

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k083445

B. Purpose for Submission:

Device modification (addition of urine as a sample matrix)

C. Measurand:

Immunoglobulin IgG

D. Type of Test:

Nephelometry, Quantitative and Semi-quantitative

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

N Antisera to Human Immunoglobulins (IgG, IgA, and IgM)

N/T Protein Control LC

G. Regulatory Information:

1. Regulation

21 CFR § 866.5510, Immunoglobulins A, G, M, D, and E Immunological test system

21 CFR § 862.1660, Quality Control material (Assayed and Unassayed)

2. Classification

Class II

Class I

3. Product Code

CFN, Method Nephelometric, Immunoglobulins (G, A, M)

JJY, Multi-analyte Controls, All kinds (Assayed and Unassayed)

4. Panel

Immunology (82); Chemistry (75)

H. Intended Use:

1. Intended use(s):

N Antisera to Human Immunoglobulins (IgG, IgA, and IgM) – In vitro diagnostic reagents for the quantitative determination of immunoglobulins (IgG, IgA and IgM) in human serum, heparinized and EDTA plasma, and IgG in human urine and cerebrospinal fluid (CSF) by means of immunonephelometry on the BN™ Systems. Measurement of immunoglobulins aid in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

N/T Protein Control LC is intended for use as an assayed intralaboratory quality control for assessment of precision and analytical bias in immunochemical determination of the proteins IgG in CSF, IgA in CSF, IgM in CSF, IgG in urine, transferrin in urine, albumin in urine and CSF, α 1-microglobulin in urine and total protein in urine and CSF, using the BN™ Systems.

2. Indication(s) for use:

Same as Intended Use.

3. Special conditions for use statement(s):

For Prescription only.

4. Special instrument requirements:
BN ProSpec® Analyser (k001647)

I. Device Description:

N Antisera to Human Immunoglobulins (IgG, IgA, and IgM) reagent is packaged in either 2 mL or 5 mL bottles and ready for use.

N/T Protein Control LC consists of 3 lyophilized vials containing human urine and serum proteins, polygeline and rabbit albumin.

J. Substantial Equivalence Information:

1. Predicate device name(s):
IMMAGE® Immunochemistry Systems IGU
Protein 3 Control
2. Predicate 510(k) number(s):
k951635, k072435
3. Comparison with predicate:

N Antisera to Human Immunoglobulins (IgG, IgA, and IgM)

Similarities		
Item	New Device	Predicate Device
Technology	Nephelometry	Same
Storage conditions	2-8 °C	Same
Components	Calibrators and Controls are sold separately	Same

Differences		
Item	New Device	Predicate
Intended Use/ Indication for Use: Reagent IgG Antisera	In vitro diagnostic reagents for the quantitative measurement of immunoglobulins (IgG, IgA, and IgM) in human serum, heparinized and EDTA plasma, and IgG in human urine and cerebrospinal fluid (CSF) by means of nephelometry on the BN™ Systems. Measurements of these immunoglobulins aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.	IGU reagent, when used in conjunction with IMMAGE® Immunochemistry Systems and Urine Protein Calibrator, is intended for the quantitative determination of Urine Immunoglobulin G (IGU) in human urine by rate nephelometry.

Sample type	Heparinized and EDTA plasma, and IgG in human urine and cerebrospinal fluid	IgG in serum, cerebrospinal fluid and urine
Analyzer	Dade Bearing BN ProSpec®	Beckmann Coulter IMMAGE® Immunochemistry Systems
Antibody source	Rabbit polyclonal	Processed goat sera
IgG reporting Units	mg/L	mg/dL
IgG Urine Reference Interval	<9.6 mg/L	<0.80 mg/dL
Assay Range Differences	3.6 to 58 mg/L No hook effect to 648.4 mg/L	Initial: 0.3 to 6.0 mg/dL Extended: 0.3 to 1296 mg/dL
Packaging	1 vial at 2 mL 1 vial at 5 mL	IGU antibody - 3.9 mL IGU Antigen Excess Solution - 1.2 mL

N/T Protein Control LC

Similarities		
Item	Device	Predicate
Control	N/T Protein Control LC	Protein 3 Control
Composition	Multi-analyte, lyophilized, human urine and serum based product with polygeline and rabbit albumin	Same
Traceability	Traceable to ERM®-DA470(CRM 470)	Same

Differences		
Item	Device	Predicate
Intended Use	N/T Protein Control LC is intended for use as an assayed intralaboratory quality control for assessment of precision and analytical bias in immunochemical determination of the proteins IgG in CSF, IgA in CSF, IgM in CSF, IgG	PROT3 CON is an assayed intralaboratory quality control for the assessment of precision and analytical bias on the Dimension Vista® System in the quantitative determination of: α 1-Microglobulin

Differences		
Item	Device	Predicate
	in urine, transferrin in urine, albumin in urine and CSF, α 1-microglobulin in urine and total protein in urine and CSF, using the BN™ Systems.	(A1MIC), specialty Albumin (sALB*), Immunoglobulin G (IGG-C*, IGG-U**), Transferrin (TRF-U**), Microalbumin (MALB), * For cerebrospinal fluid(CSF), ** For urine
Packaging	3 vials, lyophilized (1 ml each reconstituted)	4 vials, lyophilized (1 ml each reconstituted)
Analyzer	BN ProSpec® Analyser	Dimension Vista® system

