510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K171642

B. Purpose for Submission:

Clearance of a new assay on a previously cleared instrument

C. Measurand:

Ferritin

D. Type of Test:

Quantitative, chemiluminescence immunoassay

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Atellica™ IM Ferritin (Fer) Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.5340, Ferritin immunological test system

2. Classification:

   Class II

3. Product code:

   DBF

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   See below.

2. Indication(s) for use:

   The Atellica IM Ferritin (Fer) assay is for in vitro diagnostic use in the quantitative determination of ferritin in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer. This assay can be used as an aid in the diagnosis of iron deficiency anemia and iron overload.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Atellica IM analyzer (K161954); Atellica IM system previously cleared as the Trinidad IM system in K151767.

I. Device Description:

Each Attelica IM Fer assay consists of:

- Lite Reagent: 5.0 mL reagent pack contains goat polyclonal anti-ferritin antibody labeled with acridinium ester (~0.64 µg/mL) in HEPES buffer, stabilizers, surfactant, sodium azide (<0.1%), and preservatives.
- Solid Phase Reagent: 22.5 mL reagent pack contains mouse monoclonal anti-ferritin antibody covalently linked to paramagnetic particles (~32.2 µg/mL) in sodium barbitial buffer, stabilizers, surfactant, sodium azide (<0.1%), and preservatives.

Atellica IM CAL C (calibrator) is required but not provided; Atellica IM Multi-Diluent 1 and Atellica IM Fer MCM (master curve material) are optional and not provided.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):

   Siemens ADVIA Centaur Ferritin Assay, K992157 and K041133

2. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The Atellica IM Ferritin (Fer) assay is for in vitro diagnostic use in the quantitative determination of ferritin in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer. This assay can be used as an aid in the diagnosis of iron deficiency anemia and iron overload.	For *in vitro* diagnostic use in the quantitative determination of ferritin in serum or plasma using the ADVIA Centaur, ADVIA Centaur XP, and ADVIA Centaur XPT systems to aid in the diagnosis of iron deficiency anemia and iron overload
Assay Principle	Chemiluminescence sandwich immunoassay	Same
Measurement	Quantitative	Same
Sample Type	Serum, lithium heparin plasma, and EDTA plasma	Same
Reagents:	Lite Reagent: Goat polyclonal anti-ferritin antibody (~0.64 µg/mL) labeled with acridinium ester in buffer Solid Phase Reagent: Mouse monoclonal anti-ferritin antibody (~32.2 µg/mL) covalently coupled to paramagnetic particles in buffer	Same
Traceability	Traceable to the World Health Organization (WHO) 2nd International Standard (WHO 80/578)	Same
Calibrators	2-point calibration	Same

Differences		
Item	Device	Predicate
Analyzer	Atellica IM	ADVIA Centaur
Assay Range	0.9–1650 ng/mL	0.5–1650 ng/mL

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

CLSI EP05-A3: Evaluation of Precision of Qualitative Measurement Methods Procedures;

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-Second Edition

CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition

CLSI EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline- Second Edition

CLSI EP09-A3: Method comparison and bias estimation using patient samples; Approved Guideline- Third Edition

L. Test Principle:

The Atellica IM Fer assay is a 2-site sandwich immunoassay using direct chemiluminescent detection technology, which uses constant amounts of two anti-ferritin antibodies. The first antibody, in the Lite Reagent, is a goat polyclonal anti-ferritin antibody labeled with acridinium ester. The second antibody, in the Solid Phase Reagent, is a mouse monoclonal anti-ferritin antibody covalently coupled to paramagnetic particles. A direct relationship exists between the amount of ferritin present in the patient sample and the amount of relative light units (RLUs) detected by the system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision was determined in accordance with CLSI EP05−A3. Eleven samples [six patient samples (four unaltered serum pools, two spiked serum pools); three serum-based controls; and two serum-based calibrators] were assayed on an Atellica IM Analyzer in duplicate in two runs per day for 20 days for a total of 80 replicates per sample. Results are summarized below:

