EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR LIAISON XL MUREX Anti-HDV DECISION SUMMARY

I Background Information:

A De Novo Number

DEN250032

B Applicant

Diasorin Inc.

C Proprietary and Established Names

LIAISON XL MUREX Anti-HDV (LIAISON XL MUREX Anti-HDV; LIAISON XL MUREX Control Anti-HDV)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
SGW	Class II	21 CFR 866.3176 - Device to detect antibodies to hepatitis D Virus	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for LIAISON XL MUREX Anti-HDV

B Measurand:

Anti-Hepatitis Delta Virus (Anti-HDV)

C Type of Test:

chemiluminescence immunoassay (CLIA)

III Indications for Use:

A Intended Use(s):

The LIAISON XL MUREX Anti-HDV assay uses chemiluminescence immunoassay (CLIA) technology for the qualitative detection of antibodies to the hepatitis D virus (anti-HDV) in adult human serum, lithium, sodium heparin, and K2-EDTA plasma. The assay is intended as an aid in the presumptive diagnosis of HDV infection in individuals who are HBsAg positive and at risk for HDV infection. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide evidence of infection with HDV. This test doesnot determine the state of infection or associated disease.

The test must be performed on the LIAISON XL Analyzer.

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

B Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For In Vitro Diagnostic Use Only

C Special Instrument Requirements:
LIAISON XL Analyzer

IV Device/System Characteristics:

A Device Description:
The LIAISONXL MUREX Anti-HDV is an *in vitro* diagnostic device consisting of five (5) reagents provided in individual compartments within a plastic container called Reagent Integral. The assay configuration allows for the performance of 100 tests.

Reagent Integral Composition

Table 1: Reagent Integral Composition:

Magnetic particles (2.45 mL)	Magnetic particles coated with biotinylated recombinant HDAg (obtained in E. coli), streptavidin, BSA, phosphate buffer, < 0.1% sodium azide.
Calibrator 1 (0.7 mL)	BSA, phosphate buffer, EDTA, 0.2% ProClin™ 300, an inert yellow dye.
Calibrator 2 (0.7 mL)	Diluted and inactivated serum/plasma containing low anti-HDV levels, BSA, phosphate buffer, EDTA, 0.2% ProClin™ 300, an inert blue dye.
Specimen diluent (25 mL)	BSA, casein, borate buffer, EDTA, 0.2% ProClin™ 300, detergents and preservative.
Conjugate (23 mL)	Mouse monoclonal IgG to human IgG and Mouse monoclonal IgG to human IgM conjugated to an isoluminol derivative, non-specific IgG (mouse polyclonal), BSA, phosphate buffer, 0.2% ProClin™300, preservatives, an inert blue dye.

All reagents are supplied ready to use. The order of reagents reflects the layout of containers in the Reagent Integral.

Additionally required materials
LIAISON XL MUREX Control Anti-HDV is quality control material provided in a separate box consisting of 2 levels of controls (2 control levels x 2 vials x 1.0 mL, ready to use). Each control

vial allows at least 20 tests to be performed. Quality control should be performed once per day of use. Follow applicable government or local regulations for quality control.

Table 2: LIAISON XL MUREX Control Anti-HDV set Composition:

Negative control (2 x 1.0 mL)	Human serum/plasma non-reactive for HDV antibodies, 0.2% ProClin™ 300, preservatives.
Positive control (2 x 1.0 mL)	Inactivated human serum/plasma reactive for HDV antibodies, 0.2% ProClin™ 300, preservatives.

Materials required but not provided with the device
LIAISON XL Analyzer

LIAISON XL Analyzer (Model I0050), is a fully automated system with continuous loading combining the chemiluminescence technology with magnetic microparticles as solid phase. The LIAISON XL Analyzer performs the complete sample processing (sample pre-dilutions, sample and reagent dispensing, incubations, wash processes) as well as the measurement and evaluation.

The addition of the Workcell Upgrade Kit extends the sampling arm to allow for connection to any third-party laboratory automation having compatible connection capability for the performance of pre- and post-analytical sample handling processes. The LIAISON XL Workcell Upgrade Kit also maintains the LIAISON XL Analyzer's performance as a stand-alone instrument.

