

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

A. 510(k) Number:

k092283

B. Purpose for Submission:

New device

C. Measurand:

IgG subclasses, IgG1, IgG2, IgG3, IgG4

D. Type of Test:

Quantitative assays using immunochemical reactions measured by nephelometry

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

Dimension Vista® IgG1 Flex® reagent cartridge

Dimension Vista® IgG2 Flex® reagent cartridge

Dimension Vista® IgG3 Flex® reagent cartridge

Dimension Vista® IgG4 Flex® reagent cartridge

G. Regulatory Information:

1. Regulation section:

21 CFR§866.5510 – Immunoglobulins A, G, M, D, and E Immunological Test System

2. Classification:

Class II

3. Product code:

DFZ: IgG (Gamma Chain Specific), Antigen, Antiserum, Control

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

Dimension Vista® Immunoglobulin G Subclass 1 Flex® reagent cartridge:

The IgG1 method is an *in vitro* diagnostic test for the quantitative measurement of immunoglobulin G subclass 1 in human serum, heparinized plasma and EDTA plasma on the Dimension Vista® System. Measurements of immunoglobulin G subclass 1 aid in the diagnosis of plasma cell antibody forming abnormalities in conjunction with clinical and other laboratory findings.

Dimension Vista® Immunoglobulin G Subclass 2 Flex® reagent cartridge:

The IgG2 method is an *in vitro* diagnostic test for the quantitative measurement of immunoglobulin G subclass 2 in human serum, heparinized plasma and EDTA plasma on the Dimension Vista® System. Measurements of immunoglobulin G subclass 2 aid in the diagnosis of plasma cell antibody forming abnormalities in conjunction with clinical and other laboratory findings.

Dimension Vista® Immunoglobulin G Subclass 3 Flex® reagent cartridge:

The IgG3 method is an *in vitro* diagnostic test for the quantitative measurement of

immunoglobulin G subclass 3 in human serum, heparinized plasma and EDTA plasma on the Dimension Vista® System. Measurements of immunoglobulin G subclass 3 aid in the diagnosis of plasma cell antibody forming abnormalities in conjunction with clinical and other laboratory findings.

Dimension Vista® Immunoglobulin G Subclass 4 Flex® reagent cartridge:

The IgG4 method is an *in vitro* diagnostic test for the quantitative measurement of immunoglobulin G subclass 4 in human serum, heparinized plasma and EDTA plasma on the Dimension Vista® System. Measurements of immunoglobulin G subclass 4 aid in the diagnosis of plasma cell antibody forming abnormalities in conjunction with clinical and other laboratory findings.

2. Indication(s) for use:
Same as intended use
3. Special conditions for use statement(s):
For prescription use only
4. Special instrument requirements:
Dimension Vista System (k051087)

I. Device Description:

Dimension Vista Immunoglobulin G Subclass 1 Flex reagent Cartridge:

Reagents are contained in segregated wells in a plastic cartridge. Wells 1 and 2 contain buffers and polyethylene glycol. Wells 3-10 are empty. Wells 11 and 12 contain liquid sheep polyclonal antisera to human IgG1. The antisera contain specific antibodies which form immune complexes with IgG1. There are 2 Flex cartridges per carton. Calibrators and controls are required, but not provided.

Dimension Vista Immunoglobulin G Subclass 2 Flex reagent Cartridge:

Reagents are contained in segregated wells in a plastic cartridge. Wells 1 and 2 contain buffers and polyethylene glycol. Wells 3-10 are empty. Wells 11 and 12 contain liquid sheep polyclonal antisera to human IgG2. The antisera contain specific antibodies which form immune complexes with IgG2. There are 2 Flex cartridges per carton. Calibrators and controls are required, but not provided.

Dimension Vista Immunoglobulin G Subclass 3 Flex reagent Cartridge:

Reagents are contained in segregated wells in a plastic cartridge. Wells 1 and 2 contain buffers and polyethylene glycol. Wells 3-10 are empty. Wells 11 and 12 contain liquid sheep polyclonal antisera to human IgG3. Polystyrene particles are coated with antibodies specific to human IgG3. There are 2 Flex cartridges per carton. Calibrators and controls are required, but not provided.

