

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

A. 510(k) Number:

k101203

B. Purpose for Submission:

New device

C. Measurand:

Albumin (microalbumin) in serum, plasma, urine, and CSF

D. Type of Test:

Quantitative, immunoturbidimetric

E. Applicant:

Roche Diagnostics

F. Proprietary and Established Names:

Tina-quant albumin gen 2

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5040, Albumin immunological test system

2. Classification:

Class II

3. Product code:

DCF

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

Refer to indications for use, below.

2. Indication(s) for use:

The Tina-quant Albumin Gen. 2 assay is an immunoturbidimetric assay intended for the quantitative determination of albumin in serum, plasma, urine, and CSF on Roche/Hitachi cobas c systems. Measurement of albumin aids in the diagnosis of kidney and intestinal diseases.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Roche/Hitachi cobas c 501 analyzer

I. Device Description:

The Tina-quant Albumin Gen. 2 assay consists of three reagents:

R1 TRIS buffer: 50 mmol/L, pH 8.0; PEG: 4.2 %; EDTA: 2.0 mmol/L; preservative

R2 Polyclonal anti-human albumin antibodies (sheep); TRIS buffer: 100 mmol/L, pH 7.2; preservative

R3 Reagent for antigen excess check. Albumin in diluted serum (human); NaCl: 150 mmol/L; phosphate buffer: 50 mmol/L, pH 7.0; preservative

The calibrator is C.f.a.s. PUC (cleared under k050026) and the recommended control materials are Precinorm / Precipath PUC (cleared under k050026) and Precinorm / Precipath Protein (cleared under k981401). The calibrator and controls are sold separately.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Hitachi Tina Quant microalbumin urine assay (urine)

Behring N Antiserum to Human Albumin Nephelometric method (urine, serum, CSF)

2. Predicate 510(k) number(s):

k932950
k972929

3. Comparison with predicate:

Urine Matrix Similarities		
Item	Device	Predicate k932950
Indications for Use	Same	Quantitative measurement of albumin in urine. Measurement of albumin aids in the diagnosis of kidney and intestinal diseases.
Assay Type	Same	Immunoturbidimetric
Measuring Range	12 – 400 mg/L	3 mg/L up to the value of the highest calibrator
Detection limit	Limit of Blank (LoB) 2 mg/L Limit of Detection (LoD) 3 mg/L Limit of Quantitation (LoQ) 12 mg/L	Lower Detection Limit = 3 mg/L

Urine Matrix Differences		
Item	Device	Predicate k932950
Analyzers	Roche/Hitachi cobas c 501 analyzer	Hitachi 747 analyzer
Calibrator	C.f.a.s. (Calibrator for Automated Systems) PUC (Proteins in Urine/CSF)	Microalbumin calibrators (included in kit)
Calibration Frequency	Calibrate after reagent lot change and as required following quality control procedures	Perform full calibration every two weeks
Reagent Stability	On-board in use: 12 weeks at 2-8° C	On-board in use: 4 weeks at 2-12° C

Serum and Plasma Matrices Similarities		
Item	Device	Predicate k972929
Indications for Use	Same	Quantitative measurement of albumin in serum, CSF, and urine. Measurement of albumin aids in the diagnosis of kidney and intestinal diseases.
Assay Type	Same	Immunoturbidimetric
Analytical Specificity	No interference was found at common therapeutic concentrations using common drug panels.	No interference from commonly used drugs is known.

Serum and Plasma Matrices Differences		
Item	Device	Predicate k972929
Sample Type	Serum and Plasma: Li-heparin and K2-EDTA	Serum
Analyzers	Roche/Hitachi cobas c 501 analyzer	BN Systems
Calibrator	C.f.a.s. (Calibrator for Automated Systems) PUC (Proteins in Urine/CSF)	N Protein Standard SL (human)
Calibration Frequency	Same	After each reagent lot change and as required following quality control procedures.

