510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193650

B Applicant

DiaSorin Inc.

C Proprietary and Established Names

LIAISON Ferritin

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DBF	Class II	21 CFR 866.5340 - Ferritin Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New assay

B Measurand:

Ferritin

C Type of Test:

Quantitative, Chemiluminescent Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The DiaSorin LIAISON Ferritin assay is a quantitative automated chemiluminescent immunoassay (CLIA) for the in vitro detection of ferritin in human serum, serum separator tubes (SST), or lithium (Li) Heparin plasma to aid in the diagnosis of iron deficiency anemia and iron overload.

This assay must be performed on the LIAISON XL Analyzer.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only
For in vitro diagnostic use only

D Special Instrument Requirements:

LIAISON XL analyzer (K103529)

IV Device/System Characteristics:

A Device Description:

The LIAISON Ferritin assay contains 100 determinations:

- Magnetic particles - coated with monoclonal anti-ferritin antibody (mouse) in a BSA-containing buffer with 0.09% sodium azide; 2.3 mL
- Calibrator 1, low: containing ferritin from human liver in a human serum albumin-containing buffer with 0.09% sodium azide; 1.0 mL
- Calibrator 2, high: containing ferritin from human liver in a human serum albumin-containing buffer with 0.09% sodium azide; 1.0 mL
- Conjugate: containing monoclonal anti-ferritin antibody (mouse) labeled with isoluminol in a BSA-containing buffer with 0.09% sodium azide; 28.0 mL
- Specimen Diluent, containing human serum albumin and 0.09% sodium azide; 25.0 mL

B Principle of Operation:

Ferritin present in calibrators, samples or controls binds to an anti-ferritin mouse monoclonal antibody is coated on the magnetic particles (solid phase). After a wash step, an anti-ferritin antibody conjugate binds to the ferritin already bound to the solid phase. After a final wash cycle, the starter reagents are added to trigger a chemiluminescence reaction. The light signal is

measured by a photomultiplier as relative light units (RLU) and is in proportion of the ferritin concentration present in calibrators, samples, or controls.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Elecsys Ferritin

B Predicate 510(k) Number(s):

K971833

C Comparison with Predicate(s):

Device & Predicate Device(s):	K193650	K971833
Device Trade Name	LIAISON Ferritin	Elecsys Ferritin
General Device Characteristic Similarities		
Intended Use/ Indications For Use	The DiaSorin LIAISON Ferritin assay is a quantitative automated chemiluminescent immunoassay (CLIA) for the in vitro detection of ferritin in human serum, serum separator tubes (SST), and lithium (Li) Heparin plasma to aid in the diagnosis of iron deficiency anemia and iron overload. This assay must be performed on the LIAISON XL Analyzer.	Immunoassay for the in vitro quantitative determination of ferritin in human serum and plasma. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Results	Quantitative	Same
Sample Size	10 µL	Same
Storage	2–8°C	Same
General Device Characteristic Differences		
Assay Type	Chemiluminescence immunoassay (CLIA)	Electrochemiluminescence immunoassay (ECLIA)
Instrumentation	LIAISON XL Analyzer	Elecsys and cobas e Analyzer
Traceability	WHO NIBSC 94/572	WHO NIBSC 80/602
Sample Types	Human serum, SST serum, and Li heparin plasma	Serum collected using standard sampling tubes; Li-, Na-heparin, K3-EDTA, and sodium citrate plasma
Measuring Range	0.46–2,200 ng/mL	0.50–2,000 ng/mL

Device & Predicate Device(s):	K193650	K971833
Solid Phase	Magnetic particles, coated with mouse monoclonal anti-ferritin antibody	Streptavidin-coated microparticles
Conjugate	Mouse monoclonal anti-ferritin antibody labelled with isoluminol	Mouse Monoclonal anti-ferritin antibody labeled with ruthenium complex

VI Standards/Guidance Documents Referenced:

- CLSI EP5-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline.
- CLSI EP15-A3, User Verification of Precision and Estimation of Bias; Approved Guideline.
- CLSI EP07-A, Interference Testing in Clinical Chemistry, Approved Guideline.
- CLSI EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures; A Statistical Approach; Approved Guideline.
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline.
- CLSI EP28-A3C, Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline.

