510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k110736

B. Purpose for Submission:
New device

C. Measurand:
Ferritin

D. Type of Test:
Quantitative, immuno-turbidimetric

E. Applicant:
Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:
ADVIA® 1650 Chemistry Ferritin (FRT) Reagent
ADVIA® Chemistry Liquid Specific Protein Calibrator

G. Regulatory Information:

1. Regulation section:
21 CFR §866.5340 Ferritin immunological test system
21 CFR §862.1150 Calibrator

2. Classification:
Class II

3. Product code:
DBF: Ferritin, antigen, antiserum, control
JIX: Calibrator, multi-analyte mixture

4. Panel:
Immunology (82)
Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
The ADVIA® 1650 Chemistry Ferritin (FRT) Reagent:
For *in vitro* diagnostic use in the quantitative determination of ferritin in human serum and plasma on the ADVIA® 1650 Chemistry system. Measurements of ferritin aid in the diagnosis of diseases affecting iron metabolism, such as hemochromatosis (iron overload) and iron deficiency anemia.

The ADVIA® Chemistry Liquid Specific Protein Calibrators: For *in vitro* diagnostic use in the calibration of ADVIA® Chemistry systems for the Alpha-Acid-Glycoprotein (AAG), Alpha-1-Antitrypsin (AAT), Anti-streptolysin-O_2 (ASO_2), Complement C3 (C3), Complement C4 (C4), Ferritin (FRT), Haptoglobin (HAPT), Immunoglobulin A_2 (IGA_2), Immunoglobulin G_2 (IGG_2), Immunoglobulin M_2 (IGM_2), Prealbumin (PREALB), Rheumatoid Factor (RF), and Transferrin (TRF) methods.

2. Indication(s) for use:
Same as Intended Use.

3. Special conditions for use statement(s):

Prescription use only.

4. Special instrument requirements:
ADVIA® 1650 Chemistry system (k990346)

I. Device Description:

The ADVIA® 1650 Chemistry Ferritin reagents are ready-to-use liquid reagents. They are supplied in two different package sizes, 200 or 800 tests per wedge with 4 wedges per kit.

There are two reagents. Reagent I consists of glycine buffer, pH 8.3 (170mmol/L), sodium chloride (100 mmol/L), bovine serum albumin (0.5%) and sodium azide (0.09%). Reagent 2 contains latex particles coated with rabbit anti-ferritin antibodies, glycine buffer, pH 7.3 (170 mmols/L), sodium chloride (100 mmols/L), bovine serum albumin (0.1%) and sodium azide (0.09%).

ADVIA® Chemistry Liquid Specific Protein Calibrator is a multi-analyte, liquid, human serum based product containing multiple analytes. They are supplied as ready-to-use 1.0-mL solutions in 6 vials, one for each of 6 calibrator levels. The low level (Level 1) is a zero-level calibrator with no analytes present in the formulation. The target ferritin concentrations of Levels 2 – 6 are 25, 50, 100, 225 and 475 mg/dL. All analytes except ferritin and C-reactive protein (CRP) were cleared previously in k103701. There are no changes to the existing products except the addition of ferritin value assignment process and the addition of the ferritin analyte to the intended use of the device.

The recommended controls are three serum pools previously cleared in k992550

J. Substantial Equivalence Information:

1. Predicate device name(s) and predicate K number(s):
N Latex Ferritin reagent (k993273)
Randox Liquid Protein Calibrator (k061056)

2. Comparison with predicate:

Ferritin Reagent

SIMILARITIES		
Item	Device	Predicate
Analyte	Ferritin	Same
Intended Use	For *in vitro* diagnostic use in the quantitative determination of ferritin as an aid in the diagnosis of diseases affecting iron metabolism such as hemochromatosis and iron deficiency anemia	For quantitaive determination of ferritin
Measurement	Quantitative	Same
Sample type	Serum, plasma	Same
Format	Liquid	Same
Antibodies	rabbit anti-ferritin antibodies	Same
Use of Calibrators	Yes	Same

DIFFERENCES		
Item	Device	Predicate
Plasma sample type	Lithium heparin and EDTA plasma	Heparinized plasma
Reportable range	6 – (450-500) ng/mL	Up to 640 ng/mL
Method Principle	Turbidimetric	Nephelometric
Reagents	Two: R1 and R2	Three: Reagent, Supplementary A and B
Expected values	Men: 20 – 250 ng/mL Women: 10 – 120 ng/mL	Men: 20 – 290 ng/mL Women, premenopausal: 4.5 – 170 ng/mL, postmenopausal: 24 – 260 ng/mL
Specificity (different isoforms)	Liver: 97.6% Spleen: 80.3% Placenta: 57.5% Heart: 20.9%	Liver; 94.3% Spleen: 90.4% Placenta: 103.4% Heart: 7.8%
Instrument	ADVIA® Chemistry Systems	BN System
Reagent on-board stability	60 days	28 days

