Range (years)	Gender	LIAISON XL MUREX HCV Ab				
		+ (reactive)		- (non-reactive)		Total
		n	%	n	%	
Unk	Unk	0	0.0	2	100.0	2
Total		**183**	**5.6%**	**3068**	**94.4%**	**3251**

Hepatitis C Infection Status

The clinical agreement study involved the testing the 3,654 prospective and retrospective specimens on FDA approved reference assays for hepatitis C to determine Hepatitis C infection status. HCV infection status was determined according to the CDC algorithm for interpretation of results. Table 5 shows the HCV infection status algorithm.

Table 5

HCV Infection Status Algorithm					
Reference Assay	**Comparator Assay 1**	**Comparator Assay 2**	**Intermediate HCV Status**	**HCV RNA by PCR**	**HCV Infection Status**
Reactive/ Equivocal	Non-Reactive	Non-Reactive	Not determined	Non-Reactive	Not HCV infected
Reactive/ Equivocal	Reactive	Non-Reactive	Not determined	Non-Reactive	Not determined
	Non-Reactive	Reactive			
Reactive/ Equivocal	Reactive	Non-Reactive	Not determined	Reactive	HCV Infected
	Non-Reactive	Reactive			
	Non-Reactive	Non-Reactive			
Non-Reactive	Not applicable		Not HCV infected	Not Applicable	Not HCV infected
Reactive/ Equivocal	Reactive	Reactive	HCV infected	Not Applicable	HCV Infected

Five (5) samples (3 prospective and 2 retrospective) were excluded from the analysis as HCV infection status could not be determined by the algorithm. After exclusions there were 3,251 prospective samples and 398 retrospective samples. Overall, 3,283 subjects were determined to be not HCV infected and 366 were classified as HCV infected by the reference assays.

Clinical Agreement Study Analysis

Comparison of results of the LIAISON XL MUREX HCV Ab results to HCV infection status as determined by the reference assay/s according to the algorithm are presented with positive percent (%) agreement and negative percent (%) agreement and 95% confidence intervals (Wilson method). The overall population consisted of 3649 subjects (3251 prospective and 398 retrospective samples). Table 6 compares LIAISON XL MUREX HCV Ab results to HCV infection status for individual prospective populations.

Table 6

HCV Category	HCV Infection Status				Total
	Not Infected		HCV Infected		
	LIAISON XL MUREX HCV Ab		LIAISON XL MUREX HCV Ab		
	+	-	+	-	
Individuals at Risk for HCV infection (Adult)	2	1142	52	0	1196
Individuals with Signs and Symptoms of hepatitis Infection	5	734	108	3	850
Pediatric at risk or with signs and symptoms of hepatitis infection	0	201	0	0	201
Dialysis Patients	0	187	12	1	200
Pregnant Women (10 weeks to 39 weeks gestational age)	1	800	3	0	804
TOTAL	**8**	**3064**	**175**	**4**	**3251**

Clinical Endpoints

With regard to safety, as an *in vitro* diagnostic test, the LIAISON XL MUREX HCV Ab test involves taking a sample of plasma or serum from a patient. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood samples are drawn. Safety issues regarding false positive and negative test results are discussed in section VIII.

With regard to effectiveness, the clinical performance of the LIAISON XL MUREX HCV Ab was evaluated versus multiple FDA approved anti-HCV tests for patients at risk for infection with hepatitis C and for patients with signs and symptoms of hepatitis C, as well as pregnant women for its ability to correctly determine the presence or absence of antibodies to HCV.

With regard to success/failure criteria, the assay performed adequately with positive percent agreement of 100% a negative percent agreement of 90.7% in subjects diagnosed with a current HCV Infection. It also had a negative percent agreement of 99.5% in subjects with no HCV antibodies.

B. Accountability of PMA Cohort

The clinical agreement study involved the testing of 3,654 samples on FDA approved reference assays in order determine the HCV infection status for each of the samples tested. The samples were collected from six (6) different countries: Russia (n=1; <0.1%),

Germany (n=4; 0.1%), Italy (n=5; 0.1%), Vietnam (n=37; 1.0%), Colombia (n=227; 6.2%), and the United States (n=3380; 92.5%). The U.S. samples were from multiple states including California, Florida, Maryland, Massachusetts, Michigan, New York, Pennsylvania, Tennessee, Texas, and Virginia. Table 7 shows the age, gender, and results of the cohort.