VII Performance Characteristics (if/when applicable):

A Analytical Performance: All results presented below were within the manufacturer's pre-determined acceptance criteria for each study.

1. Precision/Reproducibility:

A 20-day precision study was performed following CLSI EP05-A3 guideline. Six serum samples and two controls, spanning the assay range were tested. Each sample was tested in duplicate per run in two separate runs per day, over 20 operating days (N=80) with two reagent lots on two LIAISON XL analyzers (n = 320):

Sample ID	Mean (ng/mL)	Repeatability		Between Run		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Panel 1	5.8	0.15	2.5	0.15	2.5	0.17	3.0	0.33	5.6
Panel 2	18.3	0.35	1.9	0.50	2.7	0.45	2.5	0.83	4.6
Panel 3	178.0	2.58	1.5	4.60	2.6	4.04	2.3	7.25	4.1
Panel 4	1093.0	18.77	1.7	32.10	2.9	30.70	2.8	61.43	5.6
Panel 5	404.9	6.67	1.6	11.00	2.7	8.56	2.1	18.48	4.6
Panel 6	1883.0	35.84	1.9	49.45	2.6	51.35	2.7	119.84	6.4
Kit control 1	32.8	0.61	1.9	0.70	2.1	0.97	2.9	1.42	4.3
Kit control 2	300.0	5.81	1.9	8.51	2.8	10.97	3.7	16.12	5.4

Sample ID	Mean (ng/mL)	Between Lot		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV
Panel 1	5.8	0.14	2.4	0.12	2.0	0.33	5.6
Panel 2	18.3	0.02	0.1	0.34	1.9	0.83	4.6
Panel 3	178.0	2.90	1.6	0	0	7.25	4.1
Panel 4	1093.0	38.05	3.5	0	0	61.43	5.6
Panel 5	404.9	10.17	2.5	0	0	18.48	4.6
Panel 6	1883.0	89.41	4.7	0	0	119.84	6.4
Kit control 1	32.8	0	0	0.47	1.4	1.42	4.3
Kit control 2	300.0	5.77	1.9	0	0	16.12	5.4

The reproducibility of the LIAISON Ferritin assay was evaluated on two analyzers with two reagent lots. Six human sera samples and two controls were tested in six replicates per run, one run per day for five days (n=30) on each lot (n=120 per sample). The results are summarized below:

Sample ID	Mean (ng/mL)	Repeatability		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV
Panel 1	5.6	0.11	1.9	0.19	3.3	0.53	9.4
Panel 2	17.4	0.29	1.7	0.58	3.3	1.38	7.9
Panel 3	169.9	2.03	1.2	6.17	3.6	9.17	5.4
Panel 4	1046.0	14.92	1.4	30.36	2.9	69.60	6.7
Panel 5	391.9	6.46	1.6	10.23	2.6	22.62	5.8
Panel 6	1807.0	35.34	2.1	68.74	3.8	134.35	7.4
Kit control 1	31.3	0.45	1.4	1.18	3.8	2.14	6.8
Kit control 2	287.3	5.01	1.7	13.48	4.7	18.79	6.5

Sample ID	Mean (ng/mL)	Between Lot		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV
Panel 1	5.6	0.14	2.5	0.46	8.2	0.53	9.4
Panel 2	17.4	0.59	3.4	1.06	6.1	1.38	7.9
Panel 3	169.9	6.47	3.8	0	0	9.17	5.4
Panel 4	1046.0	60.82	5.8	0	0	69.60	6.7
Panel 5	391.9	19.10	4.9	0	0	22.62	5.8
Panel 6	1807.0	108.87	6.0	0	0	134.35	7.4
Kit control 1	31.3	1.00	3.2	1.41	4.5	2.14	6.8
Kit control 2	287.3	12.10	4.2	0	0	18.79	6.5

