510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k050113

B. Purpose for Submission:
Addition of CSF as sample matrix to previously cleared Tina-Quant® IgG Gen.2 application for measurement in human serum and plasma.

C. Measurand:
IgG

D. Type of Test:
Immunoturbidimetric, Quantitative

E. Applicant:
Roche Diagnostics

F. Proprietary and Established Names:
Tina-Quant® IgG Gen.2

G. Regulatory Information:
1. Regulation section:
   21CFR§866.5510 Immunoglobulins A,G,M,D,E Immunological Test system
2. Classification:
   Class II
3. Product code:
   DEW IgG, Antigen, Antiserum, Control
4. Panel:
   Immunology (82)

H. Intended Use:
1. Intended use(s):
   Immunoturbidimetric assay for the quantitative in vitro determination of IgG in human serum, plasma, and cerebrospinal fluid (CSF) on Roche automated clinical chemistry analyzers.
2. Indication(s) for use:
   Measurement of IgG aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.
3. Special conditions for use statement(s):
   For prescription use only.
4. Special instrument requirements:
   For Roche/Hitachi 904, 911, 912, 917, MODULAR P:

I. Device Description:

Tina-Quant® IgG Gen.2 consists of the following:

R1 TRIS* buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6%; preservative and stabilizers.

R2 Anti-human IgG antibody (goat): dependent on titer; TRIS* buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative.

*TRIS = Tris(hydroxymethyl)-aminomethane

Calibrators for the standard application include Preciset Serum Proteins or C.f.a.s. Proteins; the calibrator for the sensitive application is C.f.a.s. PUC (Proteins in Urine/CSF). These were cleared as k040264. The recommended control materials for the standard application are Precinorm Protein and Precipath Protein; the recommended control materials for the sensitive application are Precinorm PUC (Proteins in Urine/CSF) and Precipath PUC. These were cleared as k041812. IgG analyte values were added to these calibrators and controls and were assigned k050026.

Calibrators and controls are sold separately.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Dade Behring N Antisera to Human Immunoglobulins (IgG, IgA, and IgM) IgG assay on the BN II
2. Predicate 510(k) number(s):
   k943997
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	Tina-Quant ® IgG Gen.2	**Dade-Behring N Antisera to Human Immunoglobulins IgG on BN II**
Intended Use	Immunoturbidimetric assay for the quantitative in vitro determination of IgG in human serum, plasma, and cerebrospinal fluid (CSF) on Roche automated clinical chemistry analyzers.	In vitro diagnostic reagents for the quantitative determination of immunoglobulims (IgG, IgA, and IgM) in human serum as well as of IgG in human urine and cerebrospinal fluid (CSF)
Traceability / Standardization	CRM 470	CRM 470
Sample Types	Serum, plasma, CSF	Serum, plasma, urine, CSF

Differences		
Item	Device	Predicate
Calibrator	Sensitive application (CSF): C.f.a.s. (Calibrator for	N Proteins Standard SL (human)

Differences		
Item	Device	Predicate
	automated systems) PUC	
Instrument	Roche/Hitachi family of analyzers	BN Systems
Expected values	10-30 mg/L	Below 34 mg/L
Analytical Sensitivity	2 mg/L	Established by lower limit of reference curve

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

None referenced.

L. Test Principle:

The immunoturbidimetric methodology utilized in this assay is the basis for the already cleared TinaQuant IgG Gen.2 application for measurement in human serum and plasma. During the reaction, anti-IgG antibodies react with antigen in the sample to form an antigen-antibody complex. Following agglutination, the complex is measured turbidimetrically. PEG is added to the reaction to allow the reaction to progress rapidly to end point and improve sensitivity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:

   Within-run precision: The within-run precision for the Sensitive (CSF) application was determined by 21replicate determinations of two controls and two human CSF samples on the Hitachi 917 analyzer.

Within-Run Precision

Analyte:	IgG
Instrument:	Hitachi 917
Reagent:	IGGC2 Lot E01
Calibrator:	CfaS-PUC Lot 15575299 c= 227 mg/L, autodilution

Results:	Control low	Control high		
Data No.	PN-PUC (155.0mg/L)	PP-PUC (313.0mg/L)	Sample (L)	Sample (H)
1	167.03	322.36	11.71	227.06
2	168.84	324.70	11.30	219.44
3	167.12	316.44	12.53	227.87
4	167.72	325.79	11.81	221.62
5	166.43	320.14	12.07	226.43
6	168.01	321.37	12.32	224.95
7	168.18	322.67	11.05	222.16
8	167.69	312.74	10.94	221.61
9	165.50	327.71	11.86	221.14
10	169.38	320.36	11.76	220.51
11	167.82	321.66	13.45	220.26
12	166.29	326.14	11.20	220.12
13	168.25	315.50	12.89	225.12
14	168.86	320.88	10.74	218.93
15	170.07	318.32	10.89	220.22
16	167.80	309.90	11.81	218.89
17	167.02	320.85	11.35	220.07
18	167.80	321.44	11.92	221.93
19	169.23	317.80	11.56	221.16
20	167.88	324.43	11.30	217.68
21	166.95	323.24	11.71	222.24
n	21	21	21	21
Max.	170.07	327.71	13.45	227.87
Min.	165.50	309.90	10.74	217.68
Range	4.57	17.81	2.71	10.19
Average	167.80	320.69	11.72	221.88
SD.	1.10	4.41	0.67	2.83
CV(%)	0.65	1.38	5.74	1.27