Dimension Vista Immunoglobulin G Subclass 4 Flex reagent Cartridge:

Reagents are contained in segregated wells in a plastic cartridge. Wells 1 and 2 contain buffers and polyethylene glycol. Wells 3-10 are empty. Wells 11 and 12 contain liquid sheep polyclonal antisera to human IgG4. Polystyrene particles are coated with antibodies specific to human IgG4. There are 2 Flex cartridges per carton. Calibrators and controls are required, but not provided.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Siemens N Antisera to Human IgG Subclasses 1 and 2 assays
Siemens N Latex IgG3 and IgG4

2. Predicate 510(k) number(s):
 N Antiserum to Human IgG Subclasses 1 and 2 -k860894
 N Latex IG3 and IG4 - 510(k) Exempt and CLIA Categorized under classification
 866.5530 code DAS in 3/2004.
3. Comparison with predicate:

Similarities		
Item	Device	Predicates
Intended Use	The IGG1-4 methods are <i>in vitro</i> diagnostic tests for the quantitative measurement of immunoglobulin G subclasses in human serum, heparinized plasma and EDTA plasma on the Dimension Vista® System. Measurements of immunoglobulin G subclasses aid in the diagnosis of plasma cell antibody forming abnormalities.	Same
Technology	Nephelometric	Same
Assay format	Quantitative	Same
Reagents	Liquid, require no preparation	Same
Antibody	Polyclonal from sheep	Same
Matrix	Human serum, heparinized plasma and EDTA plasma	Same
Storage	2-8°C	Same

Differences		
Item	Device	Predicate
Instrument	Dimension Vista System	BN II and BN ProSpec System

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

Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)
 Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)
 Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
 Evaluation of the Linearity of Quantitative Analytical Methods (EP6-P2)
 Protocols for Determination of Limits of Detection and Limits of Quantitation (NCCLS/CLSI EP17-A)
 Draft Guidance Document for 510(k) Submission of Immunoglobulins A, G, M, D and E Immunoglobulin System In Vitro Devices

L. Test Principle:

Dimension Vista® IGG 1 and 2

Proteins contained in human body fluids form immune complexes in an immunochemical reaction with specific antibodies. These complexes scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

Dimension Vista® IGG 3 and 4

Polystyrene particles coated with antibodies specific to human IGG3 or 4 are aggregated when mixed with samples containing IGG3 or 4. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision testing for the IGG1-4 methods were performed over 20 days according to CLSI EP5-A2, at a single site. A single instrument, a single reagent lot and two operators were used. On each day of testing, each sample was run in duplicate, in two separate runs. The test samples consisted of 3 levels of Dimension Vista® Protein 1 Control, 2 serum samples and 2 plasma samples.

Serum and plasma pools for all methods were established at levels that encompassed the analytical measuring range for each method. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2.

IgG1

Material	Mean (g/L)	Repeatability		Within Lab	
		%CV	SD (g/L)	%CV	SD (g/L)
PROTICON L	3.64	3.0	0.11	3.7	0.13
PROTICON M	4.85	3.5	0.17	3.8	0.18
PROTICON H	7.77	1.8	0.14	2.0	0.15
Serum pool	3.38	2.9	0.1	3.6	0.12
Serum pool	19.92	3.3	0.65	3.4	0.68
Plasma pool	4.99	2.9	0.15	3.8	0.19
Plasma pool	10.66	1.9	0.2	2.4	0.26

IgG2

Material	Mean (g/L)	Repeatability		Within Lab	
		%CV	SD (g/L)	%CV	SD (g/L)
PROTICON L	1.76	2.0	0.04	5.3	0.09
PROTICON M	2.77	2.8	0.08	4.5	0.12
PROTICON H	4.24	3.0	0.13	3.5	0.15
Serum pool	1.32	3.3	0.04	5.0	0.07
Serum pool	7.20	2.8	0.20	4.1	0.3
Plasma pool	1.50	2.3	0.03	5.7	0.09
Plasma pool	7.29	2.9	0.21	3.8	0.28