Calibrators

SIMILARITIES		
Item	Device	Predicate
Intended Use	For *in vitro* diagnostic use in the calibration of specific assays	Same
Analytes Included	Anti-streptolysin Complement C3 and C4 CRP Ferritin Haptoglobin IgA, IgG, IgM , Prealbumin Transferrin	Same
Form	Ready-to-use solutions	Same
Traceability for Ferritin	WHO Third International Standard - NIBSC 94/572	Same
Matrix	Buffered base	Same
Analyte source	Derived from human source	Same
Number of levels	6 levels (lowest level is a zero-level without any analytes)	Same
Volume	1.0 mL each vial	Same

DIFFERENCES		
Item	Device	Predicate
Analytes Included	Alpha-acid-glycoprotein (AAG), Alpha-1-Antitrypsin, Rheumatoid Factor.	
Instrument	ADVIA® Chemistry Systems	Abbott Spectrum, Architect *i*2000, Architect *i* 2000sr; Bayer ADVIA® 1650, 2400, 1200; Dade Dimension RXL, AR, Hitachi 704, 717, 911, 917, 912, 747; AU800, AU600, AU400, AU2700, AU5400; Synchron CX4, CX5, CX7, LX20; ILAB300, ILAB900, ILAB1800, ILAB600; Cobas Mira, Mira S, Mira Plus

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods

CLSI EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation.

L. Test Principle:

In the ADVIA® 1650 Chemistry Ferritin method, a diluted sample reacts with buffer containing latex particles coated with polyclonal rabbit anti-Ferritin antibody. The formation of the antibody-antigen complex results in increased turbidity, which is measured as the amount of light absorbed at 658 nm. Using a standard curve from the absorbance of calibrators, ferritin concentration of a sample can be determined.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Individual serum pools at various concentrations of ferritin and serum-based control materials were tested. Each sample was assayed in duplicate, 2 runs per day, for at least 20 days, yielding 80 observations for each sample. The results are summarized in the table below:

Samples	Mean	Within-Run (Repeatability)		Total (Within-Lab Precision)	
	ng/mL	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
Serum Pool 1	12.0	0.44	3.7	1.04	8.7
Serum Control 1	28.8	0.40	1.4	0.89	3.1
Serum Control 2	185.3	0.78	0.4	1.49	0.8
Serum Pool 2	222.8	0.87	0.4	3.99	1.8
Serum Control 3	297.0	1.06	0.4	2.45	0.8
Serum Pool 3	347.0	3.78	1.1	4.97	1.4

b. *Linearity / assay analytical range:*
A high serum pool and a low serum pool were used to prepare nine (9) different ferritin concentrations evenly distributed throughout the assay range. The mean observed ferritin concentration of triplicate measurements at the nine (9) ferritin concentrations was compared with the expected concentration. A weighted least squares linear regression analysis of the linearity data shows that the assay is linear from 6.0 ng/mL to 450 to 500 ng/mL with a slope of 1.03 (95% confidence interval (CI): 1.01 – 1.05) and y-intercept of -0.03 (95% CI: -0.08 – 0.03). Deviation from linearity was ≤10%.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceability: The Ferritin values assigned to the calibrators are traceable to the Third International Standard NIBSC 94/572.

Stability of the ADVIA® 1650 Chemistry Ferritin Reagent: Shelf-life stability was determined upon storage of the reagents at 2-8ºC for 1, 2, 3, 8 or 13 weeks, 6, 12 or 18 months. On-board stability was evaluated upon storage of the 20-mL wedges in the instrument for 0, 8, 20, 31, 43, 59 or 62 days and 70-mL reagent wedges for 0, 7, 22, 31, 44, 56, 60 and 63 days. Sample recovery at each time point was compared to day 0. Data supports the shelf life stability claim of 18 months at 2-8ºC and on-board stability claim of 60 days.

Stability of the ADVIA® Chemistry Liquid Specific Protein Calibrators: Calibrator vials were opened one time and then closed and kept in the refrigerator at 2-8ºC for 29 days. Controls were run in quadruplet as samples using calibration curves generated with the once-opened calibrators and fresh unopened calibrators. Recoveries between the two sets of calibrators were compared. Test results support open-vial stability claim of 28 days. In addition, the data for stability of unopened calibrator vials were provided. Tests results support shelf-life of 24 months at 2-8ºC for unopened calibrator vials.

d. *Detection limit:*
The performance at low levels was evaluated according to CLSI guideline EP17-A. A human serum pool without ferritin and four human serum pools with mean values ranging from 3.95 ng/mL to 6.13 ng/mL were tested in six (6) replicates on two instrument systems using two lots of reagents for five (5) days with two (2) runs per day. Results show that the limit of blank, the limit of detection and the limit of quantitation are 1.2 ng/mL, 4.5 ng/mL and 6.0 ng/mL, respectively.