CSF Matrix Similarities		
Item	Device	Predicate k972929
Indications for Use	Same	Quantitative measurement of albumin in serum, CSF, and urine. Measurement of albumin aids in the diagnosis of kidney and intestinal diseases.
Assay Type	Same	Immunoturbidimetric
Analytical Specificity	No interference was found at common therapeutic concentrations using common drug panels.	No interference from commonly used drugs is known.

CSF Matrix Differences		
Item	Device	Predicate k972929
Analyzers	Roche/Hitachi cobas c 501 analyzer	BN Systems
Calibrator	C.f.a.s. (Calibrator for Automated Systems) PUC (Proteins in Urine/CSF)	N Protein Standard SL (human)
Measuring Range	95 - 3000 mg/L	Reference curves are generated by multi-point calibration. Serial dilutions on N Protein Standard SL are automatically prepared by the instrument using N Diluent.
Detection limits	LoB: 2 mg/dL LoD: 3.6 mg/dL LoQ: 9.5 mg/dL	Established by the lower limit of the reference curve

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

- CLSI EP5-A2, Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline - 2nd edition
- CLSI EP6, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
- CLSI EP17-A, Protocols for Determination of Limits of Detection and Limits

L. Test Principle:

The Roche Tina-quant Albumin Gen 2 assay is an immunoturbidimetric assay for the quantitative in vitro determination of albumin in human serum, plasma, urine and CSF on the Roche/Hitachi cobas c 501 analyzer. The test principle is a particle enhanced immunoturbidimetric assay. Human albumin (the antigen) agglutinates with latex particles coated with anti-albumin antibodies. The precipitate is determined turbidimetrically following agglutination.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Urine Assay

This data was collected as follows:

Specimen description: urine controls and human urine

Number of analyzers: one

Number of days/replicants: one triplicate run per day for 21 days

Lots of product used: one

Number of calibrations: one

Operators: one

Repeatability

Sample type	Urine Control	Urine Control	Human Urine	Human Urine
n	21	21	21	21
mean	30.7	108.3	14.3	252.1
SD	0.24	0.79	0.22	4.11
CV (%)	0.8	0.7	1.6	1.6

Intermediate Precision (Between Day)

Sample type	Urine Control	Urine Control	Human Urine	Human Urine
n	21	21	21	21
mean	31.3	104.2	13.5	60.7
SD	0.50	1.11	0.34	1.42
CV (%)	1.6	1.1	2.5	2.3

Intermediate Precision (Total)

Sample type	Urine Control	Urine Control	Human Urine	Human Urine
N	63	63	63	63
total mean	31.2	104.5	13.6	60.6
total SD	0.5	1.2	0.4	1.4

total CV (%)	1.7	1.2	2.8	2.3
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Serum/Plasma Assay

This data was collected as follows:

Specimen description: serum controls and human serum

Number of analyzers: one

Number of days/replicants: one triplicate run per day for 21 days

Lots of product used: one

Number of calibrations: one

Operators: one

Repeatability

Sample type	Control	Control	Human Serum	Human Serum
N	21	21	21	21
Mean	39.9	66.6	27.6	62.5
SD	0.5	1.4	0.3	0.9
CV (%)	1.2	2.1	1.3	1.5

Intermediate Precision (Between Day)

Sample type	Control	Control	Human Serum	Human Serum
N	21	21	21	21
Mean	41.9	71.2	7.4	36.3
SD	0.5	1.3	0.1	0.7
CV (%)	1.3	1.8	1.4	2.0

Intermediate Precision (Total)

Sample type	Control	Control	Human Serum	Human Serum
N	63	63	63	63
total mean	42.3	70.5	7.8	36.2
total SD	0.9	1.6	0.7	0.7
total CV (%)	2.0	2.2	9.5	2.1

CSF Assay

This data was collected as follows:

Specimen description: CSF controls and human CSF

Number of analyzers: one

Number of days/replicants: one triplicate run per day for 21 days

Lots of product used: one

Number of calibrations: one

Operators: one

Repeatability

Sample type	Control	Human CSF	Human CSF	Control
N	21	21	21	21
Mean	99.2	173.9	382.7	454.3
SD	1.39	2.96	3.72	3.63
CV (%)	1.40	1.70	0.97	0.80