IgG3

Material	Mean (g/L)	Repeatability		Within Lab	
		%CV	SD (g/L)	%CV	SD (g/L)
PROTICON L	0.27	2.7	0.007	3.6	0.010
PROTICON M	0.36	3.0	0.011	3.9	0.014
PROTICON H	0.52	3.7	0.019	5.2	0.027
Serum pool	0.23	2.4	0.005	3.8	0.009
Serum pool	1.28	4.6	0.059	5.7	0.074
Plasma pool	0.20	1.9	0.004	3.5	0.007
Plasma pool	0.52	3.5	0.018	3.9	0.020

IgG4

Material	Mean (g/L)	Repeatability		Within Lab	
		%CV	SD (g/L)	%CV	SD (g/L)
PROTICON L	0.44	3.4	0.015	4.5	0.020
PROTICON M	0.62	3.8	0.024	4.4	0.027
PROTICON H	0.81	4.4	0.035	4.6	0.038
Serum pool	0.18	2.4	0.005	3.3	0.006
Serum pool	1.01	3.6	0.036	3.7	0.037
Plasma pool	0.15	3.1	0.005	3.2	0.005
Plasma pool	0.87	3.5	0.031	3.8	0.033

b. *Linearity/assay reportable range:*

Linearity

The linearity for the IGG1-4 methods was determined according to the CLSI EP-6-A. One serum sample was serially diluted with System Diluent, and run in replicates of five. The observed value represents the mean of the five replicates. The bias was determined at each level. The acceptance criteria were defined as: the absolute value for the Difference (g/L) [G] must not exceed the Limit (g/L) [H] or the absolute value for the Relative Difference (%) [I] must not exceed the Limit (%) [J]. The Limit (g/L) [H] is defined as 15% of Expected value [D] at Dilution factor level 0.075. For all of the assays, the acceptance criteria were met.

IgG1

Testing was performed using a human serum sample (26.29 g/L) that was serially diluted ten times. Expected concentrations vs. observed concentrations were plotted. Regression analysis showed a slope of 0.996 and y intercept of -0.027. The linear range was determined to be 2.34-26.29 g/L. The analytical measuring range was established from the linear range and the results of the Limit of Quantitation study and determined to be 2.20-23.40 g/L.

IgG2

Testing was performed using a human serum sample (9.9 g/L) that was serially diluted eleven times. Measured concentrations vs. observed concentrations were plotted. Regression analysis showed a slope: 0.993 and y intercept of 0.0098. The linear range was determined to be 0.50-9.91 g/L. The analytical measuring range was

established from the linear range and the results of the Limit of Quantitation study and determined to be 0.44-8.30 g/L.

IgG3

Testing was performed using a human serum sample (2.27 g/L) that was serially diluted eleven times. Measured concentrations vs. observed concentrations were plotted. Regression analysis showed a slope of 1.04 and y intercept of -0.0086. The linear range was determined to be 0.057-2.55 g/L. The analytical measuring range was established from the linear range and the results of the Limit of Quantitation study and determined to be 0.035-1.57 g/L.

IgG4

Testing was performed using a human serum sample (2.833 g/L) that was serially diluted ten times. Measured concentrations vs. observed concentrations were plotted. Regression analysis showed a slope of 0.961 and y intercept of 0.017. The linear range was determined to be 0.045- 2.833 g/L. The analytical measuring range was established from the linear range and the results of the Limit of Quantitation study and determined to be 0.057-2.55 g/L.

Recovery

A recovery study was performed by mixing equal volumes of two patient samples of known quantity for each of the IGG 1-4 assays.

For IgG1, recovery ranged from 93-100% with a mean of 96%

For IgG2, recovery ranged from 91.2-96.2%, with a mean of 93.2%

For IgG3, recovery ranged from 91-105%, with a mean of 99%.

For IgG4, recovery ranged from 99-105%, with a mean of 102%.