To perform the assay, the following materials are needed in addition to the specific assay Reagent Integrals:

LIAISON XL Cuvettes (code X0016).
LIAISON XL Disposable Tips (code X0015)
LIAISON XL Starter Kit (code 319200)
LIAISON XL Wash/System Liquid (code 319100)
LIAISON XL Waste Bags (code X0025).

B Principle of Operation

The method for the qualitative determination of specific antibodies to hepatitis D virus (HDV) is an indirect chemiluminescence immunoassay (CLIA). The recombinant antigen specific for HDV is used for coating magnetic particles (solid phase). During the first incubation, the HDV antibodies present in the calibrator, samples or controls bind to the solid phase through the recombinant HDV antigen. During the second incubation, mouse monoclonal antibodies to human IgG and mouse monoclonal antibodies to human IgM, both linked to an isoluminol derivative (isoluminol-antibody conjugate), react with antibodies to HDV 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 indicates the presence or absence of antibodies to HDV presence in the calibrator, samples, or controls.

LIAISON XL MUREX Anti-HDV results are reported as Index value, which is used for sample grading to provide a qualitative reportable result. The Index value is calculated by dividing the signal generated by the analyzer (relative light units, RLU) to a value obtained by multiplying the calibrator mean signal (RLU) per an "a" coefficient. The 'coefficient a' is the factor by which the

Cut-off can be optimized to achieve the required balance of assay specificity and sensitivity, to obtain a correct sample

Test Result Interpretation

The presence or absence of HDV antibodies in the specimens is qualitatively determined by comparing the chemiluminescence reaction signal to the specific assay calibration. The analyzer automatically calculates the Index value and grades the results.

The value discriminating between the presence and the absence of HDV antibodies is 2.00 Index. Sample results should be interpreted as follows:

LIAISON XL MUREX Anti-HDV		
Index	**Results**	**Interpretation**
< 2.00	Non-reactive	A result below 2.00 Index indicates antibodies to HDV were not detected, or the level of antibodies to HDV are below the detection threshold.
≥ 2.00	Reactive	Presumptive evidence of antibodies to HDV. Follow medical guideline recommendations for supplemental testing.

C Instrument Description Information

1. Instrument Name:
   LIAISON XL Analyzer

2. Specimen Identification:
   Barcode scanning

3. Specimen Sampling and Handling:
   The LIAISON XL Analyzer performs the complete sample processing (sample pre-dilutions, sample and reagent dispensing, incubations, wash processes) as well as the measurement and evaluation. The addition of the Workcell Upgrade Kit extends the sampling arm to allow for connection to any third-party laboratory automation having compatible connection capability for the performance of pre- and post-analytical sample handling processes. The LIAISON XL Workcell Upgrade Kit also maintains the LIAISON XL Analyzer's performance as a stand-alone instrument.

4. Calibration:
   Testing of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the assigned master curve.
   Recalibration in triplicate is mandatory whenever at least one of the following conditions occurs:
   - A new lot of Reagent Integral or of Starter Kit is used.
   - The previous calibration was performed more than twelve (12) weeks before.
   - Control values lie outside the expected ranges.
   - The analyzer has been serviced.

Calibrator values are stored in the reagent integral Radio Frequency Identification transponder (RFID Tag).

5. Quality Control:
   Quality control should be performed once per day of use. Follow applicable government or local regulations for quality control.