Intermediate Precision (Between Day)

Sample type	Control	Control	Human CSF	Human CSF
N	21	21	21	21
Mean	92.4	392	163	365
SD	1.61	5.16	2.53	3.17
CV (%)	1.7	1.3	1.5	0.9

Intermediate Precision (Total)

Sample type	Control	Control	Human CSF	Human CSF
N	63	63	63	63
total mean	91.0	389	166	366
Total SD	2.9	6.5	3.8	4.8
total CV (%)	3.2	1.7	2.3	1.3

b. *Linearity/assay reportable range:*

To evaluate linearity, the sponsor analyzed dilutions of urine, serum, and CSF. The diluent used was NaCl. Albumin levels were measured and the recovered value was compared to the theoretical value. Pure samples (0% and 100%) were run n=6, with mean measured value reported. Diluted samples were run n=3 with mean measured values reported. The concentrations tested spanned the measuring range for each analyzer / matrix combination. Data were calculated per EP6 guidelines. The linearity data were analyzed with regards to linear, quadratic and cubic polynomials. A linearity check was performed with a first order (linear) regression and then with higher order models (quadratic and cubic). None of the higher order models were significant.

Linear regressions were as follows:

Urine:

Slope: 0.9962 (95% CI 0.99 to 1.00)

Intercept: 0.6942 (95% CI -0.60 to 1.99)

Correlation Coefficient: 0.999

Serum/Plasma:

Slope: 1.0129 (95% CI 0.99 to 1.03)

Intercept: -0.3664 (95% CI -1.47 to 0.74)

Correlation Coefficient: 0.997

CSF:

Slope: 0.9933 (95% CI 0.984 to 1.00)

Intercept: 5.5101 (95% CI -3.66 to 14.68)

Correlation Coefficient: 0.999

The claimed measuring ranges for the assay are:

Urine

12 - 400 mg/L

Serum/Plasma

3 - 101 g/L

CSF

95 - 3000 mg/L

The extended measuring range using automated rerun with dilution was validated by performing an experiment comparing the instrument auto-rerun result with a simple manual dilution. Two cobas c501 analyzers were used per experiment. Three samples were manually diluted in triplicate per analyzer. Sample medians were compared to the instrument auto-rerun results.

Recoveries were as follows:

Urine matrix:	102 – 109 %
Serum/plasma matrix:	93 – 105 %
CSF matrix:	103 – 106 %

A known high-dose hook effect occurs with the Urine and CSF applications. Due to the antigen excess check reagent R3, no unflagged high-dose hook effect will occur up to an albumin concentration of 40,000 mg/L for urine samples and 30,000 mg/L for CSF samples. The high dose hook effect and the correct flagging were tested with 2 serially spiked samples under customer conditions on the cobas c501 analyzer.

Note: analyte concentrations that would cause a hook effect in serum or plasma are outside of the physiological range and were not tested.

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

The C.f.a.s. PUC calibrator, Precinorm PUC/Precipath PUC and Precinorm Protein/Precipath Protein controls are traceable to the reference preparation IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).

d. Detection limit:

The analytical limits at low levels are as follows:

Urine: Limit of Blank 2 mg/L
 Limit of Detection 3 mg/L
 Limit of Quantitation 12 mg/L

Serum/Plasma: Limit of Blank 1 mg/L
 Limit of Detection 2 mg/L
 Limit of Quantitation 3 mg/L

CSF: Limit of Blank 20 mg/L
 Limit of Detection 36 mg/L
 Limit of Quantitation 95 mg/L

e. Analytical specificity:

The effects of endogenous interference on the quantitation of albumin were determined for serum/plasma, urine and CSF sample types. Pooled human serum, urine and CSF samples were spiked with varying levels of interferents. The resulting sample series (ten dilution steps per samples) were tested in triplicate and the median values used to calculate recovery, by comparing the measured albumin concentration to the expected albumin concentration (which is the albumin concentration when no interferent was added). Significant interference was considered present if the % recovery exceeded +/- 10% of the expected 100% recovery.