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

There are no reference standards for IgG1 to IgG 4. IGG1-4 calibrator and control value assignment and stability data were provided in k071980. The calibrator master lot values for IgG 1-4 are assigned versus ERM-DA 470 (CR 470) using independently determined values for subclasses compared to total IgG value of the reference material.

d. *Detection limit:*

For each of the IgG subclasses, three serum samples with known concentrations of the IgG subclass were spiked with ERM®-DA 470 – a reference material certified for the mass concentration of 12 serum proteins (diluted with system diluent). For each IgG subclass, two concentrations were tested, both chosen to challenge the low end of the analytical measuring range and the extended low end. At each concentration, three samples were tested; three replicates per sample per run, for each of 5 runs. Testing was performed in one day with a single reagent lot, calibrator lot, instrument and operator and the mean and SD for the 15 replicates of each sample was calculated. The per sample bias (Bias = Mean - sample concentration) and the average bias, across the three samples, were calculated. The pooled SD across the three samples per the formula in Appendix B of CLSI EP17-A was calculated. The observed Total Analytical Error was calculated as Average Bias +2*Pooled SD. Based on the calculated Total Analytical Error, the LOQ was determined. The

extended low range was calculated to measure low concentrations, such as those seen in children, for each of the IgG subclasses.

IgG1

Concentrations tested were 2.2 g/L (initial assay range) and 0.44 g/L (extended low assay range). These levels were chosen to challenge the low end of the analytical measuring range (1:400 dilution) and the extended low range (1:20 dilution). The limit of quantitation (LoQ) was determined to be 2.2 g/L. The extended limit of quantitation for IgG1 was determined to be 0.44 g/L.

IgG2

Concentrations tested were 0.44 g/L (initial assay range) and 0.11 g/L (extended low assay range). These levels were chosen to challenge the low end of the analytical measuring range (1:100 dilution) and the extended low range (1:5 dilution). The Limit of Quantitation (LoQ) for IgG2 was determined to be 0.44 g/L. The extended low range was determined to be 0.11 g/L.

IgG3

Two concentrations were tested, 0.04 g/L (initial assay range) and 0.002 g/L (extended low assay range). These levels were chosen to challenge the low end of the analytical measuring range (1:2000 dilution) and the extended low range (1:20 dilution). The Limit of Quantitation (LoQ) for IgG3 was determined to be 0.04 g/L. The extended low range was determined to be 0.002 g/L.

IgG4

Two concentrations were tested, 0.06 g/L (initial assay range) and 0.003 g/L (extended low assay range). These levels were chosen to challenge the low end of the analytical measuring range (1:200 dilution) and the extended low range (1:20 dilution). The Limit of Quantitation (LoQ) for IgG4 was determined to be 0.06 mg/L. The extended low range was determined to be 0.003 g/L.

Hook effect

The possibility of a hook effect occurring when using the IGG1-4 assays was evaluated. No hook effect was seen in concentrations up to: 78.6 g/L for IgG1; 51.9 g/L for IgG2; 35.7 g/L for IgG3; and 35.1 g/L for IgG4.

e. Analytical specificity:

Interference testing was performed according to CLSI/NCCLS EP7-A2 to determine the effect of various endogenous and exogenous substances on the Dimension Vista IGG1-4 assays. For all interferents except rheumatoid factors (RF), the percent bias was determined by testing a control sample without the interferent and comparing it to the value obtained from a test sample to which the potential interferent had been added. Test samples were prepared by spiking the potential interferent into serum.

IgG1 concentrations ranged from 4.79 - 12.8 g/L

IgG2 concentrations ranged from 1.48 - 7.31 g/L

IgG3 concentrations ranged from 0.225 - 0.781 g/L

IgG4 concentrations ranged from 0.471 - 1.892 g/L

To evaluate interference from rheumatoid factors, samples with known levels of IgG subclasses 1-4, which had elevated RF concentrations and samples with no detectable RF concentration, were used to prepare samples for the study. One to one mixtures of samples of non-detectable levels of RF with samples with high concentrations of RF were prepared and the IGG1-4 assays concentrations determined in replicates of five on the Dimension® Vista System. For lipemic samples: special handling instructions include clarification by centrifugation (10 min at approximately 15,000 xg) prior to testing. Since specimens should be free of particulate matter, lipemic or turbid samples, which cannot be clarified by centrifugation, must not be used. Recovery for the IGG1-4 were tested and met the acceptance criteria of bias <10%.