V Standards/Guidance Documents Referenced:

EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition
EP07 3rd Edition Interference Testing in Clinical Chemistry
EP37 1st Edition Supplemental Tables for Interference Testing in Clinical Chemistry
EP15-A3 User Verification of Precision and Estimation of Bias; Approved Guideline - Third Edition
I/LA21-A2 Clinical Evaluation of Immunoassays; Approved Guideline-Second Edition
EP25-A (Replaces EP25-P) Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.
EP12-A2 User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline-Second Edition
EP14-A3 Evaluation of Commutability of Processed Samples; Approved Guideline-Third Edition
EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition
EP28-A3c (Formerly C28-A3c) Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition
GP44-A4 (Formerly H18-A4) Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guidelines
ISO 15223-1 Fourth edition 2021-07
Medical devices-Symbols to be used with information to be supplied by the manufacturer-Part 1;General requirements
ISO 17511 Second Edition 2020-4
In vitro diagnostic medical devices-Requirements for establishing metrological traceability of values assigned to calibrators trueness control material and human samples

VI Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:

   Precision Study: To evaluate the within-laboratory precision of the LIAISON XL Murex anti-HDV assay, a twenty-day precision study was performed using a panel of nine samples spanning the range of negative, low positive and positive. Kit Controls were also included in the study. The panel samples and kit controls were tested with the LIAISON XL Murex Anti-HDV assay in two replicates per run, two runs per day for twenty operating days on one

LIAISON XL Analyzer, on three reagent lots. The precision panel and study results are presented in Table 3 and Table 4, respectively.

Table 3 Precision Panel (In house prepared)

Sample ID	Reactivity Level (CO = 2 Index)	Measured Concent. (Index)	HDV Positive Spiker		HDV Negative Matrix		Dilution Factor
			Code	Lot	Code	Lot	
HDV-01-U1	Negative	<0.100	-	-	M09_2030	#79532	-
HDV-01-U9	Negative	0.593	M29_3117	# 1	M09_2030	#79534	30000
HDV-01-U2	High Negative	1.31	M29_4318	# 3	M09_2030	#79532	80
HDV-01-U3	High Negative	1.30	M29_4318	# 4	M09_2030	#79532	84
HDV-01-U4	Cut-Off	2.31	M29_4318	# 5	M09_2030	#79532	77
HDV-01-U10	Cut-Off	2.21	M29_4318	# 4	M09_2030	#79532	70
HDV-01-U11	Low Positive	4.49	M29_3117	# 1	M09_2030	#79532	191
HDV-01-U5	Moderate Positive	7.04	M29_3117	# 1	M09_2030	#79532	88
HDV-01-U6	High Positive	9.91	M29_3117	# 1	M09_2030	#79532	34

Table 4. Results of twenty (20) Days Precision results for LIAISON XL Murex Anti-HDV three lots combined on LIAISON XL instrument

Sample ID	N	Mean (Index)	Intra-Run		Run-to-Run		Day -to-Day		Lot-to-Lot (Between Lot)		OVERALL	
			StDev	%CV	StDev	%CV	StDev	%CV	StDev	%CV	StDev	%CV
RS1320	240	7496*	1876	25.0%	1887	25.2%	576	7.7%	232	3.1%	2707	36.1%
RS1321	240	7470*	1666	22.3%	2002	26.8%	765	10.2%	143	1.9%	2692	36.0%
RS1322	240	7178*	1660	23.1%	2235	31.1%	0.000	0.0%	269	3.8%	2767	38.6%
RS1323	240	2.47	0.065	2.6%	0.079	3.2%	0.071	2.9%	0.102	4.1%	0.149	6.0%
RS1324	240	2.35	0.060	2.5%	0.041	1.8%	0.096	4.1%	0.099	4.2%	0.143	6.1%
RS1325	240	2.39	0.053	2.2%	0.054	2.3%	0.111	4.6%	0.105	4.4%	0.157	6.6%
HDV-01-U01	240	5517*	2077	37.6%	2106	38.2%	1112	20.2%	393	7.1%	3147	57.0%
HDV-01-U09	240	0.534	0.027	5.1%	0.016	3.0%	0.027	5.1%	0.018	3.4%	0.044	8.2%