The **between-day precision** for the Sensitive application was determined by measuring one determination of two controls and two human CSF samples for twenty-one days on the Hitachi 917 analyzer.

Between-Day Precision

Analyte:	IgG
Instrument:	Hitachi 917
Reagent:	IgGGC2 Lot E02
Calibrator:	CfaS-PUC Lot 15575299 c= 227 mg/L, autodilution

Results:	Control Low	Control High	Human CSF	
Day	PN-PUC (155.0mg/L)	PP-PUC (313.0mg/L)	Sample (L)	Sample (H)
1	161.74	318.66	12.19	226.34
2	166.86	334.50	13.36	227.87
3	168.59	331.05	12.13	225.50
4	168.87	325.74	13.74	221.65
5	167.98	323.17	13.93	226.33
6	165.85	324.10	13.35	229.63
7	166.08	332.99	12.75	226.78
8	167.19	336.13	12.28	227.41
9	168.43	328.01	12.68	223.94
10	167.37	316.72	12.78	226.40
11	166.14	328.63	15.98	228.94
12	164.73	338.95	12.37	227.93
13	169.19	333.32	13.19	228.08
14	166.62	330.52	13.39	221.01
15	167.83	318.32	13.08	222.77
16	162.34	323.98	13.78	226.96
17	165.50	333.12	12.84	226.79
18	169.18	337.33	13.41	228.87
19	165.29	326.40	13.49	222.60
20	169.08	318.09	14.16	224.02
21	164.54	321.73	12.62	227.65
n	21	21	21	21
Max.	169.19	338.95	15.98	229.63
Min.	161.74	316.72	12.13	221.01
Range	7.45	22.23	3.85	8.62
Average	166.64	327.69	13.21	226.07
SD.	2.12	6.77	0.86	2.48
CV(%)	1.27	2.07	6.52	1.10

b. Linearity/assay reportable range:

To determine the linear range, CSF samples are diluted with NaCl and measured on the Hitachi 917 using the Tina-Quant IgG Gen2 Sensitive Application (for CSF). Recovery is determined by comparison of the measured value to the theoretical value. The theoretical values were calculated according to the dilution factors. The acceptance criteria for linearity are based on recovery; and are as follows: for values below 15 mg/L, recovery is within ± 3 mg/dL. For values above 15 mg/L, the acceptance criterion is recovery within ± 10% of the theoretical value.

The assay reportable range for the Tina-Quant IgG Gen2 Sensitive Application (for CSF) is 2-200 mg/L. The linearity data support a linear range from 0 to 330.4 mg/L.