IgG1

Substance Tested	Substance Concentration	IgG subclass 1 mg/dL [g/L]	Bias* %
Hemoglobin (hemolysate)	1000 mg/dL [0.155 mmol/L]	348 [3.48]	+1
		2151 [21.51]	+3
Bilirubin (unconjugated)	60 mg/dL [1026 µmol/L]	334 [3.34]	-2
		2138 [21.38]	-1
Bilirubin (conjugated)	60 mg/dL [1026 µmol/L]	340 [3.40]	-1
		2106 [21.06]	-3

IgG2

Substance Tested	Substance Concentration	IgG subclass 2 mg/dL [g/L]	Bias* %
Hemoglobin (hemolysate)	1000 mg/dL [0.155 mmol/L]	114 [1.14]	-1
		769 [7.69]	+2
Bilirubin (unconjugated)	60 mg/dL [1026 µmol/L]	118 [1.18]	+3
		747 [7.47]	+1
Bilirubin (conjugated)	60 mg/dL [1026 µmol/L]	115 [1.15]	0
		747 [7.47]	+1

IgG3

Substance Tested	Substance Concentration	IgG subclass 3 mg/dL [g/L]	Bias* %
Hemoglobin (hemolysate)	1000 mg/dL [0.155 mmol/L]	23 [0.23]	+2
		119 [1.19]	+2
Bilirubin (unconjugated)	60 mg/dL [1026 µmol/L]	24 [0.24]	-3
		122 [1.22]	-4
Bilirubin (conjugated)	60 mg/dL [1026 µmol/L]	24 [0.24]	0
		122 [1.22]	+2

IgG4

Substance Tested	Substance Concentration	IgG subclass 4 mg/dL [g/L]	Bias* %
Hemoglobin (hemolysate)	1000 mg/dL [0.155 mmol/L]	8 [0.08]	-1
		351 [3.51]	-1
Bilirubin (unconjugated)	60 mg/dL [1026 µmol/L]	8 [0.08]	-3
		306 [3.06]	+9
Bilirubin (conjugated)	60 mg/dL [1026 µmol/L]	8 [0.08]	-3
		306 [3.06]	+9

The following substances were determined not to interfere with the IGG1-4 method when present in serum and plasma at the concentrations indicated. Inaccuracies (biases) due to these substances are less than 10 % at IgG 1 concentrations of 479 mg/dL to 1280 mg/dL [4.79 g/L to 12.8 g/L], IgG 2 concentrations of 148 mg/dL to 731 mg/dL [1.48 g/L to 7.31 g/L, IgG3 concentrations of 22.8 mg/dL to 72.0 mg/dL [0.228 g/L to 0.720 g/L], and IgG4 concentrations. of 42.9 mg/dL to 194.2 mg/dL [0.429 g/L to 1.942 g/L].

Substance	Test Concentration	SI Units
Acetaminophen	20 mg/dL	1328 µmol/L
Amikacin	15 mg/dL	256 µmol/L
Ammonium heparin	3 U/mL	3000 U/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic acid	5 mg/dL	284 µmol/L
Caffeine	6 mg/dL	308 µmol/L
Carbamazepine	3 mg/dL	127 µmol/L
Chloramphenicol	5 mg/dL	155 µmol/L
Chlordiazepoxide	5 mg/dL	167 µmol/L
Chlorpromazine	0.2 mg/dL	6.27 µmol/L
Cholesterol	500 mg/dL	12.9 mmol/L
Cimetidine	2 mg/dL	79.2 µmol/L
Creatinine	30 mg/dL	2652 µmol/L
Dextran	6000 mg/dL	1500 µmol/L
Diazepam	0.5 mg/dL	17.6 µmol/L
Digoxin	5 ng/mL	6.15 nmol/L
Erythromycin	6 mg/dL	81.6 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25 mg/dL	1770 µmol/L
Furosemide	6 mg/dL	181 µmol/L
Gentamicin	12 mg/dL	151 µmol/L
Ibuprofen	50 mg/dL	2425 µmol/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Lithium chloride	2.3 mg/dL	3.2 mmol/L
Lithium heparin	3 U/mL	3000 U/L

Substance	Test Concentration	SI Units
Nicotine	0.1 mg/dL	6.2 µmol/L
Penicillin	25 U/mL	25000 U/L
Pentobarbital	8 mg/dL	354 µmol/L

f. Assay cut-off:
Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

The new assays (Dimension Vista IGG 1-4) were compared to the predicate assays (N Antiserum to Human IgG subclasses 1 and 2 and the N Latex IgG3 and IgG4 on the BN Prospec System). Single determinations from 129-150 serum and plasma (lithium and sodium heparin) samples were run according to EP9-A2 on both the new and predicate assays for both the reportable and extended range. Passing-Bablok regression analysis was used to analyze the data for the initial measuring range.