2. Linearity:

Linearity studies were conducted to evaluate the linearity consulting CLSI EP06-A. Four serum samples were evaluated to interrogate the entire measuring range: they were approximately 50, 500, 1500, and 2000 ng/mL. For each sample, a series of seven evenly spaced dilutions were prepared by mixing a ferritin-free serum and a high serum pool. All samples were tested in triplicate on the LIAISON analyzer. The linear and polynomial regression analyses of the mean observed reads (y) against the mean expected values (x) was performed. The percent recovery obtained for all dilutions for each sample was always between 90–110% and no 2nd or 3rd order polynomial fit was statistically better than a linear fit at the 5% significance level for any of the samples used in the study. The linear equations generated are shown below:

	Slope (95th CI)	Intercept (95th CI)	Correlation coefficient	Sample Range
Sample A (~50 ng/mL)	0.99 (0.95–1.03)	0.27 (-0.41–1.25)	1.00	1.5–44.9
Sample B (~500 ng/mL)	1.00 (0.91–1.11)	-0.00 (-9.55–20.53)	0.997	1.2–506.0
Sample C (~1500 ng/mL)	1.02 (0.98–1.05)	0.03 (-14.50–33.40	1.00	1.4–1561.0
Sample D (~2000 ng/mL)	1.01 (0.98–1.04)	-1.40 (-26.6–51.2)	1.00	1.4–2095.0

Extended Range:

An extended range study was conducted using five serum samples at concentrations: ranging from 1938 ng/mL, 25013 ng/mL, 50,009 ng/mL, 75,000 ng/mL, and 100,000 ng/mL. The samples were diluted directly using the LIAISON XL Analyzer instrument with Specimen Diluent present on board, in a ratio of 1:50. Each diluted sample was tested in triplicate. The results of diluted samples were compared to the expected concentration. The percent recovery of the tested samples ranged from 99% to 108%.

3. Analytical Specificity/Interference:

Interference studies were conducted according to CLSI EP07-A2 and CLSI EP37-A to evaluate the performance of the LIAISON Ferritin assay in the presence of endogenous and other potential interfering substances including commonly used drugs. Aliquots from three human serum sample pools with ferritin concentrations of approximately 20 ng/mL, 200 ng/mL, and 2000 ng/mL were split and spiked with interferent solvent and one was spiked with potential interferents. Each sample/substance combination was tested in replicates of 18, with the exception of HAMA and RF which were tested in replicates of six. The sponsor defines non-significant interference as within ± 10% bias between the mean spiked sample value and the mean control value. The following substances did not show significant interference at the concentrations listed:

Endogenous Substances:	Concentration Tested
Human albumin	60 mg/mL
Triglyceride	30 mg/mL
Hemoglobin	10 mg/mL
Conjugated bilirubin	0.2 mg/mL
Unconjugated bilirubin	0.2 mg/mL
Human anti-mouse antibodies (HAMA)	54.5 µg/ml
Rheumatoid Factor (RF)	33.1 IU/mL
Exogenous Substance:	**Concentration Tested**
Acetominophen	0.2 mg/mL
Acetylsalicylic acid	0.5 µg/ml
Ampillicin	53.0 µg/mL
L-Ascorbic acid	1.76 mg/mL
Dobesilate calcium monohydrate	33.3 µg/mL
Ferrous sulfate	15.2 µg/mL
Ibuprofen	500.0 µg/mL
Levodopa	256.0 µg/mL
Methotrexate hydrate	909.0 µg/mL
Metronidazole	119.0 µg/mL
N-Acety-L cysteine	2.87 mg/mL
Phenylbutazone	200 µg/mL
Prednisone	180.0 µg/mL
Rifampicin	64.3 µg/mlL
Theophylline	40.0 µg/mL
Valproinacid	505.0 µg/mL

4. Assay Reportable Range:

   The assay reportable range is 0.46 ng/mL to 2200.00 ng/mL. The manufacturer recommends values below 0.46 ng/mL should be reported as <0.46 ng/mL.

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

   Traceability:

   The LIAISON Ferritin Assay is traceable to the WHO reference standard 94/572.