HDV-01-U02	240	1.33	0.029	2.2%	0.019	1.5%	0.069	5.2%	0.065	4.9%	0.093	7.0%
HDV-01-U03	240	1.34	0.042	3.1%	0.018	1.4%	0.039	2.9%	0.067	5.0%	0.081	6.1%
HDV-01-U04	240	2.38	0.059	2.5%	0.039	1.6%	0.066	2.8%	0.115	4.8%	0.134	5.6%
HDV-01-U10	240	2.24	0.102	4.5%	0.077	3.5%	0.071	3.2%	0.057	2.5%	0.152	6.8%
HDV-01-U11	240	4.43	0.217	4.9%	0.164	3.7%	0.183	4.1%	0.176	4.0%	0.355	8.0%
HDV-01-U05	240	6.90	0.191	2.8%	0.138	2.0%	0.129	1.9%	0.347	5.0%	0.389	5.6%
HDV-01-U06	240	9.63	0.176	1.8%	0.126	1.3%	0.200	2.1%	0.525	5.5%	0.519	5.4%

(*) For negative samples and controls with obtained dose less than 0.100 Index, final statistic (Mean, Standard deviation and CV %) was calculated on the RLUs. As per Acceptance criteria, the only criterion requested for negative samples (Index < 2) is the correct classification.

All the samples tested during the twenty (20) Days Precision study on the combined lots were correctly classified as REACTIVE (Index ≥ 2) and NON-REACTIVE (Index < 2). Regarding the Overall/Total CV%, the positive samples of the precision panel (HDV-01-U04 to HDV-01-U06, plus HDV-01-U10 and HDV-01-U11) generated Overall CV% between 5.4% – 8.0%, while for positive controls (RS1323, RS1324, RS1325) the CV % was between 6.0% – 6.6%.

Multi-Site Reproducibility Study: To evaluate the reproducibility of the LIAISON XL Murex anti-HDV, six samples from the same panel used in the precision study was tested at three sites, using one reagent lot at three replicates per run in two runs per day for five days. The means, standard deviation, and coefficient of variation (%CV) of the results were computed for each of the tested specimens across sites. A summary of all sites combined study results is illustrated in Table 5.

Table 5. Reproducibility study results on the LIAISON XL Murex Anti-HDV by all site combined.

Panel ID	Sample ID	N	Mean (Index or RLU)	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative Control	RS1320*	90	3885	547	14.1	0.0	0.0	0.0	0.0	91	2.3	555	14.3
Positive Control	RS1323	90	2.57	0.172	6.7	0.035	1.4	0.092	3.6	0.235	9.2	0.305	11.9
Sample 1	HDV-01-U1*	90	2082	280	13.4	0.000	0.0	223	10.7	39.4	1.9	360	17.3
Sample 2	HDV-01-U2	90	1.34	0.073	5.4	0.017	1.3	0.080	5.9	0.113	8.4	0.156	11.6
Sample 3	HDV-01-U3	90	1.34	0.067	5.0	0.000	0.0	0.081	6.1	0.094	7.0	0.141	10.5
Sample 4	HDV-01-U4	90	2.46	0.138	5.6	0.017	0.7	0.091	3.7	0.192	7.8	0.254	10.3
Sample 5	HDV-01-U5	90	7.61	0.337	4.4	0.000	0.0	0.045	0.6	0.612	8.0	0.700	9.2

Sample 6	HDV-01-U6	90	10.60	0.343	3.2	0.104	1.0	0.058	0.5	0.737	6.9	0.815	7.7

*For negative samples and controls (with obtained dose less than 1 Index), final statistic (Mean, Standard deviation and CV %) was calculated on the RLUs.

The highest %CV on a positive sample is 11.9% (RS1323, kit control). Samples RS1320 and HDV-01-U1, are < 0.100 Index and the reproducibility values are calculated using RLUs.

2. Linearity:
   Not applicable.

3. Analytical Specificity/Interference:

   Analytical specificity: A study was conducted to evaluate the LIAISON XL Murex Anti-HDV for potential cross-reactivity with specimens from individuals with medical conditions unrelated to HDV infection. Cross reactivity was evaluated by testing 371 samples.
   The results revealed no cross reactivity with the tested potential cross reactants (Table 6).