e. *Analytical specificity:*
   i. Endogenous Interference: Human serum pools with various concentrations of ferritin were spiked with hemoglobin up to 1000 mg/dL, unconjugated bilirubin and conjugated bilirubin up to 60 mg/dL, intralipid up to 1000 mg/dL, and rheumatoid factor up to 2500 IU/mL prior to analysis with the ADVIA® 1650 Chemistry Ferritin Reagent. Ferritin concentration observed at each level of an interferent was compared to the observed ferritin concentration of the un-spiked human serum pool. Low level of interference (<10%) was observed in the samples with ferritin concentration at approximately 300 ng/mL. Visibly hemolyzed or lipemic samples will produce erroneous results for samples with low ferritin concentrations:

ADVIA 1650			
Interferent	Interferent Level	Ferritin Level (ng/mL)	Interference
Bilirubin	60 mg/dL (1026 µmol/L)	10.9	NSI*
	60 mg/dL (1026 µmol/L)	297.7	NSI*
Hemoglobin	62.5 mg/dL (0.6 g/L)	11.4	44.4%
	1000 mg/dL (10.0 g/L)	75.2	NSI*
	1000 mg/dL (10.0 g/L)	300.4	NSI*
Lipemia	250 mg/dL (2.8 mmol/L)	11.3	NSI*
	500 mg/dL (5.7 mmol/L)	11.3	-31.0%
	750 mg/dL (8.5 mmol/L)	76.1	NSI*
	1000 mg/dL (11.3 mmol g/L)	76.1	-10.1%
	1000 mg/dL (11.3 mmol g/L)	303.4	NSI*
Rheumatoid Factor	2500 IU/mL	11.4	NSI*
	2500 IU/mL	304.1	NSI*

*NSI = Not Significant Interference (<10%)

ii. Specificity of Assay to Ferritin Isoforms: Specificity was tested using a human serum pool with ferritin concentration within normal range, which was spiked with a concentrated solution of a specific ferritin isoform (liver isoform at concentrations up to 200 ng/mL, spleen isoform at concentrations up to 200 ng/mL, heart isoform at the concentrations up to 300 ng/mL, and placenta isoform at concentrations up to 300 ng/mL). The specificity was evaluated by comparing recoveries of spiked sample and un-spiked sample relative to the amount of isoform spiked into a sample. The results are summarized below. The isoform values have clinical relevance regarding the presence of iron overload in certain organs or tissues. It should be noted that the ferritin assay does not identify the tissue isoforms.

Liver Isoform		
Amount of isoform spiked, ng/mL	Observed recovery - Ferritin, ng/mL	Specificity, %
0	22.8	NA
50	71.5	97.4%
100	118.9	96.2%
200	221.1	99.2%
	Average	97.6%
Spleen Isoform		
Amount of isoform spiked, ng/mL	Observed recovery - Ferritin, ng/mL	Specificity, %
0	85.2	NA
50	125.3	80.1%
100	164.8	79.6%
200	247.5	81.1%
	Average	80.3%

Placenta Isoform		
Amount of isoform spiked, ng/mL	Observed recovery - Ferritin, ng/mL	Specificity, %
0	19.9	NA
75	66.0	61.7%
225	147.7	56.9%
300	185.3	55.2%
	Average	57.9%
Heart Isoform		
Amount of isoform spiked, ng/mL	Observed recovery - Ferritin, ng/mL	Specificity, %
0	21.6	NA
75	37.5	21.3%
225	68.4	20.8%
300	83.0	20.5%
	Average	20.9%

iii. High Dose Hook Effect: Human serum sample was prepared by spiking a normal serum pool with human liver ferritin to achieve concentrations upto approximately 42,000 ng/mL. Serial dilutions were made in saline and all samples were tested. No hook effect was observed up to 42,000 ng/mL ferritin.

f. Assay cut-off:

See expected values/reference interval

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained with forty seven serum samples on the ADVIA 1650 Chemistry Ferritin device and the predicate device, were analyzed using Deming regression and are summarized below.

Regression Equation
y = 1.00x + 0. 0 Slope 95% CI: 0.97 to 1.03; Intercept 95% CI: -3.4 to 3.4

b. Matrix comparison:

Forty two matched serum, lithium heparin plasma, and EDTA plasma samples covering the assay range were evaluated on the ADVIA® 1650 Chemistry Ferritin Reagent device. Comparability between serum and plasma was analyzed using Deming regression and results are summarized below:

Sample type	Regression Equation
Lithium Heparin	y = 1.00x + 0.1 Slope 95% CI: 0.99 to 1.01 Intercept 95% CI:-0.9 to 1.0
EDTA	y = 0.97x - 1.2 Slope 95% CI: 0.96 to 0.99 Intercept 95% CI: -2.6 to 0.2

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

4. Clinical cut-off:

See Expected values/Reference interval.

5. Expected values/Reference interval:

The following are suggested reference intervals for this method (from literature):

Men:	20–250 ng/mL
Women:	10–120 ng/mL

Each laboratory should establish its own range.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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