   Stability:

   Real-time shelf-life stability testing supports a shelf-life of 24 months for unopened reagents stored at the labeling recommendation (2–8°C). Opened assay component stability studies

support the claims that the reagents can be stored at the labeling recommendation (2–8°C) for 8 weeks.

Testing serum, SST serum, and Li-heparin samples demonstrated the samples are stable for one month at -20°C; at 20–25°C (i.e., room temperature) up to 24 hours; and at 2–8°C up to seven days.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were conducted using serum samples.

A LoB study was conducted using two reagent lots and five serum samples stripped of ferritin. The blank samples were tested over four runs (triplicate measurements/sample/run) over three days yielding 60 results per reagent lot (N=60 measurements per lot, 120 measurements per instrument). The four runs for each reagent lot were repeated on a second different LIAISON XL Analyzer, for a total of 240 measurements. The LoB was calculated for each of the two reagent lots using the equation from the CLSI EP17-A2 as follows:

LoB = Mean (Blank Dose) + 1.653 * Standard Deviation (Blank Dose)

The claimed LoB for the candidate device is 0.004 ng/mL, the higher of the two kit lots.

A LoD study was conducted using two reagent lots and four human serum samples with ferritin concentration ranging from 0.002 ng/mL to 0.303 ng/mL). Each sample was tested in triplicate in four runs over three days (12 replicates per sample per reagent lot) yielding a total of 48 results per reagent lot. The four runs for each reagent lot were repeated on a second different LIAISON XL Analyzer, for a total of 96 measurements. The LoD was calculated for each of the two reagent lots using the equation from the CLSI EP17-A2 as follows:

LoD = LoB + 1.655 * Standard Deviation (Sample Dose)

The overall assay's LoD was defined as the highest of the two kit lots LoD. The claimed LoD is 0.073 ng/mL.

A LoQ study was conducted using nine different samples ranging from 0.000 to 3.388 ng/mL. Each sample was tested in triplicate in four runs over four days (12 replicates per sample per reagent lot per instrument) yielding a total of 108 results per reagent lot per instrument. Two lots were tested on three instruments. The LoQ was estimated using the precision profile of the samples according to CLSI EP17-A2. The sponsor defined the LoQ as the concentration of ferritin showing an imprecision of 20%. The overall assay's LoQ was defined as the highest of the three (3) kit lots LoQ. The claimed LoQ is 0.461 ng/mL.

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
A method comparison study was performed by testing 173 human serum samples in singlicate on the candidate device (LIAISON Ferritin) and the predicate device. The samples

tested in the study spanned the claimed measuring range and covered medical decision points. The ferritin concentration in the samples tested in the study ranged from 2.0 ng/mL to 1932.0 ng/mL with the candidate device and 1.4 ng/mL to 1920.0 ng/mL with the predicate device. The results of the Passing-Bablok regression analysis are as shown below:

N	Slope (95% CI)	Intercept (95% CI)	R^2
173	0.96 (0.95–0.98)	-1.12 (-2.13 – -0.32)	0.995

2. Matrix Comparison:

A study comparing serum, SST serum, and lithium heparin plasma was performed using 43 matched samples (37 native and 6 contrived) covering the measuring range (3.8–1946 ng/mL, serum). A Passing-Bablok linear regression analysis is shown below:

	Slope (95% CI)	Intercept (95% CI)	Pearson r
Serum vs. SST	1.00 (0.97–1.04)	0.02 (-0.77– 0.64)	0.999
Serum vs. Li-heparin	0.98 (0.94 – 0.99)	-1.73 (-2.14– -0.52)	0.999

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Previously established ferritin reference ranges were verified by testing 78 serum specimens (39 female, 39 male) collected from five different sites in the U.S. The specimens were selected to reflect typical racial/ethnic distribution within the U.S. using www.census.gov as a reference.

	N	Age Range (years)	Median (ng/mL)	95th Percentile
Female	39	18–92	52.2	6.3–317.1 ng/mL
Male	39	21–82	124.3	3.6–362.4 ng/mL

In the labeling, the sponsor states, "*It is recommended that each laboratory establish its own range of expected values for the population taken into consideration.*"

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.