Serum/Plasma Results:

Lipemia: No interference was observed up to the highest L index value tested which was 1852. The L index corresponds to turbidity. The device labeling claims no interference at an Intralipid concentration of approximately 1500 mg/dL.

Icterus: No interference was observed for unconjugated bilirubin I index levels up to 64. No interference was observed for conjugated bilirubin I index levels up to 74. The I Index Value corresponds to approximately 1 mg/dL bilirubin.

Hemolysis: No interference was observed up to the highest H index value tested which is 1077. The H Index Value corresponds approximately to 1 mg/dL hemoglobin.

Rheumatoid factor: No effect was observed up to the highest concentration tested, which was 1392 IU/mL.

In very rare cases gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.

Urine Results:

Icterus: No conjugated bilirubin interference was observed up to an I index of 52. The I Index Value corresponds to approximately 1 mg/dL bilirubin.

Hemolysis: No hemolysis interference was observed up to an H index of 487. The H Index Value corresponds approximately to 1 mg/dL hemoglobin

No interference was seen with the following compounds/concentrations:

acetone	≤ 60 mmol/L
ammonium chloride	≤ 0.11 mol/L (≤6 g/L)
calcium	≤ 40 mmol/L
creatinine	≤ 0.18 mol/L (20 g/L)
γ-globulin	≤ 500 mg/L
glucose	≤ 0.19 mol/L (35.0 g/L)
urea	≤ 0.8 mol/L
uric acid	≤ 5.95 mmol/L (1.2 g/L)
urobilinogen	≤ 378 μmol/L (200 mg/L)

CSF results

The sponsor defined significant interference when the recovery was greater than ± 10 % of initial value at an albumin concentration of 240 mg/L (3.65 μmol/L, 24 mg/dL).

Hemolysis: No significant interference up to an H index of 1131.

The H Index Value corresponds approximately to 1 mg/dL hemoglobin

Icterus: No bilirubin interference was observed up to an I index of 66. The I Index Value corresponds to approximately 1 mg/dL bilirubin.

Due to the antigen excess check reagent R3 no unflagged high-dose hook effect will occur up to an albumin concentration of 30000 mg/L (456 μ mol/L, 3000 mg/dL).

Commonly used drugs were added to native patient samples and analyzed for potential interference. Thirteen commonly used drugs were tested with the urine application and 18 commonly used drugs were tested with the serum/plasma application. Each drug was added in two defined concentrations and the resulting samples were measured in triplicate using the cobas c501 analyzer. Drug interference testing was performed with urine and serum samples. The median value is compared to the reference value (albumin sample with no drug added) and the deviation from the reference value is calculated. Significant interference was defined as +/- 10% deviation from the reference value observed with the lower drug concentration.

No interference was found at therapeutic concentrations of the following drugs in urine:

- Acetaminophen
- N-Acetyl cysteine
- Salicylic Acid
- Ascorbic Acid
- Calciumdobesilate
- Na₂-Cefoxitin
- Gentamycin Sulfate
- Ibuprofen
- Levodopa
- Methyldopa
- Ofloxacin
- Phenopyridine
- Doxycyclin

No interference was found at therapeutic concentrations of the following drugs in serum:

- Acetylcystein
- Ampicillin – Na
- Ascorbic acid
- Ca - Dobesilate

Cyclosporine
Cefoxitin
Heparin
Intralipid
Levodopa
Methyldopa
Metronidazole
Phenylbutazone
Doxycyclin
Acetylsalicylic acid
Rifampicin
Acetaminophen
Ibuprofen
Theophylline

Due to the antigen excess check reagent R3, no unflagged high-dose hook effect will occur up to an albumin concentration of 40000 mg/L (608 µmol/L).