Subclass	N=	Range tested mg/dL (g/L)	Slope (95% CI)	Intercept (95% CI)	r ²
IgG1	129	222 – 2285 (2.22 – 22.85)	1.002 (0.983, 1.022)	-0.165 (-0.321, -0.027)	0.988
IgG2	147	63 – 762 (0.63 – 7.62)	1.000 (0.987, 1.018)	-0.020 (-0.070, 0.020)	0.988
IgG3	142	4 – 155.2 (0.040 – 1.552)	1.047 (1.030, 1.061)	-0.002 (-0.005, 0.002)	0.987
IgG4	150	6.2 – 250 (0.062 – 2.50)	1.020 (1.004, 1.035)	-0.009 (-0.015, -0.004)	0.988

The performance of the low and high samples run with a new dilution was demonstrated by running a method comparison study versus the BN Prospec in the extended range low and high. The low extended range was validated by evaluating serum samples at a lower dilution. The high extended range was validated by evaluating serum samples at a higher dilution.

Extended Low Range

Subclass	N=	Range tested mg/dL (g/L)	Slope (95% CI)	Intercept (95% CI)	r ²
IgG1	24	45-188 (0.45-1.88)	1.000 (0.931, 1.073)	+ 0.010 (-0.061, 0.061)	0.984
IgG2	28	11-44 (0.11-0.44)	1.000 (0.923-1.083)	0.0 (-0.023-0.019)	0.968
IgG3	23	0.3-3.3 (0.003-0.033)	1.00 (1.00-1.00)	0.0 (0.0-0.0)	0.975
IgG4	29	0.3-3.7 (0.003-0.037)	1.00 (0.97-1.00)	0.0 (0.0-0.0)	0.997

Extended High Range

Subclass	N=	Range tested mg/dL (g/L)	Slope (95% CI)	Intercept (95% CI)	r ²
IgG1	24	2784-9262 (27.84-92.62)	1.025 (0.961, 1.101)	-4.019 (-7.733, -0.638)	0.969
IgG2	28	845-4068 (8.45-40.68)	0.998 (0.928-1.054)	-0.639 (-1.843-0.903)	0.956
IgG3	23	231.4-534.8 (2.314-5.348)	1.008 (0.924-1.124)	0.159 (-0.292-0.457)	0.961
IgG4	29	300.4-939.7 (3.004-9.397)	1.004 (0.878-1.131)	-0.135 (-0.733-0.452)	0.934

b. Matrix comparison:

A separate study was performed using matched serum and plasma samples on the Dimension Vista® System. In this study, matched samples of serum, lithium heparin, sodium heparin and EDTA were tested on the Dimension Vista® System. For each plasma type, the % recovery and regression analyses compared to serum were performed. The acceptance criteria: a correlation coefficient of ≥ 0.950 and a mean of % differences in recovery versus serum of $\leq 7\%$. All samples met the acceptance criterion.

IgG1 (n= 24 for low and high range)

	Linear Regression vs. Serum			% Recovery Statistics			
	Li Hep	Na Hep	EDTA		Li Hep	Na Hep	EDTA
Slope	0.96	1.00	1.01	Mean	-2.5	-3.2	-3.1
Y-int	0.13	-0.22	-0.28	Min	-6.2	-6.9	-9.3
R	0.999	1.000	0.999	Max	3.9	0.6	2.3
Syx:	0.23	0.22	0.39				
Slope 95% CI low	0.938	0.982	0.980				
Slope 95% CI high	0.97	1.01	1.04				

IgG2 (n=28 for low and high ranges)