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

Standards:

CLSI EP05-A2 Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition

NCCLS EP6-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

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

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

Guidance Documents:

Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material Draft Guidance Document for 510(k) Submission of Immunoglobulins A, G, M, D, and E Immunoglobulin System in Vitro Devices

L. Test Principle:

Proteins contained in human body fluids react with specific antibodies in the reagent, to form immune complexes in an immunochemical reaction. These complexes in the reaction mixture cause the scatter of a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of IgG in the sample. The result is evaluated by comparison with a standard of known concentration. This is the same well established nephelometric principle as the predicate.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility testing was done in accordance with CLSI EP5-A, on ten days with four replicates per day (N=40)

Material	Total Mean	Intra-assay	Run-to Run	Inter-assay
	mg/L	CV	CV	CV
NT Prot 3 Control	18.7	1.1%	0.8%	1.3%

Urine pool low	5.5	2.9%	3.2%	4.1%
Urine pool high	19.9	1.2%	2.5%	2.8%

Additional low and high end reproducibility testing was done in accordance with CLSI EP5-A, on five days, with two runs per day, with four replicates per run (N=40)

Material	Total Mean	Intra-assay	Run-to Run	Inter-assay
	mg/L	CV	CV	CV
Urine pool low	3.9	2.1%	1.4%	2.3%
Urine pool high	51.3	1.7%	2.8%	3.0%

b. Linearity/assay reportable range:

Linearity:

Linearity across the assay range was confirmed by testing a human urine sample with high concentration (59.7 mg/L) of IgG. This sample was serially diluted with System N Diluent down to the lower detectable measuring range (3.33 mg/L). Each dilution was tested in replicates of five. Data were analyzed in accordance to CLSI EP06-A and EP17-A. Percent recovery was calculated using the formula: (Mean of test/expected concentration) x 100. All dilutions met the acceptance criteria of 85 to 115%. Test results that fall outside the measuring range are flagged. The linear regression analysis was performed. Data showed a regression equation: $y = 0.9824x + 0.0891$, $r = 0.9994$. Reportable range for IgG-U device is approximately 3.6 to 58.0 mg/L for urine samples.

Hook Effect:

The possibility of antigen excess occurring when using the device was evaluated with sample (pool concentration) above the assay range. The samples were analyzed, indicating no antigen excess effect observed up to at least 648.4mg/L.

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

The calibrator and controls are traceable to the reference material Calibrator ERM® - DA470 (CRM 470).

Stability:

Data was provided to support shelf life, open vial, and on-board storage. When stored at 2- 8 °C, the data supported a 24 month shelf life. Open vial stability for the N Antiserum was 4 weeks and 14 days for the N/T Protein Controls LC and N Protein Standard. On-board stability data supported 4 and 2 weeks for the 5 mL and 2 mL vial of N Antiserum reagent, respectively, and 7 days for the N/T Protein Controls LC.

c. Detection limit:

Data were analyzed according to EP17-A. Detection limit represents the lower limit of the reportable range of urine IgG. The analytical sensitivity is defined as the minimal detectable level of analyte, which can be distinguished from zero. The value was calculated as the mean value of fifteen replicates of three human urine samples and sample diluent. It was determined to be 3.6 mg/L.

e. Analytical specificity:

Interference testing was performed according to CLSI EP7-A2. No interference for

urine sample matrix was observed in the presence of the following interferents: Hemoglobin up to 10 mg/dL; Bilirubin (unconjugated) up to 2 mg/dL; Bilirubin (conjugated) up to 3 mg/dL. Additional substances (listed below) also demonstrated no interference at the concentrations listed:

Substance	Substance Test Concentration	IgG Concentration
Acetone	1000 mg/dL	7.70 mg/L
Ascorbic acid	900 mg/dL	20.9 mg/L
Ethanol	1000 mg/dL	7.70 mg/L
Oxalic acid	10 mg/dL	24.9 mg/L
Riboflavin	6.75 mg/dL	28.5 mg/L
Sodium Chloride	6000 mg/dL	7.37 mg/L
Bovine albumin	500 mg/dL	23.6 mg/L
Boric Acid	4500 mg/dL	21.6 mg/L
Sodium Azide	20000 mg/dL	23.6 mg/L
Sodium Fluoride	16000 mg/dL	21.4 mg/L

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The table below shows the comparison of 76 urine samples ranging from 3.3 to 59.20 mg/L IgG that were tested on the BN ProSpec® System and the Beckman Coulter IMMAGE® using the respective IgG assays. Results were analyzed by Passing-Bablok regression, yielded a slope of 0.926 with an intercept of -0.339 mg/L and a correlation coefficient of 0.985, and are summarized below:

	N	Slope (95% CI)	Intersept (95% CI)	R	R ²
BN ProSpec® vs. Beckman Immage	76	0.926 (0.882,0.185)	-0.339 (-0.921, 0.120)	0.985	0.970

b. Matrix comparison:

Both use urine as a matrix.

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, and a transference study was conducted, for the IgG Urine Expected Values of < 9.6 mg/L (Hofmann W, Guder WG. A diagnostic programme for quantitative analysis of proteinuria. J Clin Chem Clin Biochem 1989; 27: 589-600). This was confirmed by performing a Reference Interval transference study.

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.