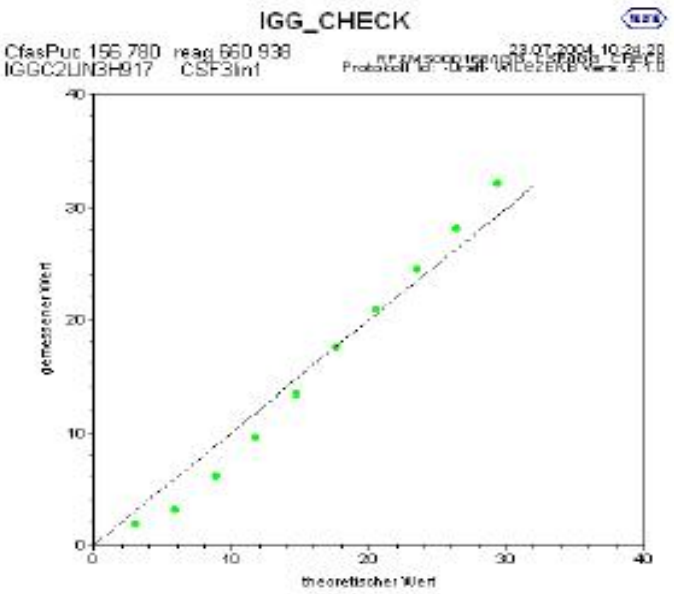
1.) Linearity Low Range

Measured Values and Recovery

Nr	Sample-Id		Dilution low	Dilution High	Measured Value	Theoretical Value	Recovery [%]
0	LIN1		10.00	0.00	1.635	0.000	-
1	LIN2		9.00	1.00	1.915	2.980	64.262
2	LIN3		8.00	2.00	3.195	5.960	53.607
3	LIN4		7.00	3.00	6.230	8.940	69.687
4	LIN5	*	6.00	4.00	9.615	11.920	80.663
5	LIN6	*	5.00	5.00	13.385	14.900	89.832
6	LIN7	*	4.00	6.00	17.565	17.880	98.238
7	LIN8	*	3.00	7.00	20.860	20.860	100.000
8	LIN9	*	2.00	8.00	24.500	23.840	102.768
9	LIN10	*	1.00	9.00	28.175	26.820	105.052
10	LIN11	*	0.00	10.00	32.045	29.800	107.534

Passing/Bablok - Regression: y = 0 + 2.98 * x

*) Dilutions used for calculation of regression line



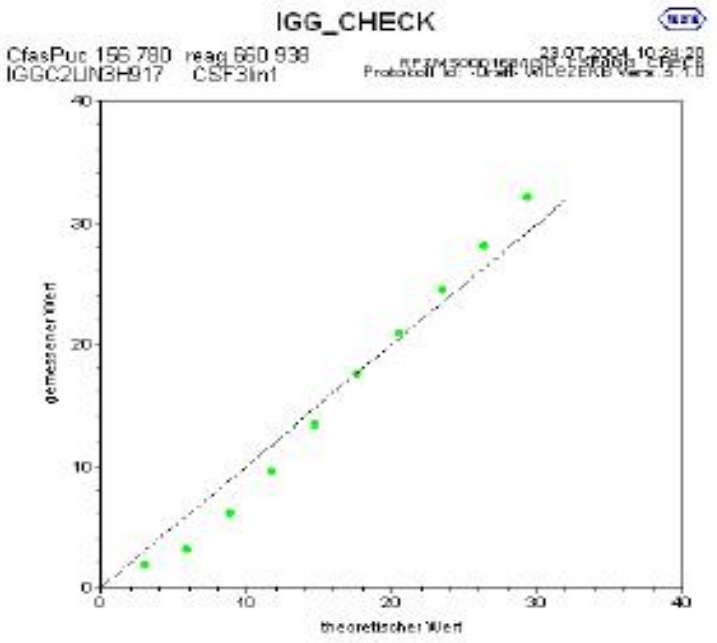
In addition, linearity is also determined for the extended measuring range with rerun which is 2-1000 mg/L. The extended measuring range is calculated based on the ability of the instrument to perform rerun pipetting. Results outside the measuring (reportable) range are reported to the user with a flag warning that the value is outside the instrument's technical limit. Users can select an automatic rerun with dilution, or manually dilute the sample with 0.9% NaCl and rerun, multiplying the results by an appropriate factor. This function is the same as the already cleared serum and plasma applications.

1.) Linearity Low Range

Measured Values and Recovery						
Nr	Sample-Id	Dilution low	Dilution High	Measured Value	Theoretical Value	Recovery [%]
0	LIN1	10.00	0.00	1.635	0.000	-
1	LIN2	9.00	1.00	1.915	2.980	64.262
2	LIN3	8.00	2.00	3.195	5.960	53.607
3	LIN4	7.00	3.00	6.230	8.940	69.687
4	LIN5 *	6.00	4.00	9.615	11.920	80.663
5	LIN6 *	5.00	5.00	13.385	14.900	89.832
6	LIN7 *	4.00	6.00	17.565	17.880	98.238
7	LIN8 *	3.00	7.00	20.860	20.860	100.000
8	LIN9 *	2.00	8.00	24.500	23.840	102.768
9	LIN10 *	1.00	9.00	28.175	26.820	105.052
10	LIN11 *	0.00	10.00	32.045	29.800	107.534

Passing/Bablok - Regression: y = 0 + 2.98 * x

*) Dilutions used for calculation of regression line



c. Traceability, Stability, Expected values (controls, calibrators, or methods):
The method has been standardized against CRM 470 (RPPHS, Reference Preparation for Proteins in Human Serum).

d. Detection limit:
Twenty-one replicates of the zero calibrator (0.9% NaCl) were tested in each of three independent runs on a Hitachi 917 analyzer using the Tina-Quant IgG

Gen2 Sensitive application (for CSF). The detection limit represents the lowest measurable level that can be distinguished from zero. It is calculated as the mean plus three standard deviations. The lower detection limit is 2 mg/L.