Table 6. Cross reactivity study results on the LIAISON XL Murex Anti-HDV

Potential Cross reactants	**Number of Samples Tested**	**Number Negative on the competitor assays**	**Number Positive on LIAISON Murex Anti-HDV**
Anti-nuclear autoantibodies (ANA)	10	10	0
Autoimmune Hepatitis	10	10	0
Borrelia burgdorferi (anti-B. burgorferi antibodies)	10	10	0
Chlamydia trachomatis	10	10	0
Trypanosoma cruzi	10	10	0
CMV (anti-CMV positive)	10	10	0
Dengue Fever	10	10	0
Anti-E.coli antibodies	13	13	0
Epstein-Bar Virus (anti-EBV positive)	11	11	0
Influenza	10	10	0
Neisseria gonorrhea	10	10	0
Human anti-mouse antibodies (HAMA)	10	10	0
Hepatitis A Virus (anti-HAV positive)	10	10	0
Hepatitis B Virus (anti-HBV positive)	10	10	0
Hepatitis C Virus (anti-HCV positive)	10	10	0
Hepatitis E Virus (anti-HEV positive)	10	10	0
Hemodialysis patients	10	10	0
Liver cancer	12	12	0
Human Immunodeficiency Virus	10	10	0
Herpes Simplex Virus (anti-HSV positive)	10	10	0
HTLV-I/II	5	5	0
Fatty liver disease	25	25	0

Measles virus (anti-Measles antibodies)	9	9	0
Monoclonal gammopathies	10	10	0
Multiple transfusion recipients	10	10	0
Mumps virus (anti-Mumps antibodies)	10	10	0
Mycoplasma Pneumoniae	15	15	0
Multiple myeloma	11	11	0
Parvovirus B19 (anti-Parvovirus B19 positive)	10	10	0
PBC	10	10	0
Rheumatoid Factor (anti-Fc Immunoglobulin)	10	10	0
Rubella (anti-Rubella positive)	9	9	0
Toxoplasma. gondii (anti-T. gondii antibodies)	10	10	0
Treponema Pallidum	11	11	0
VZV	10	10	0
TOTAL	**371**	**371**	**0**

Endogenous interferences: A study was conducted to evaluate the endogenous interferences on the LIAISON XL Murex Anti-HDV assay. Potentially interfering substances were evaluated at four sample levels, negative, high negative, around the cut-off and low positive. The results revealed no interferences observed with tested endogenous interferents (Table 7).

Table 7. Endogenous interference study results on the LIAISON XL Murex Anti-HDV

Substances	Tested concentrations	Substances	Tested concentrations
Unconjugated bilirubin	40 mg/dL	Human Serum Albumin	6000 mg/dL
Conjugated bilirubin	40 mg/dL	Cholesterol	400 mg/dL
Hemoglobin	1000 mg/dL	Total IgG	2000 mg/dL
Triglycerides	3000 mg/dL	Total IgM	400 mg/dL
Total protein (high	≥ 120 g/L	Total protein (low)	≤ 60 g/L

Exogenous interferences: Commonly found exogenous interferences among the intended used populations were tested on LIAISON XL Murex anti-HDV at four sample levels, negative, high negative, around the cut-off and low positive (Table 8). The results revealed no interferences observed with tested exogenous interferents (Table 9).

Table 8 Specificity Panel

Analytical Level (CO = 2 Index)	Target Dose (Index)	Tested Sample ID	Positive Specimen	Negative Specimen	Dilution Factor (1 in x)
Negative	< 1 Index	HDV-HN	M2900004318 Lot #5	M0900002030 Lot #79532	280
High Negative	1.0 – 1.99	HDV-CO	M2900004318 Lot #5	M0900002030 Lot #79532	140

Cut-Off	Approx. 2.0	HDV-LP	M2900004318 Lot #5	M0900002030 Lot #79532	75
Low Positive	3.0 – 5.0	HDV-POS	M2900003117 Lot # 1	M0900002030 Lot #79532	191

The studies of exogenous potentially interfering substances at four (4) anti-HDV analytical levels (negative, high negative, around the cut off value and low positive) showed no interference on the LIAISON® XL Murex Anti-HDV at the concentrations listed in Table 8 (to be reported in the IFU). All samples were correctly classified as negative (non-reactive, Index < 2.0) and positive (reactive, Index ≥ 2.0) and the percentage interference was within 10% for all the conditions tested.

