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

A. 510(k) Number:
K042735

B. Purpose for Submission:
Modified device

C. Analyte:
IgG, IgA, IgM

D. Type of Test:
IgG, IgA, IgM: serum, heparinized (sodium heparin, ammonium heparin, and lithium heparin) and EDTA plasma
IgG: CSF

E. Applicant:
Dade Behring Inc.

F. Proprietary and Established Names:
N Antisera to Immunoglobulins (IgG, IgA, and IgM) Assay

G. Regulatory Information:
1. <u>Regulation section:</u>
21 CFR 866.5510 Immunoglobulins A,G,M,D,E immunological test system
2. <u>Classification:</u>
Class II
3. <u>Product Code:</u>
CFN, Method, Nephelometric, Immunoglobulins (G,A,M)
4. <u>Panel:</u>
Immunology

H. Intended Use:
1. <u>Intended use(s):</u>
In vitro diagnostic reagents for the quantitative determination of immunoglobulins (IgG, IgA and IgM) in human serum, heparinized and EDTA plasma as well as IgG in human cerebrospinal fluid (CSF) by means of immunonephelometry on the BN [TM] Systems.

2. <u>Indication(s) for use:</u>
In vitro diagnostic reagents for the quantitative determination of immunoglobulins (IgG, IgA and IgM) in human serum, heparinized and EDTA plasma as well as IgG in human cerebrospinal fluid (CSF) using the

BN^{TM} Systems. Measurements of these immunoglobulins aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

3. <u>Special condition for use statement(s):</u>
   For prescription use only

4. <u>Special instrument Requirements:</u>
   BN^{TM} Systems including BN^{TM} 100, BN^{TM} II System, and BN^{TM} ProSpec System.

Feature	BN^{TM} 100	BN^{TM} II System	BN^{TM} ProSpec
1. Intended Use	The BN^{TM} 100 allows fully automatic determination of proteins in various body liquids. Precipitation as well as agglutination reactions (latex) can be performed quantitatively and quickly	The BN^{TM} II is a system for the quantitative determination of proteins in serum, plasma, urine, and CSF.	The BN^{TM} ProSpec is a system for the quantitative determination of proteins in serum, plasma, urine, and CSF
2. Measuring Methods	Nephelometry	Nephelometry	Nephelometry
3. Measuring Principles	End-point measurement; Fixed-time kinetic measurement	End-point measurement; Fixed-time kinetic measurement; VLinIntegral	End-point measurement; Fixed-time kinetic measurement; VLinIntegral
4. Physical characteristics:			
a. Light Sources	LED	LED	LED
b. Wavelengths	840 nm	840 nm	840 nm
c. Pipetting	Yes	Yes	Yes
d. Interfacing	Bi-directional	Bi-directional	Bi-directional, host query, ASTM
e. Data Input/Output	Computer & Printer	Computer & Printer	Computer & Printer
f. Barcode Identification	Yes	Yes	Yes
g. Dimensions	47.3 x 94 x5 1 cm (h x w x d)	71.5 x 124 x 63 cm (h x w x d)	66 x 110 x 66 cm (h x w x d)
h. Dilutor Volume	500 μL	Left 1000 μL (Variable) Middle 2500 μL (Variable) Right 250 μL (Variable)	500 μL (Variable)
i. Transfer Arm	1	2	1

j. Cuvette Washing	Yes	Yes	No (disposable)
5. Operating Features			
a. Random Access Continuous Access Stat Processing	Yes Yes Yes	Yes Yes Yes	Yes Yes Yes
b. Primary Tube Handling	No	Yes	Yes
c. Maximum Capacity On-Board	75 Samples 30 Standards/ Calibrators/Controls 14 Reagents	75 Samples 30Standards/ Calibrators/Controls 14 Reagents	75 Samples 30Standards/ Calibrators/Controls 14 Reagents
d. Throughput	Approximately 100/hour	Approximately 150/hour	Approximately 70/hour
e. Calibration Interval	1-4 weeks or longer based on control results	1-4 weeks or longer based on control results	1-6 weeks or longer based on control results
f. QC Availability	Program item Controls traceable over 30 days	Co-Med QC Program (commercially available)	PASS QC Program (commercially available)
g. On-Board Reagent Storage up to 10^0C	No (Room Temperature)	No (Room Temperature)	Yes
h. Temperature Control: Standards & Controls/Samples	No (Room Temperature)	No (Room Temperature/+ 37^0C))	Yes (Room Temperature/+ 37^0C)

I. Device Description:

The device consists of N antiserum to human IgG; N antiserum to human IgA, N antihuman IgM. One vial each containing 5 mL or 2 mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   N Antisera to Human Immunoglobulins (IgG, IgA, and IgM) Assay

2. Predicate K number(s):
   K860894

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
	Modified N Antisera to Human Immunoglobulins	N Antisera to Human Immunoglobulins
Reagents	N Antiserum to human IgG,A,M	Same
Instrument	BN^{TM} Systems	Same

Differences		
Item	**Device**	**Predicate**
Sample Type	IgG,A,M: serum, heparinized and EDTA plasma. IgG: CSF	IgG,A,M: serum IgG: CSF

K. Standard/Guidance Document Referenced (if applicable):
Not referenced

L. Test Principle:
Proteins contained in human body fluids from immune complexes in an immunochemical reaction with specific antibodies. These complexes scatter a beam of light passes through the sample. The intensity of the scattered light is proportional to the concentration to the concentration of the relevant 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:

      The intra-assay precision
      The intra-assay precision was determined by using three concentration levels of specimen over five days, testing two independent runs per day (am/pm), assaying four replicates (e.g. 5 x 2 x 4 = 40 replicates).