	Linear Regression vs. Serum			% Recovery Statistics			
	Li Hep	Na Hep	EDTA		Li Hep	Na Hep	EDTA
Slope	0.96	0.95	0.95	Mean	-2.1	-1.4	-4.0
Y-int	0.05	0.08	0.03	Min	-4.5	-5.0	-9.5
R	0.999	1.000	0.997	Max	1.7	2.8	2.7
Syx:	0.09	0.08	0.20				
Slope 95% CI low	0.94	0.936	0.912				
Slope 95% CI high	0.98	0.97	1.00				

IgG3 (n=23 for low range, n=30 for high range)

	Linear Regression vs. Serum			% Recovery Statistics			
	Li Hep	Na Hep	EDTA		Li Hep	Na Hep	EDTA
Slope	0.99	0.98	0.99	Mean	-1.4	-0.9	-2.2
Y-int	-0.01	0.01	-0.01	Min	-6.6	-3.4	-9.1
R	0.999	0.999	0.999	Max	2.5	1.9	2.0
Syx:	0.02	0.02	0.02				
Slope 95% CI low	0.965	0.966	0.962				
Slope 95% CI high	1.02	1.00	1.02				

IgG4 (n=29 for low range and n=28 for high range)

	Linear Regression vs. Serum			% Recovery Statistics			
	Li Hep	Na Hep	EDTA		Li Hep	Na Hep	EDTA
Slope	1.00	1.02	0.99	Mean	1.0	2.2	-1.9
Y-int	0.00	0.00	-0.01	Min	-2.8	-1.5	-8.2
R	1.000	1.000	0.999	Max	8.9	8.8	2.4
Syx:	0.02	0.03	0.04				
Slope 95% CI low	0.994	1.000	0.967				
Slope 95% CI high	1.01	1.04	1.01				

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:

A literature reference was used for the IgG1-4 expected values:

The expected values for the IgG1 method are:

Age Group	IgG1 (mg/dL)	IgG1 [g/L]
>1 to ≤ 3 years	265 - 938	2.65 – 9.38
>3 to ≤ 6 years	362 - 1228	3.62 – 12.28
>6 to ≤ 12 years	377 - 1131	3.77 – 11.31
>12 to ≤ 18 years	362 - 1027	3.62 – 10.27
>18 years	405 - 1011	4.05 – 10.11

The expected values for the IgG2 method are:

Age Group	IgG2 (mg/dL)	IgG2 [g/L]
>1 to ≤ 3 years	27.58 – 215.8	0.28 – 2.16
>3 to ≤ 6 years	57.1 – 290.4	0.57 – 2.90
>6 to ≤ 12 years	67.8 – 388.2	0.68 – 3.88
>12 to ≤ 18 years	81.1 – 471.9	0.81 – 4.72
>18 years	169 - 786	1.69 – 7.86

The expected values for the IgG3 method are:

Age Group	IgG3 (mg/dL)	IgG3 [g/L]
>1 to ≤ 3 years	8.7 – 86.4	0.087 – 0.864
>3 to ≤ 6 years	12.9 – 78.9	0.129 – 0.789
>6 to ≤ 12 years	15.8 – 89.0	0.158 – 0.890
>12 to ≤ 18 years	13.8 – 105.8	0.138 – 1.058
>18 years	11.00 – 85.0	0.11 – 0.85

The expected values for the IgG4 method are:

Age Group	IgG4 (mg/dL)	IgG4 (g/L)
>1 to ≤ 3 years	0.89 – 74.21	0.009 – 0.742
>3 to ≤ 6 years	1.28 – 144.60	0.013 – 1.446
>6 to ≤ 12 years	1.17 – 169.88	0.012 – 1.699
>12 to ≤ 18 years	4.91 – 198.47	0.049 – 1.985
>18 years	3.00 - 201	0.03 – 2.01

The expected values were confirmed by running a reference interval transference study following the NCCLS/CLSI Guideline C28-A2. Twenty normal clinical samples were run in triplicate, and the mean of the three runs was calculated. The acceptance criterion for this study was that not more than two of twenty (10%) values could be outside the published range. The acceptance criterion was met for all of the assays within the adult and pediatric reference ranges.

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.