Table 9 Exogenous substances and the concentration assessed

Interfering Substances	**Tested concentrations**	**Interfering Substances**	**Tested concentrations**
Biotin	3500 ng/mL	Ethanol	0.2 g/100 mL
Vitamin A	800 µg/dL	Interferon alpha 2a	6000 IE/mL
Vitamin B12	2850 pg/mL	Interferon alpha 2b	6000 IE/mL
Vitamin C	20 mg/dL	Interferon alpha 1b	6000 IE/mL
Vitamin D	450 ng/mL	Telbivudine	600 mg/L
Vitamin E	120 mg/L	Entecavir	0.5 mg/L
Folic Acid	160 ng/mL	Tenofovir	0.0978 mg/dL
Acetaminophen	20 mg/dL	Lamivudine	300 mg/L
Ibuprofen	50 mg/dL	Adefovir dipivoxil	10 mg/L
Acetylsalicylic acid	50 mg/dL	Bulevirtide (Gilead)	5 mg/L
Caffeine	6 mg/dL	-	-

4. Assay Reportable Range:
   Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

a. Reagent Integral Stability:

Reagent Integral long-term stability:

Shelf life of the LIAISON Murex anti-HDV kit reagents was evaluated by testing three lots of kit reagents stored for different time-points at the designated storage condition (2-8º C). Stability panel samples and kit controls were tested in three replicates and the results was compared to the time zero testing results. Stability claim for LIAISON XL Anti-HDV is 24 months.

In-Use Reagent Integral

Calibration stability: This study evaluated stability of LIAISON XL Murex Anti-HDV calibration by simulating normal conditions of use as specified in the instructions for use. Calibration stability claim is 8 weeks (56 days).

Open Kit/Onboard Stability: This study evaluated open kit reagents stored onboard for a period of time. Open kit stability claim is 12 weeks (84 days).

b. Kit control stability:

Kit control shelf life:

Shelf life of the kit controls was evaluated by testing three lots of kit controls stored at 2-8ºC. Stability testing consisted of three replicates in one run with the LIAISON Murex anti-HDV test using one LIAISON Murex analyzer at each time point.

The study supports control stability claim of 24 months.

Open kit control stability:

This study evaluated open kit controls stored onboard for a period of time. Open kit control stability claim is 12 weeks (84 days).

c. Transport stability

The purpose of this study was to ensure that the product maintains its specifications and performance during the shipment and delivery phases to the client.

Study evaluated the reagents under four stress conditions compared to reference refrigerated storage (2-8°C): extended room temperature exposure at 30°C for 5 days and 10 days, short-term extreme heat exposure at 37°C for 1 day, and freezing at -20°C for 1 day.

Results show the shipment of LIAISON XL Anti-HDV kit and Controls are expected to maintain performance despite temperature execution. All reagents are shipped at 2-8^{0}C with data logger to monitor temperature.

d. Sample storage stability:

This study evaluated the effect of stability of samples stored at different conditions on results of LIAISON XL Murex Anti-HDV. The testing panels consisted of serum and plasma samples, including two samples each of negative (0.100-0.990 Index), high negative (1.00-1.99 Index), cut-off (approximately 2.0 Index), low positive (2.0-5.0 Index), and moderate positive (greater than 5.0 Index) levels.

Table 10 presents the sample storage claims met for each of the condition tested.

Table 10. Sample stability results

Storage Condition	Room temperature (+15 to 30°C)	Refregerated (+2 to +8 °C)	Freeze thaw (FT) cycles	Long term storage at -20°C
Matrix	Days	Days	# of FT cycles	Months
Serum	3	7	6	6
Serum SST	3	7	6	6
K2-EDTA plasma	3	3	6	6
Sodium Heparin plasma	3	3	6	6
Lithium Heparin plasma	3	3	6	6

6. Detection Limit:

   Not Applicable

7. Assay Cut-Off:

   The cut-off was established by testing a total of 208 samples (100 negative and 108 positive). The assay's cut-off evaluated with observed results and further validated and optimized with clinical study results has a value of 2 Index.