      IgG
      5.0g/L   3.0% CV
      8.4g/L   1.8% CV
      12.1 g/L   2.6% CV

      IgA
      1.0 g/L   1.6% CV
      1.7g/L   3.3% CV
      2.5 g/L   2.5% CV

      IgM
      0.27 g/L   3.8% CV
      0.69g/L   3.2% CV
      0.90 g/L   2.6% CV

The inter-assay precision
The inter-assay precision was determined by using three levels of concentration specimen. The samples were assayed in two independent run with 4 replicates in 5 days (n=40)

IgG
5.0g/L	2.1% CV
8.4g/L	1.4% CV
12.1 g/L	1.5% CV

IgA
1.0 g/L	3.7% CV
1.7g/L	2.7% CV
2.5 g/L	2.1% CV

IgM
0.27 g/L	4.0% CV
0.69g/L	1.9% CV
0.90 g/L	1.7% CV

Total precision
IgG
5.0g/L	3.4% CV
8.4g/L	2.7% CV
12.1 g/L	2.1% CV

IgA
1.0 g/L	4.1% CV
1.7g/L	4.0% CV
2.5 g/L	3.1% CV

IgM
0.27 g/L	5.3% CV
0.69g/L	3.4% CV
0.90 g/L	2.8% CV

b. *Linearity/assay reportable range:*
The assay ranges for serum or plasma specimens of the N Antisera to human Immunoglobulins G,A,M are approximately:
IgG 1.4 to 46 g/L   (1:400 dilution)
IgA 0.25 to 8.0 g/L   (1:20 dilution)
IgAs 0.06 to 2.0 g/L   (1:5 dilution)
IgM 0.2 to 6.4 g/L   (1:20 dilution)
IgMs 0.05 to 1.6 g/   (1:5 dilution)

The assay ranges for CSF specimens of the N Antisera to human Immunoglobulins G is approximately:
CSF IgG 3.6 to 115 mg/L.

(**Methods and acceptance criteria undisclosed**)
c. *Traceability (controls, calibrators, or method):*
   The device does not contain controls and calibrators.

d. *Detection limit:*
   Typical lower limit of the detection are:
   Serum or plasma IgG 0.19 g/L,
   CSF IgG 0.5 mg/L
   Serum or plasma IgA 0.016 g/L
   Serum or plasma IgM. 0.043 g/L

The analytical sensitivity of the assay is established by the lower limit of the reference curve, and depend upon the concentrations of the proteins in N Protein Standard SL.

e. *Analytical specificity:*
   The specificity of the N Antisera Human Immunoglobulins (IgG, IgA, and IgM) assay were tested against normal human serum and plasma pool, antigens to human, and preparations of human IgG, IgA, IgM and Bence-Jonse proteins, type Kappa and Lambda in different analytical methods. There are no known cross-reactivities of the antisera.

f. *Assay cut-off:*
   IgG 7.0 to 16.0 g/L
   IgA 0.7 to 4.0 g/L
   IgM 0.4 to 2.3 g/L

2. Comparison studies:
   a. *Method comparison with predicate device:*
      One hundred (100) serum samples were assayed with N Antisera to humanimmunoglobulins on a BN System ii (y) and a radial immunodiffusion (RID) method (x). Correlation of the results yielded following data:

Protein		Coefficient of correlation
IgG	y(BN) = 1.09X (RID) – 0.12 g/L	0.97
IgA	y(BN) = 0.99X (RID) + 0.06 g/L	0.99
IgM	y(BN) = 1.08X (RID) – 0.06 g/L	0.99

   b. *Matrix comparison:*
      Serum/Heparin Plasma Comparison-BN II
      IgG (n=67)

Heparin plasma sample = 0.973 serum sample + 0.068 g/L
95% Confidence Interval
Slope   (0.953, 0.997)
Intercept   (-0.068, 0.263)
Pearson correlation coefficient (r = 0.989; r^2 = 0.978)
NOTE: Recovery study showed deviation of heparinized plasma for
IgG assay (lithium Heparin vs. Sodium Heparin -1.158%; lithium
Heparin vs. Ammonium Heparin -0.153%; Ammonium Heparin vs.
Sodium Heparin -1.007%)

