510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k083906

B. Purpose for Submission:

New Device

C. Measurand:

Cystatin C

D. Type of Test:

Latex enhanced turbidimetric assay

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

ADVIA Chemistry Cystatin C Reagent

ADVIA Chemistry Cystatin C Calibrator

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NDY	II	21 CFR 862.1225 Creatinine, test system	75 (Chemistry)
JIT	II	21 CFR 862.1150, Calibrator	75 (Chemistry)

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

Reagent: For in vitro diagnostic use in the quantitative determination of Cystatin-C (CYSC) in human serum or plasma (lithium heparin, potassium EDTA) on the ADVIA Chemistry systems. Measurement of Cystatin C aids in the diagnosis and treatment of renal disease.

Calibrator: For in vitro diagnostic use in the calibration of Cystatin C method on ADVIA Chemistry systems.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Siemens ADVIA Chemistry systems- 1200, 1650/1800 and 2400

I. Device Description:

The ADVIA Chemistry Cystatin C Reagent is composed of two reagents: Reagent 1 is buffer and sodium azide and Reagent 2 is comprised of latex particles coated with anti-cystatin C antibody (rabbit) and sodium azide.

The ADVIA Chemistry Cystatin C Calibrator is a five level calibrator set. Five 2.0 mL vials are supplied with each kit and contain recombinant human Cystatin C in serum. The human source donor material was tested by FDA-approved methods and was found nonreactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis C (HCV), and antibody to HIV 1 and 2.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Siemens N Latex Cystatin C reagent kit

2. Predicate K number(s):

k041878

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	Quantitative determination of cystatin C (CYSC) in human serum or plasma on the ADVIA	Quantitative determination of cystatin C in human

Similarities		
Item	Device	Predicate
	Chemistry systems. Measurement of cystatin C aids in the diagnosis and treatment of renal disease.	serum and heparinized plasma by means of particle-enhanced immunonephelometry using the BN* Systems. Cystatin C measurements are used in the diagnosis and treatment of renal disease
Antibody	Rabbit Polyclonal antibodies to human Cystatin C	Same
Form	Liquid	Liquid
Traceability	Internal standard of highly purified human cystatin C	Same
Calibrator similarities		
Intended use	For use in the calibration of cystatin C method on ADVIA Chemistry systems	Used for preparing reference curves for the immunonephelometric determination of cystatin c using the BN systems

Differences		
Item	Device	Predicate
Matrix	Serum, heparinized plasma, EDTA plasma.	Serum and heparinized plasma.
Methodology	Latex enhanced turbidimetric assay.	Particle enhanced immunonephelometric assay.
Range	0.1 to 8.0 mg/L	0.05 to8.0 mg/L
Calibrator differences		
Form	Liquid, ready-to-use	Lyophilized
Levels	5 (5+ one zero-level DI water)	1 diluted on system to 6 levels
Matrix	Human serum base	Human urinary protein
Analyte	Cystatin C	Cystatin C and a1-microglobulin.

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

EP 05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline- 2nd edition.

L. Test Principle:

The CYSC latex reagent is a suspension of uniform latex particles coated with anti-cystatin-C antibody. Serum or plasma samples containing cystatin C are mixed with the latex reagent and agglutination takes place that causes an increase in turbidity. The turbidity is measured at 571 and 805 nm. The cystatin C concentration in serum or plasma is determined from a calibration curve that is generated with the calibrators.

The CYSC calibrators consist of a 5-level calibrator set (approx concentrations 0.4, 1.2, 2.4, 4.8 and 8.0 mg/L) which is a ready to use liquid in five 2.0 ml vials.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   The studies were conducted on the ADVIA 1650/1800 instrument.

   a. *Precision/Reproducibility:*

   Within run and total imprecision was assessed according to CLSI EP05-A2. The ADVIA Chemistry Cystatin C Reagent assay was used to measure cystatin C concentrations in four serum-based control materials, four serum pools spiked with pure cystatin C and three plasma pools (Li Heparin) two of which were spiked with pure cystatin C. Samples at the medical decision levels, normal ranges and abnormal ranges were run in duplicate twice a day for 10 days (n=40). The results for within-run, between run and total precision are shown in the table below:

Product	Mean (mg/L)	N	Within Run SD	Within Run CV(%)	Between Run SD	Between Run CV(%)	Between Day SD	Between Day CV(%)	Total SD	Total CV(%)
Control	0.32	40	0.00	1.0	0.00	0.5	0.00	1.3	0.01	1.7
Control	0.50	40	0.00	0.7	0.01	2.2	0.00	0.0	0.01	2.4
Control	0.60	40	0.00	0.7	0.00	0.4	0.00	0.4	0.01	0.9
Control	2.57	40	0.02	0.8	0.00	0.0	0.01	0.3	0.02	0.9
Serum Pool	0.63	40	0.01	1.0	0.00	0.4	0.00	0.0	0.01	1.1
Serum Pool	1.99	40	0.01	0.5	0.01	0.7	0.01	0.3	0.02	0.9
Serum Pool	4.86	40	0.02	0.5	0.01	0.3	0.04	0.9	0.05	1.0
Serum Pool	7.17	40	0.14	2.0	0.00	0.0	0.20	2.8	0.24	3.4
Plasma Pool	0.73	40	0.01	0.9	0.00	0.4	0.00	0.1	0.01	1.0
Plasma Pool	2.17	40	0.01	0.6	0.01	0.4	0.01	0.4	0.02	0.8
Plasma Pool	5.14	40	0.06	1.1	0.00	0.0	0.04	0.7	0.07	1.3

b. *Linearity/assay reportable range:*

Linearity of the CYSC latex reagent was assessed via percent recovery of serum and plasma samples across the assay range of 0.1 to 8 mg/L. Low and mid level of the dilution series were prepared from a spiked serum pool.

Serum samples were diluted with saline to form seventeen equally spaced samples that ranged from 0.02 to 8.43 mg/L. The resulting linear regression equation was y=1.02x -0.140 with a correlation coefficient of 0.99. The resulting data are shown below.

Level	value 1	value 2	Observed	Expected	Observed vs. Expected, %
1	0.02	0.00	0.01	0.00	N/A
2	0.47	0.47	0.47	0.52	90.2
3	0.93	0.92	0.93	1.04	88.8
4	1.41	1.40	1.41	1.56	89.9
5	1.91	1.90	1.91	2.08	91.4
6	2.42	2.38	2.40	2.60	92.1
7	2.99	2.97	2.98	3.13	95.3
8	3.50	3.48	3.49	3.65	95.7
9	4.07	4.00	4.04	4.17	96.8
10	4.65	4.58	4.62	4.69	98.4
11	5.18	5.09	5.14	5.21	98.6
12	5.69	5.67	5.68	5.73	99.1
13	6.37	6.29	6.33	6.25	101.3
14	6.78	6.79	6.79	6.77	100.2
15	7.39	7.31	7.35	7.29	100.8
16	7.78	7.77	7.78	7.81	99.5
17	8.43	8.24	8.34	8.34	100.0

The sponsor conducted a lower range linearity study to assess the lower assay range. Nine equally spaced serum samples (diluted with saline) that ranged from 0.12 to 1.18 mg/L were assessed for linearity. The percent deviations were less than 7.4% and the linear regression equation was y=0.980x+ 0.05 with a correlation coefficient of 0.997.

Linear Fit to Levels 1-5							
Level	value 1	value 2	value 3	Observed (mean result), mg/L	Fitted, mg/L	Deviation mg/L	%Dev.
1	0.12	0.12	0.12	0.12	0.15	-0.03	N/A
2	0.32	0.31	0.31	0.31	0.29	0.02	6.8
3	0.46	0.47	0.47	0.47	0.43	0.03	7.4
4	0.58	0.58	0.58	0.58	0.58	0.00	0.7
5	0.69	0.69	0.7	0.69	0.72	-0.02	-3.3
6	0.83	0.83	0.83	0.83	0.86	-0.03	-3.3
7	0.97	0.97	0.97	0.97	1.00	-0.03	-3.0
8	1.08	1.07	1.08	1.08	1.14	-0.06	-5.7
9	1.18	1.18	1.18	1.18	1.28	-0.10	-8.0

Using the combined results from the linearity studies, the sponsor claimed a linear range of 0.1 to 8.0 mg/L.

The ADVIA chemistry system has an auto-rerun mechanism that is triggered by a result above the upper range of an assay. Saline is used to dilute the original sample (up to three times) to bring the sample to a measureable value.

The sponsor conducted a high dose (hook effect) study to determine if high doses of cystatin C interfered with the assay. Ten samples were prepared by spiking a serum pool with Cystatin C to achieve concentrations of 55 mg/L. There was no interference observed for concentrations up to 55 mg/L.

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

There is no international recognized reference standard for Cystatin C. The ADVIA Chemistry CYSC method is traceable to an internal standard containing highly purified human Cystatin C. The ready to use 5 level (zero not included) calibrators are traceable to an in-house preparation with concentrations of recombinant Cystatin C in human serum. The high calibrator is prepared by spiking Cystatin C to the target concentration into human serum which is then serially diluted to achieve the remaining concentrations.