Sample	Mean (ng/mL)	Repeatability		Between-Run		Between-Day		Within-Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample Pool 1	8.2	0.1	1.8	0.2	2.4	0.4	4.4	0.4	5.4
Sample Pool 2	41.9	0.6	1.4	1.0	2.5	1.3	3.2	1.8	4.2
Sample Pool 3	65.4	0.8	1.3	1.5	2.2	2.4	3.6	2.9	4.4
Sample Pool 4	118.3	1.4	1.2	2.9	2.5	3.5	3.0	4.8	4.0

Sample	Mean (ng/mL)	Repeatability		Between-Run		Between-Day		Within-Lab (Total)	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample Pool 5	487.1	8.0	1.6	9.4	1.9	16.2	3.3	20.4	4.2
Sample Pool 6	1453.6	49.5	3.4	48.1	3.3	59.9	4.1	91.4	6.3
Control 1	51.8	0.8	1.6	1.6	3.2	1.7	3.2	2.5	4.8
Control 2	132.7	1.6	1.2	4.7	3.6	3.3	2.5	6.0	4.5
Control 3	374.0	5.0	1.3	14.1	3.8	14.3	3.8	20.7	5.5
CAL Low	4.2	0.15	3.5	0.16	3.9	0.21	5.0	0.31	7.2
CAL High	779.9	20.7	2.7	23.0	3.0	31.9	4.1	44.5	5.7

b. *Linearity/assay reportable range:*

Linearity studies were conducted according to CLSI EP06-A. A dilution series of 11 samples with ferritin concentrations distributed throughout the assay range were prepared by diluting a high serum pool spiked with ferritin (1757.5 ng/mL) with a low serum pool (<0.5 ng/mL). Samples were tested in triplicate on an Atellica IM Analyzer using one reagent lot. The weighted Deming regression equation for the linear range (0.9–1650.0 ng/mL) was y = 0.914x–0.888, R^2 = 0.999. The 95th confidence interval (CI) of the slope was 0.86–0.965; the 95th CI of the intercept was -2.235–0.460.

Sample auto-dilution:
A study showed the on-system auto-dilution with factors of 2-fold, 5-fold, and 10-fold showed results are all within ±10% of manually diluted samples above the measuring range.

High dose hook effect:
To test for high dose hook effect associated with the Atellica IM Fer assay, 11 samples created by serially diluting a high serum sample containing ~100,000 ng/mL ferritin with Multi-Diluent 1 were tested. The assay did not demonstrate a hook effect up to 80,000 ng/mL ferritin.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

The Atellica IM Fer assay standardization is traceable to World Health Organization 2nd International Standard (WHO 80/578). Assigned values for calibrators are traceable to this standardization.

Reagent Stability:

Shelf-life stability: The shelf-life of the Atellica IM Fer ReadyPack is eight months when stored at 2-8°C.

On-board and open-vial stability: A stability study demonstrated that opened the Atellica IM Fer ReadyPack stored on-board the Atellica IM Analyzer is stable for 28 days.

d. Detection limit:

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantification (LoQ) of the Atellica IM Fer assay were determined according to CLSI EP17-A2.

LoB was determined by testing a total of six blank samples (human serum-based sample pools with no detectable amounts of ferritin) using two reagent lots in two replicates, twice a day over a period of 10 days on one Atellica IM Analyzer and over a period of nine days on a second Atellica IM Analyzer. LoB was established as the ferritin value corresponding to the 95^{th} rank position. The LoB was determined to be 0.3 ng/mL.

For LoD determination, a total of seven low level human serum-based sample pools were evaluated. Four low level human serum-based sample pools were evaluated using two reagent lots for ten days on one Atellica IM Analyzer and for nine days on a second Atellica IM Analyzer. An additional three human serum-based sample pools were tested using two reagent lots on two Atellica IM Analyzers over five days. The LoD was determined to be 0.7 ng/mL.