Table 7

Age Range (years)	Gender	LIAISON XL MUREX HCV Ab				Total
		+ (reactive)		- (non-reactive)		
		n	%	n	%	
2-12	F	0	0.0	14	100.0	14
	M	0	0.0	18	100.x0	18
13-18	F	0	0.0	60	100.0	60
	M	0	0.0	44	100.0	44
19-21	F	0	0.0	119	100.0	119
	M	0	0.0	74	100.0	74
22-29	F	10	1.6	624	98.4	634
	M	6	3.0	197	97.0	203
30-39	F	17	2.6	640	97.4	657
	M	21	9.2	207	90.8	228
40-49	F	18	7.5	221	92.5	239
	M	20	12.6	139	87.4	159
50-59	F	22	10.5	187	89.5	209
	M	33	17.5	156	82.5	189
60-69	F	13	9.2	129	90.8	142
	M	14	12.0	103	88.0	117
70-79	F	3	5.0	57	95.0	60
	M	4	7.5	49	92.5	53
80-89	F	0	0.0	14	100.0	14
	M	2	16.7	10	83.3	12
90-98	F	0	0.0	4	100.0	4
	M	0	NA	0	NA	0
Unk	Unk	0	0.0	2	100.0	2
Total		**183**	**5.6%**	**3068**	**94.4%**	**3251**

C. Study Population Demographics and Baseline Parameters

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

The Prospective (unselected) subjects were defined as follows:

- Pediatric and adult subjects at risk for hepatitis infection due to medical conditions, occupation, lifestyle, behavior, or known exposure event and individuals with signs

and symptoms of hepatitis infection. The adult subjects (22 - 98 years) were of American Indian/Alaskan Native (< 0.1%), Asian (2.1%), Black/African American (27.9%), Caucasian/White (58.1%), Native Hawaiian or Pacific Islander (0.1%), Other (11.4%), and Unknown (0.3%) and included 2049 subjects.
The pediatric population (ages 2 – 21 years) were of Asian (0.5%), Black/African American (16.4%), Caucasian (37.8%), Other (43.8%), and Unknown (1.5%) ethnicities and included 201 subjects.

- Subjects currently undergoing dialysis treatment. The dialysis population (ages 22 – 91 years) consisted of 200 samples of Asian (2.0%), Black/African American (20.0%), Caucasian/White (76.0%), or Unknown (2.0%) ethnicities.
- Pregnant women with no known risk factor for hepatitis C infection. The 804 subjects (ages 15-45 years) were of Asian (0.6%), Black/African American (25.1%), Caucasian/White (23.5%), American Indian or Alaska Native (0.4%), Native Hawaiian or Pacific Islander (<1.0%) and Unknown (50.1%) ethnicities.

The retrospective (selected/archived) populations were from individuals (ages 18 – 80) diagnosed with a current HCV Infection and for individuals negative for HCV antibodies. and were of Caucasian/White (65.25%), Black/African American (30.75%), Unknown (2.50%), and Other (1.50%) ethnicities and included 400 specimens.

D. Safety and Effectiveness Results

1. Safety Results

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

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

2. Effectiveness Results

The analysis of effectiveness was based on the 3,654 evaluable patients. Key effectiveness outcomes are presented in Tables 8 to 12.

Tables 8 and 9 compares LIAISON XL MUREX HCV Ab results to HCV infection status for the combined prospective & retrospective populations.

Table 8

	HCV Infection Status			**Total**
	Not HCV Infected	**HCV Infected**	**Not Determined ***	
Reactive	10	362	4	376
Not Reactive	3273	4	1	3278
Total	**3283**	**366**	**5**	**3654**

* Samples (n=5) with a not determined HCV Infection Status were not included in PPA and NPA calculations.