The Index values obtained from assay results are automatically graded by the LIAISON Analyzer as "REACTIVE" and "NON-REACTIVE" based on the cut-off value of 2.

8. Accuracy (Instrument):
   Not Applicable

9. Carry-Over:
   A study was performed to determine the carryover in the instrument's measuring cell caused by a high signal- generating samples. No carryover was observed for the LIAISON XL Murex anti-HDV assay.

B Comparison Studies:

1. Method Comparison:

   Not Applicable

2. Matrix Comparison:
   A study was conducted to evaluate matrix equivalence by testing matched patient sets of serum and plasma samples with anticoagulants, to determine the intended matrices perform comparably on the LIAISON XL Murex Anti-HDV assay. The study evaluated performance equivalence by analyzing relative signal differences between serum, versus serum SST, lithium and sodium heparin plasma, and K2-EDTA plasma. Table 11 shows the summary of matrix equivalence study results.

Table 11. Matix equivalence study results

Reference Matrix	**Serum**			
Test Matrix	Serum with Gel SST	K2-EDTA	Lithium Heparin	Sodium Heparin
Number of samples tested	80	80	80	80
*N Bias ≤ 10%	79	79	79	79
N Bias % 10 – 15%	1	1	1	1
*N Bias > 15%	0	0	0	0
Recovery %	98.8%	98.8%	98.8%	98.8%

C Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable

2. Clinical Specificity:

   Not Applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Summary of Clinical Performance

A multisite agreement study was conducted in the United States to determine the clinical performance of the LIAISON XL MUREX anti-HDV assay. The tested clinical study population was made up of 2,802 specimens of which:

- 1945 were collected prospectively from individuals with a positive hepatitis B surface antigen (HBsAg) test. Specimens were collected contiguously as remnants of laboratory routine from three geographic regions within the United States (Eastern, Central, and Western).
- 857 specimens were obtained retrospectively from a single liver center, from patients suspected of acute or chronic liver disease or at risk for acute or choric liver diseases. All specimens were selected from patients who were HBsAg positive and treatment naive.

Hepatitis D total antibody status was determined by testing all prospective and retrospective specimens using a composite reference method of three (3) appropriate comparators measuring antibodies to hepatitis D. Consensus method of the comparators was used to determine positive or negative status. The percentage agreements with candidate device are provided in Tables 12 and 13.

Table 12. Prospective Clinical Agreement

		Composite Reference Method			
		Positive	Equivocal	Negative	Total
Candidate - LIAISON XL MUREX Anti-HDV	Positive	19	0	7	26
	Negative	0	1*	1918	1919
	Total	19	1	1925	1945

*Equivocal results by the CRM are graded against the performance of the candidate device.

Positive Percent Agreement (PPA): 95.0% (19/20); 95% CI (76.4% - 99.1%)

Negative Percent Agreement (NPA): 99.6% (1918/1925); 95% CI (99.3% - 99.8%)

Table 13. Retrospective Liver Center Clinical Agreement

		Composite Reference Method			
		Positive	Equivocal	Negative	Total
Candidate - LIAISON XL MUREX Anti-HDV	Positive	134	0	6	140
	Negative	1	0*	716	717
	Total	135	0	722	857

Positive Percent Agreement (PPA): 99.3% (134/135); 95% CI (95.9% - 99.9%)

Negative Percent Agreement (NPA): 99.2% (716/722); 95% CI (98.2% - 99.6%)

4. Summary of baseline demographic information:

Demographic Characteristics		Prospective		Retrospective	
		n	%	n	%
Age	1-9	0	0.0%	16	1.9%
	10-19	15	0.8%	35	4.1%
	20-29	76	3.9%	122	14.2%
	30-39	319	16.4%	212	24.7%
	40-49	498	25.6%	228	26.6%
	50-59	470	24.2%	148	17.3%
	60-69	352	18.1%	75	8.8%
	70-79	168	8.6%	20	2.3%
	80-89	42	2.2%	1	0.1%
	90-99	5	<0.3%	0	0.0%
Gender	Female	900	46.3%	324	37.8%
	Male	1043	53.6%	533	62.2%
	Not Provided	2	0.1%	0	0.0%
Race[1]	American Indian or Alaska Native	Not Available	Not Available	2	0.2%
	Asian	Not Available	Not Available	357	41.7%
	Black/African American	Not Available	Not Available	203	23.7%
	White	Not Available	Not Available	255	29.8%
	Multiracial	Not Available	Not Available	8	0.9%
	Other	Not Available	Not Available	1	0.1%
	Unknown	Not Available	Not Available	31	3.6%