The CYSC calibrator value assignments were determined by recovery on the ADVIA 1650. The recoveries of patient samples on ADVIA Chemistry CYSC methods were compared to the sample recoveries using N Latex Cystatin C method. This calibrator lot was established as the master calibrator lot. Subsequent batches of calibrator are value assigned against the master lot.

Stability

Real-time stability studies for the CYSC Calibrator were conducted for 12 months and the results support the sponsor's shelf-life claim of 12 months. Two lots of the calibrators were opened at day 0 and stored at 2-8 C. Periodic testing was performed with the open-vial calibrators and recoveries of controls were generated. The results were compared with fresh calibrators and the results support the sponsor's claimed open- shelf stability for the calibrators of 60 days.

d. *Detection limit:*

The Limit of Blank (LoB), Limit of Quantitation (LoQ) and Limit of Detection (LoD) were determined in accordance with the CLSI EP17-A guidance.

The LoB study was conducted to determine the highest observed measurement values for samples free of analyte. A blank sample was assayed with 2 reagents and 2 calibrator lots in multiple replicates over a period of 4 days on 2 ADVIA 1650 systems. The LoB was determined to be 0.02 mg/L and supports the sponsor's claimed LoB of 0.07 mg/L.

The LoD was conducted using a low cystatin C sample (a serum based control with an approximate value of 0.37 mg/L). The LoD equation is LoD= LoB +1.645*(low sample concentration). The sponsor's LoD was determined to be 0.03 mg/L. The results support the sponsor's claimed LoD of 0.10 mg/L.

The LoQ was calculated based on the CLSI Guidance EP17-A in which total error = bias + 2*SDs. Bias was calculated to be 0.02 mg/L. The LoQ= 0.02 +2*0.01 = 0.04 mg/L. The results support the sponsor's LoQ claim of 0.10 mg/L.

e. *Analytical specificity:*

Two serum samples containing cystatin C at concentrations within the normal range (0.6 mg/L) and abnormal range (3.0 mg/L) were evaluated for interference. The effects of interference by hemoglobin, conjugated and unconjugated bilirubin, lipemia (intralipid) and rheumatoid factor (RF) were evaluated. The samples were tested in duplicate and multiple levels (five equally diluted pools) of interfering substances were tested. Recovery calculations were performed by comparing observed Cystatin C concentration at each level of interferent versus observed Cystatin C concentration of control (no interferent). No significant interference defined as ≤ 10 % was found on the ADVIA 1650 for hemoglobin up to 1000 mg/dL, conjugated and unconjugated bilirubin up to 60 mg/dL, lipemia (intralipid) up to 1000 mg/dL and RF up to 1200 IU/mL.

A list of compounds (acetyl salicylic acid, ibuprofen, prednisone, furosemide, acetaminophen, ascorbic acid and creatinine) were evaluated for interference and were found to have no significant ($\leq 10\%$) cross reactivity or interference.

  f. *Assay cut-off:*

  Not applicable.

2. Comparison studies:

  a. *Method comparison with predicate device:*

  A split sample method comparison study was conducted between the ADVIA Chemistry Cystatin C method (assayed on the ADVIA Chemistry 1650 system) and the N Latex Cystatin C method (assayed on the (BN System). Fifty-five serum samples with values ranging from 0.13 to 7.75 m/dL were assayed with one reagent lot in singlet on each system. The linear regression equation obtained was y=1.003x+0.021 with a correlation coefficent of 0.986.

  b. *Matrix comparison:*

  A serum/plasma comparison test was performed for the ADVIA Chemistry Cystatin C assay. Fifty-three matched serum and plasma paired samples containing cystatin C across the range of the assay were analyzed in duplicate with the assay. Some samples were spiked to cover the assay range. Lithium heparin and EDTA results are shown below.

  Y=ADVIA 1650 Cystatin C (plasma) and X=ADVIA 1650 Cystatin C (serum).

	Regression Equation	R	N	(x) Range mg/dL
Li-Heparin	Y=1.01x-0.02	0.99	106	0.18-7.57
EDTA	Y=1.00x-0.03	0.99	106	0.18-7.57

3. Clinical studies:

  a. *Clinical Sensitivity:*

  Not applicable.

  b. *Clinical specificity:*

  Not applicable.

  c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

The sponsor conducted a normal reference range study using 121 serum samples from apparently healthy adult in-house volunteers. Serum samples were measured in singlicate with one reagent lot on the ADVIA 1650 system. The mean, median 1.5 and 97.5 percentile results were calculated and shown in the chart below. Ninety-five percent of the specimens fell within the Cystatin C concentrations of 0.56 to 0.95 m/dL. The results support the sponsor's reference range for serum and plasma of 0.56 to 0.95 m/dL.

Cystatin C	ADVIA 1650
N	121
Mean	0.73
2.5%	0.56
97.5%	0.95
Median	0.73

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.