In very rare cases gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

All samples were tested by the new and comparator method and there were no retests or discards. One sample was taken per patient and measured in singlicate for each Method Comparison listed below. Simple linear regression produced the following:

Urine Matrix

Method Comparison #1: the urine application was compared to the Hitachi Microalbumin assay:

$$\begin{aligned}n &= 125 \\y &= 1.028x - 4.13 \\(\text{Pearson's } r) &= 0.999 \\ \text{Sample concentration range: } &12.3 - 386 \text{ mg/L}\end{aligned}$$

Serum/Plasma Matrix

Method Comparison #1: the serum/plasma application was compared to the Behring nephelometric N Antiserum to Human Albumin assay:

n = 77 serum samples
y = 0.96x - 0.01
(Pearson's r) = 0.993
Sample concentration range: 5.7 – 100 g/L

CSF Matrix

Method Comparison #1: the CSF application was compared to the Behring nephelometric N Antiserum to Human Albumin assay:

n = 85
y = 0.99x + 0.30
(Pearson's r) = 0.992
Sample concentration range: 115 – 2640 mg/ L

b. Matrix comparison:

To validate the use of additional samples types, 75 parallel samples were collected in serum, Lithium Heparin plasma and K₂ EDTA plasma tubes. In addition, 59 serum samples were tested with gel separators. Each plasma sample was compared to the respective serum samples. The samples tested had concentrations from 11.1 g/L to 84.5 g/L. Including all matrices, recoveries ranged from 92% to 108%.

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:

Urine:

2nd morning urine¹:

Adults: < 20 mg albumin/g creatinine or
 < 2.26 g (34.35 μ mol) albumin/mol creatinine
 Children (3-5 years)²: < 20 mg/L (0.304 μ mol/L, 2 mg/dL) albumin
 < 37 mg albumin/g creatinine
 24-hour urine³: < 20 mg/L (0.304 μ mol/L, 2 mg/dL)
 < 30 mg/24 h (0.456 μ mol/24 h)

Serum/Plasma:

Reference Range Study⁴:

Adults 3.56-4.61 g/dL (35.6-46.1 g/L; 541-701 μ mol/L)

Consensus Values⁵:

Adults 3.5-5.2 g/dL (35-52 g/L; 532-790 μ mol/L)

Reference Intervals according to Tietz ⁶:

Newborns 0-4d: 2.8-4.4 g/dL (28-44 g/L; 426-669 μ mol/L)

Children 4d-14yr: 3.8-5.4 g/dL (38-54 g/L; 578-821 μ mol/L)

Children 14-18yr: 3.2-4.5 g/dL (32-45 g/L; 486-684 μ mol/L)

CSF:

Albumin in CSF⁷: 3 months to 4 years: < 45 mg/dL
 (< 6.84 μ mol/L; < 450 mg/L)
 > 4 years 10-30 mg/dL
 (1.52-4.56 μ mol/L; 100-300 mg/L)

1. Hofmann W, Guder WG. A diagnostic program for quantitative analysis of proteinuria. J Clin Chem Clin Biochem 1989;27:589-600.
2. Hubbuch A. Results of a multicenter study of provisional reference ranges for albumin in urine of children and adults. Roche publication.
3. Hasslacher CH. Aid Endokrin Stoffw 1989;10:60-63.
4. Junge W, Bossert-Reuther S, Klein G et al. Reference Range Study for serum Albumin using different methods; Clin Chem Lab Med 2007; 45, Special Supplement, pp 194, June 2007 Poster EUROMEDLAB 2007.
5. Dati F, Schumann G, Thomas L et al. Consensus 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 IFCCIBCRICAP reference material (CRM 470).
6. Burtis CA, Ashwood ER, Bruns DE (eds.). Tietz Textbook of Clinical

Chemistry and Molecular Diagnostics, 4th ed Philadelphia, Pa: WB Saunders, 2006:549.

7. Tietz NW, ed. Clinical Guide to Laboratory Tests, 3rd ed. Philadelphia, Pa: WB Saunders Company 1995:24.

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.