D Clinical Cut-Off:

Not Applicable

E Expected Values/Reference Range:

Not Applicable

F Other Supportive Performance Characteristics Data:

Not Applicable

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

VIII Identified Risks and Mitigations:

Identified Risks to Health	Mitigation Measures
False reactive/false non-reactive assay result	Certain labeling information, warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including analytical and clinical studies and risk analysis strategies.
Failure to correctly interpret the assay results	Certain labeling information, warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including analytical and clinical studies and risk analysis strategies.
Failure to correctly operate the device	Certain labeling information, warnings, limitations, results interpretation information, and explanation of procedures. Certain design verification and validation information including analytical and clinical studies and risk analysis strategies.

IX Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

The benefits of the assay are, in conjunction with other laboratory and clinical information, the diagnosis of hepatitis D virus (HDV) infection in subjects with hepatitis B virus (HBV) infection. HDV infection occurs in one of two patterns, HBV-HDV co-infection and HDV superinfection. HBV-HDV co-infection occurs when infection with both viruses occur simultaneously. This can result in extensive hepatic necrosis and can manifest with severe or fulminant hepatitis with a high case fatality rate. In HDV superinfection, patients with chronic HBV infection become infected with HDV. HDV superinfection frequently results in chronic HDV infection, which leads to accelerated progression to cirrhosis, and an increased risk of hepatocellular carcinoma (HCC), compared to patients with chronic HBV mono-infection. While there are no drugs approved in the US for treatment of HDV, diagnosis of HDV informs prognosis and guides the need for additional imaging (HCC surveillance) and laboratory testing. Diagnosis of HDV infection in subjects with HBV presents an opportunity to decrease community transmission for those at risk for HDV infection.

B Summary of the Assessment of Risk:

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, resulting in false negative or false positive diagnoses. Risk of a false positive test result includes improper patient management, including additional venipuncture for laboratory testing. Because HDV can be associated with acute fulminant hepatitis, a false positive test result may also halt further evaluation for other causes of acute fulminant hepatitis, causing a delay in diagnosis and initiation of treatment.

Risks of false negative test results include improper patient management due to missed diagnosis of HDV infection. HDV infection is always associated with HBV infection and HDV co-infection or superinfection are associated with worse prognosis than HBV infection alone. Missed diagnosis may lead to missed opportunity for laboratory testing and imaging to monitor for progression to cirrhosis or hepatocellular carcinoma.

C Patient Perspectives:

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

D Summary of the Assessment of Benefit-Risk:

The risks associated with the device (risk of false test results, failure to correctly interpret the results, and failure to correctly operate the device) are mitigated by labeling information, which will assist the operator in correctly performing the test and will assist healthcare providers in understanding the intended use of the test and evaluating the predictive value of a result based on the analytical and clinical performance of the test. In addition, the risks of false test results and failure to correctly interpret the results are mitigated by certain design verification and validation activities, including analytical and clinical studies and risk analysis strategies to reduce the likelihood of such errors. Such measures help to ensure that errors will be uncommon and will facilitate accurate assay implementation and interpretation of results. Risks can be further mitigated by including additional warnings noting limitations of safety information, including populations or situations for which the safety and efficacy of the device has not been evaluated. While general controls alone are insufficient to mitigate the risks associated with the device, given the special controls, the benefits outweigh the risks.

X Conclusion:

The De Novo request is granted, and the device is classified under the following, and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): SGW
Device Type: Device to detect antibodies to hepatitis D virus
Regulation: 21 CFR 866.3176