IgA (n=65)
Heparin plasma sample = 0.988 serum sample - 0.008 g/L
95% Confidence Interval
Slope   (0.973, 1.005)
Intercept   (-0.026, 0.012)
Pearson correlation coefficient (r = 0.998; r^2 = 0.997)
NOTE: Recovery study showed deviation of heparinized plasma for
IgA assay (lithium Heparin vs. Sodium Heparin -2.94%; lithium
Heparin vs. Ammonium Heparin -4.08%; Ammonium Heparin vs.
Sodium Heparin -1.19%)

IgM (n=64)
Heparin plasma sample = 0.981 serum sample + 0.006 g/L
95% Confidence Interval
Slope   (0.953, 1.011)
Intercept   (-0.018, 0.024)
Pearson correlation coefficient (r = 0.991; r^2 = 0.982)
NOTE: Recovery study showed deviation of heparinized plasma for
IgM assay (lithium Heparin vs. Sodium Heparin 0.6%; lithium
Heparin vs. Ammonium Heparin -0.151%; Ammonium Heparin vs.
Sodium Heparin 0.752%)

Serum/EDTA Plasma Comparison-BN II
IgG (n=37)
EDTA plasma sample = 1.012 serum sample - 0.274 g/L
95% Confidence Interval
Slope   (0.967, 1.051)
Intercept   (-0.557, 0.003)
Pearson correlation coefficient (r = 0.988; r^2 = 0.976)

IgA (n=36)
EDTA plasma sample = 0.961 serum sample - 0.011 g/L
95% Confidence Interval
Slope   (0.933, 0.998)

Intercept   (-0.041, 0.024)
Pearson correlation coefficient (r = 0.994; r^2 = 0.989)

IgM (n=36)
EDTA plasma sample = 0.939 serum sample + 0.004 g/L
95% Confidence Interval
Slope   (0.892, 0.982)
Intercept   (-0.014, 0.031)
Pearson correlation coefficient (r = 0.980; r^2 = 0.961)

3. Clinical studies:
   a. *Clinical sensitivity:*
      n/a
   b. *Clinical specificity:*
      n/a
   c. *Other clinical supportive data (when a and b are not applicable):*
      n/a

4. Clinical cut-off:
   Refer to 1/*f*

5. Expected values/Reference range:
   The reference intervals for serum or plasma were derived from a consensus document of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in **serum** based on the standardization against the IFCC/BCR/CAP Reference material (CRM 470).
   IgG 7.0 to 16.0 g/L
   IgA 0.7 to 4.0 g/L
   IgM 0.4 to 2.3 g/L
   (Reference: Dati F Schumann G., Thomas L., et al. Consensus of a Group of Professional Societies and Diagnostics Companies on guidelines for Interim Reference Ranges for 14 proteins in Serum Based on the Standardization against the IFCC/BCR/CAP Reference Material (CRM 470). International Federation of Clinical Chemistry. Community Bureau of Reference of the Commission of the European Communities. College of American Pathologists. Eur J Clin Chem Clin Biochem 1996; 34:517-520).

   Reference interval for IgG in CSF sample is less than 34 mg/L. (References: 1. Felgenhauer K. Laboratory Diagnosis of Neurological Disease. In: Thomas L ed. Clinical Laboratory Diagnostics. Frankfurt TH Books Verlagsgesellschaft, 1998:1308-26. 2. Reiber H, Peter JB, Cerebrospinal Fluid Analysis: Disease-related Data Patterns and Evaluation Programs. J Neurol Sci. 2001; 184:101-122).

References range (2.5th-97.5th percentile) for childhood and aldolescence:

IgG

Age (years)	Male (g/L)	Female (g/L)
1	3.5-8.6	4.0-9.8
4	5.1-12.6	5.3-13.0
7	6.0-14.7	5.9-14.6
10	6.6-6.2	6.4-15.9
14	6.6-16.2	6.8-16.7
18	6.5-16.0	6.9-17.0

IgA

Age (years)	Male (g/L)	Female (g/L)
1	0.17-0.96	0.17-0.94
4	0.36-1.98	0.33-1.85
7	0.48-2.66	0.44-2.44
10	0.57-3.18	0.52-2.90
14	0.64-3.52	0.62-3.43
18	0.68-3.79	0.69-3.80

IgM

Age (years)	Male (g/L)	Female (g/L)
1	0.30-1.83	0.34-2.06
4	0.35-2.13	0.42-2.55
7	0.37-2.26	0.45-2.78
10	0.38-2.35	0.48-2.94
14	0.40-2.44	0.50-3.09
18	0.41-2.51	0.52-3.22

(Reference: Richie RF, Palomaki GE, Neveux LM et al. Reference Distributions for Immunoglobulins A, G, and M: a practical, simple, and clinical relevant approach in a large cohort. J Clin Lab Anal. 1998; 12:263-270).

N. Conclusion:

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

O. Other Supportive Information:
   n/a

P. Administrative Information:

   1. Applicant contact information:

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Q. Reviewer Name and Signature:

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