The sponsor defined LoQ as the lowest amount of ferritin in a sample at which the within-laboratory %CV is ≤ 20%. To calculate LoQ, six low level human serum samples with ferritin concentrations between 0.4–4.6 ng/mL were tested using two reagent lots in eight replicates per a day over a period of five days on one Atellica IM Analyzer. Five of those samples were tested using two reagent lots in eight replicates per day over a period of five days on a second Atellica IM Analyzer. The LoQ was determined to be 0.9 ng/mL.

e. Analytical specificity:

i. Endogenous Interference:

Interference studies were performed according to CLSI EP07-A2 by testing two human serum pools (~20 ng/mL and ~200 ng/mL) spiked with interferent stock solution. Each sample was tested in triplicate and analyzed in one assay run on the Atellica IM Analyzer. The recovery was calculated by comparing to control samples spiked with the same volume of diluents. No significant interference (≤10% recovery of the control value) was detected for the following substances up to the concentrations listed in the table below:

Potential Interfering Compound	Test Concentration
Hemoglobin	900 mg/dL
Unconjugated Bilirubin	60 mg/dL
Conjugated Bilirubin	60 mg/dL
Triglycerides (Intralipid®)	2000 mg/dL

The package insert notes: *"Avoid assaying grossly hemolyzed samples because the release of intracellular ferritin can cause elevated results."*.

ii. *Exogenous Interference:*

Interference studies were performed according to CLSI EP07-A2 by testing two human serum pools (~20 ng/mL and ~200 ng/mL) spiked with interferent stock solution. Each sample was tested in triplicate and analyzed in one assay run on the Atellica IM Analyzer. The recovery was calculated by comparing to control samples spiked with the same volume of diluents. No significant interference (≤10% recovery of the control value) was detected for the following substances up to the concentrations listed in the table below:

Potential Interfering Compound	Test Concentration
Li-Heparin	3000 IU/L
N-acetylcysteine	17.6 mM
Acetylsalicylic acid	2.78 mM
Ampicillin	152 µM
Dobesilate	33.3 µg/mL
Ibuprofen	2425 µM
Levodopa	1.3 mM
Metronidazole	701 µM
Rifampicin	78.1 µM
Theophylline	222 µM
Phenylbutazone	650 µM
Valproic acid	3.5 mM
Methotrexate	2.0 mM
Prednisone	0.5 mM
Ferrous sulphate	1.0 mM
Ascorbic acid	176 mg/dL

f. Assay cut-off:

Not applicable

2. Comparison studies:

   a. *Method comparison with predicate device:*

      A total of 126 native human serum samples with ferritin concentrations across the assay measuring interval were tested using the Atellica IM Fer assay and the predicate device. There was no demographic or clinical diagnosis information associated with the samples. Final calculations were performed with 107 samples (samples outside the range of either assay were not included in final calculations) that cover the range of 3.4–1641.4 ng/mL. Results were analyzed in accordance with CLSI EP09−A3. The Pearson's correlation coefficient (r value) was 0.99 while the weighted Deming regression analysis generated the following results:

      y = 1.03x – 0.5 ng/mL (y = Atellica IM Fer, x = predicate)
      (95% CI: Intercept = -0.86 – -0.09; Slope = 1.01–1.04)

   b. *Matrix comparison:*

      A total of 56 matched sample sets (serum, EDTA plasma and Lithium heparin plasma) spanning the assay range were tested to evaluate the effect of anticoagulants on assay results. Of the 56 sets, seven were contrived (five spiked with liver ferritin and two diluted with Multi-Diluent 1); the serum sample range was 2.5–1440.7 ng/mL. The results were analyzed by Weighted Deming regression:

Serum vs Plasma	**Weighted Deming Regression**	**r**
Lithium Heparin	y = 0.95x + 1.6 slope 95% CI:0.88 – 1.05 intercept 95% CI: -5.53 – 8.60	0.998
Potassium EDTA	y= 0.96x + 0.1 slope 95% CI:0.89 – 1.00 intercept 95% CI : -4.96 – 5.14	0.997

3. Clinical studies:

   a. *Clinical Sensitivity and Specificity:*

      Not applicable

   b. Other clinical supportive data (when a. is not applicable):

      Not applicable

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

The following values for male and female, apparently healthy subjects with normal liver function enzyme tests, bilirubin, and serum iron tests, were established in accordance with CLSI EP28-A3c:

	N=	Median (ng/mL)	95th Percentile Range (ng/mL)	Age range (years)
Female	275	46.4	7.3–270.7	16-94
Male	179	55.9	10.5–307.3	15-95

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.