e. Analytical specificity:

i.) **Endogenous interferences**: The effect of hemoglobin and bilirubin interference on the quantitation of IgG in CSF via the Tina-Quant IgG Gen 2 Sensitive Application was determined on the Hitachi 917 analyzer using two native human CSF samples (with low and midrange IgG concentrations) spiked with varying concentrations of interferent. In separate experiments: hemoglobin, conjugated and unconjugated bilirubin were tested). The resulting sample series were tested and recovery was calculated by comparing the measured IgG concentration to the expected IgG concentration (measured IgG concentration with no interferent present). Significant interference was considered present if the %recovery exceeded ± 10% of the expected value. The following results are obtained:
Icterus: No significant interference up to an I index of 60(approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).
Hemolysis: No significant interference up to an H index of 800 (approximate hemoglobin concentration: 800 mg/dL or 497 µmol/L).
There is no cross-reaction between IgG and IgA or IgM for serum and plasma. Cross-reactivity studies were not performed for CSF.
Carryover: The Tina-Quant IgG Gen 2 Sensitive Application (for CSF) shows some carryover interference from IgG present in previously measured serum samples. Carryover can be avoided by performing a wash with NaOH prior to measurement of IgG in CSF. To characterize this carryover effect, 15 µL of undiluted serum was tested on a Hitachi 917 analyzer using the Fe (iron) test reagent, immediately prior to 5 determinations of IgG in CSF using the Tina-Quant IgG Gen 2 Sensitive Application. The CSF samples contained a low concentration of CSF. The experiment was repeated; employing a 1N NaOH wash between the serum iron and IgG CSF determinations. A significant carry-over effect was considered present if the calculated values were greater than ± 15% of the known value. The data show that the wash eliminates the carry-over effect.

f. Assay cut-off:

Not applicable

2. <u>Comparison studies:</u>

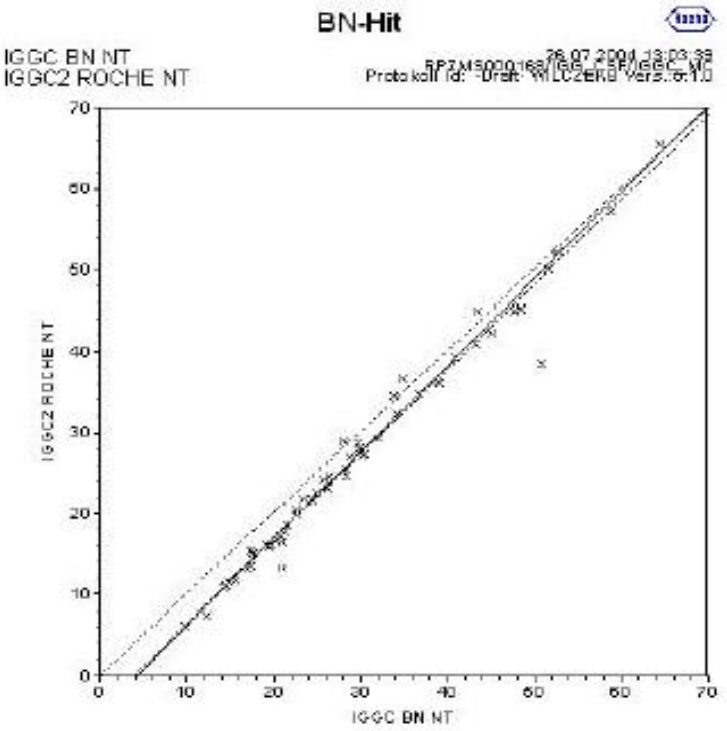
a. Method comparison with predicate device:

Fifty four (54) human CSF samples from multiple donors with concentrations between 6.17 and 65.5 mg/L were used in a method comparison study between Tina-Quant ® IgG Gen.2 Sensitive Application and the predicate device, Dade-Behring N-Antisera to Human IgG on the BNII (X). The expected range of values is 10- 30 mg/L. Samples were frozen at the site of collection and sent to Roche GmbH for testing. Comparison of the IgG values obtained with Tina-Quant ® IgG Gen.2 Sensitive Application (Y) to the

values obtained with the predicate device: Dade-Behring N-Antisera to Human IgG on the BNII (X) are summarized below:

	Passing/Bablok	Least Squares
N	54	54
Range	6.17 – 65.5 mg/L	6.17 – 65.5 mg/L
Slope	1.066	1.04
Y intercept	-4.451	-3.903
correlation	Tau = 0.939	r = 0.988
deviation	SD (md95) = 2.289	Sy.x = 1.44

Graph of Method Comparison between Tina-Quant IgG Gen.2 Sensitive Application (y) and Dade-Behring N Antisera to Human IgG on the BNII (x)



b. Matrix comparison:
Not applicable

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:
   Reference values: 10–30 mg/L (66.7–200 nmol/L) were from literature citation.

   [Reference: Reiber H, Thompson EJ, Grimsley G et al. Quality Assurance for Cerebrospinal Fluid Protein Analysis: International Consensus by an Internet-based Group Discussion. Clin Chem Lab Med 2003; 41: 331-337.]

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.