Table 9

Percent Agreement			95% CI (Wilson Approach)
Positive Percent Agreement	362/366	98.9%	97.2% - 99.6%
Negative Percent Agreement	3273/3283	99.7%	99.4% - 99.8%

The positive and negative percent agreements with 95% confidence interval between outcomes of LIAISON XL MUREX HCV Ab results to HCV infection status for prospective populations are presented below in Table 10

Table 10

HCV Category	**Positive Percent Agreement (PPA)**	**Negative Percent Agreement (NPA)**
Individuals at Risk for HCV infection (Adult)	(52/52) 100.0% *93.1%-100.0%*	(1142/1144) 99.8% *99.4%-100.0%*
Individuals with Signs and Symptoms of hepatitis Infection	(108/111) 97.3% *92.4%-99.1%*	(734/739) 99.3% *98.4%-99.7%*
Pediatric at risk or with signs and symptoms of hepatitis infection	NA	(201/201) 100.0% *98.1%-100.0%*
Dialysis Patients	(12/13) 92.3% *66.7%-98.6%*	(187/187) 100.0% *98.0%-100.0%*
Pregnant Women (10 weeks to 39 weeks gestational age)	(3/3) 100.0% *43.8%-100.0%*	(800/801) 99.9% *99.3%-100.0%*
TOTAL	**(175/179) 97.8%** ***(94.4%-99.1%)***	**(3064/3072) 99.7%** ***(99.5%-99.9%)***

Table 11 compares LIAISON XL MUREX HCV Ab results to HCV infection status for retrospective populations in subjects diagnosed with a current HCV infection and in subjects with no HCV antibodies.

Table 11

HCV Category	HCV Infection Status				Total
	Not Infected		HCV Infected		
	LIAISON XL MUREX HCV Ab		LIAISON XL MUREX HCV Ab		
	+	-	+	-	
Subjects diagnosed with a current HCV Infection	1	10	187	0	198

HCV Category	HCV Infection Status				Total
	Not Infected		HCV Infected		
	LIAISON XL MUREX HCV Ab		LIAISON XL MUREX HCV Ab		
	+	-	+	-	
Subjects with no HCV antibodies	1	199	0	0	200
TOTAL	**2**	**209**	**187**	**0**	**398**

The positive and negative percent agreements with 95% confidence interval between outcomes of LIAISON XL MUREX HCV Ab results to HCV infection status for retrospective populations in subjects diagnosed with a current HCV infection and in subjects with no HCV antibodies are presented below in Table 12.

Table 12

HCV Category	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Subjects diagnosed with a current HCV Infection	(187/187) 100.0% *98.0%-100.0%*	(10/11) 90.9% *62.3%-98.4%*
Subjects with no HCV antibodies	NA	(199/200) 99.5% *97.2%-99.9%*
TOTAL	**(187/187) 100.0%** ***98.0%-100.0%***	**(209/211) 99.1%** ***96.6%-99.7%***

3. Subgroup Analyses
   Table 6 shows pretest characteristics evaluated for assay performance.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data from adult subjects was not leveraged to support approval of a pediatric patient population.

   Samples from pediatric patients were tested in the clinical study in order to support a pediatric claim.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by

the regulation. The pivotal clinical study included 4 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 HCV Ab test for detecting anti-HCV antibodies in human adult and pediatric (2 – 21 years) serum and plasma (lithium and sodium heparin, sodium citrate and potassium EDTA) samples including separator tubes, on the LIAISON XL Analyzer has been demonstrated in the following patient populations: adults, pediatric (2 – 21 years), and pregnant women. The results of this test may be used as an aid in the diagnosis of HCV infection. The positive agreement of the assay is 98.9% with a two-sided 95% confidence interval (CI) of 97.2% - 99.6% and the negative percent agreement is 99.7% with a two-sided 95% CI of 99.4-99.8%.

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 HCV Ab test when used according to the provided can aid the physician in the diagnosis of HCV infection. The positive agreement of the assay is 98.9% with a two-sided 95% confidence interval (CI) of 97.2% - 99.6% and the negative percent agreement is 99.7% with a two-sided 95% CI of 99.4-99.8%.

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 LIAISON XL MUREX HCV Ab test can effectively assist in the diagnosis of HCV infection. Accurate diagnosis of HCV infection will guide further clinical decisions including initiation of appropriate antivirual treatment. Additionally, diagnosis and appropriate treatment can potentially decrease transmission and disease burden in the general population as well as in populations at high risk for hepatitis c infection.

1. Patient Perspectives

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

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

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity, precision, reproducibility, and analytical specificity of the LIAISON XL MUREX HCV Ab Assay when used according to instructions for use, warnings and precautions, and limitations sections of the labeling. The clinical studies and performance analysis of the clinical data in this application have shown that the assay is safe and effective for use as an aid in the diagnosis of HCV infection when used according to the directions for use in the labeling.

XIII. CDRH DECISION

CDRH issued an approval order on October 18, 2019.

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.