

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

A. 510(k) Number:

k091741

B. Purpose for Submission:

New Device

C. Measurand:

Ceruloplasmin

D. Type of Test:

Quantitative, immunoturbidimetric

E. Applicant:

Roche Diagnostics

F. Proprietary and Established Names:

Tina-Quant Ceruloplasmin

G. Regulatory Information:

1. Regulation section:
21 CFR § 866.5210, Ceruloplasmin Immunological Test System
2. Classification:
Class II
3. Product codes:
CHN; Immunochemical, Ceruloplasmin
4. Panel:
Immunology (82)

H. Intended Use:

1. Intended use(s):
Immunoturbidimetric assay for the quantitative in vitro determination of ceruloplasmin in human serum and plasma on Roche automated clinical chemistry analyzers.
2. Indication(s) for use:
Measurements obtained by this device aid in the diagnosis of copper metabolism disorders.
3. Special conditions for use statement(s):
For prescription use only
4. Special instrument requirements:
Roche/Hitachi 912/917/MODULAR P analyzers: ACN 709

I. Device Description:

The Tina-Quant Ceruloplasmin assay consists of two working reagent solutions, R1 and R2. R1 is phosphate buffer and R2 is anti-human ceruloplasmin rabbit antibody. The calibrator C.f.a.s. PAC cleared in k040245 is a lyophilized calibrator based on human serum. The control for the test is the Prealbumin/Ceruloplasmin Control set, cleared in k062379.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Roche Ceruloplasmin assay on the cobas c501 analyzer
2. Predicate K number(s):
k062114

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	Tina-Quant Ceruloplasmin Assay	Ceruloplasmin Assay on the cobas c501
Intended Use	Immunoturbidimetric assay for the quantitative in vitro determination of ceruloplasmin in human serum and plasma	Same
Indication for Use	Measurements obtained by this device aid in the diagnosis of copper metabolism disorders	Same
Assay Protocol	Immunoturbidimetric	Same
Sample Type	Serum and Li-heparin Plasma	Same
Calibrator	C.f.a.s. PAC	Same
Calibration frequency	Full calibration is recommended after reagent lot change and as required following quality control procedures	Same
Controls	Prealbumin/Ceruloplasmin Control set	Same
Traceability	Standardized against the reference preparation CRM 470 (RPPHS – Reference Preparation for Proteins in Human Serum)	Same
Reagent Stability	3 days at 2-8°C 4 weeks at -15 to -25°C	Same
Measuring Range	3-140 mg/dL	Same
Analytical Specificity	No interference was found at common therapeutic concentrations using common drug panels	Same

Differences		
Item	Device	Predicate
	Tina-Quant Ceruloplasmin Assay	Ceruloplasmin Assay on the cobas c501
Labeled Instrument Platform	Roche/Hitachi 912/917/MODULAR P analyzers	Roche Hitachi cobas c systems

Differences		
Item	Device	Predicate
Total Precision (% CV)	0.9-1.6% (concentration range 27.5-124 mg/dL) 0.6-6.3% (concentration range 3.33-135 mg/dL)	1.97 % - 5.12 %
Analytical Sensitivity	Limit of Blank (LoB) ≤ 2 mg/dL Limit of Detection (LoD) ≤ 3 mg/dL	Lower Detection Limit = 1.7 mg/dL
Expected Values	Male: 15-30 mg/dL Female: 16-45 mg/dL	20-60.0 mg/dL

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

CLSI EP5-A: "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline"

CLSI EP17-A: "Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline"

L. Test Principle:

The Tina-Quant Ceruloplasmin assay employs an immunoturbidimetric method in which anti-ceruloplasmin antibodies react with antigen in the sample to form antigen/antibody complexes which, following agglutination, can be determined turbidimetrically.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision of the Tina-Quant Ceruloplasmin on the Roche/Hitachi 917 was analyzed according to CLSI EP5-A2 guideline using pooled human sera assayed in duplicate with 2 runs per day for 21 days. Repeatability is comparable to formerly used intra-assay or within-run precision. Intermediate precision describes within device day-to-day and run-to-run precision formerly referred to as within-lab or total precision. The specifications were ≤ 30.0 mg/dL: SD ≤ 2 mg/dL and >30 mg/dL: CV $\leq 6\%$. Five samples (low and high control, low medium and high serum) were used to acquire n=84.

Sample	Repeatability*			Intermediate precision**		
	Mean mg/dL	SD mg/dL	CV %	Mean mg/dL	SD mg/dL	CV %
Control low	27.5	0.4	1.5	27.5	0.4	1.6
Control high	61.7	0.6	0.9	61.7	0.7	1.1
Serum low	26.2	0.3	1.2	26.2	0.4	1.6
Serum medium	64.9	0.5	0.8	64.9	0.7	1.0
Serum high	124	0.9	0.8	124	1.1	0.9

In a second study conducted to more thoroughly cover the measuring range, eleven samples (5 low, 3 medium, 3 high) were analyzed using a classical within-run experiment design, and these data points are presented in the following table. The specifications were ≤ 30.0 mg/dL: SD ≤ 1 mg/dL and > 30 mg/dL: CV $\leq 4\%$.

Sample	Repeatability*		
	Mean mg/dL	SD mg/dL	CV %
Serum low 1	3.33	0.2	6.3
Serum low 2	4.51	0.3	5.5
Serum low 3	6.08	0.3	4.6
Serum low 4	7.16	0.2	3.0
Serum low 5	11.0	0.2	2.0
Serum medium 1	37.1	0.5	1.5
Serum medium 2	40.7	0.4	1.1
Serum medium 3	46.1	0.5	1.0
Serum high 1	134	0.8	0.6
Serum high 2	134	1.5	1.1
Serum high 3	135	1.5	1.1

Results are acceptable within specifications.

b. *Linearity/assay reportable range:*

Linearity of the Tina-Quant Ceruloplasmin on the Roche/Hitachi 917 was evaluated by preparing two dilution series using high analyte level native human serum samples. Series one covered theoretical values from 0 to 46 mg/dL and contained 10 dilutions steps. Series two covered theoretical values from 0 to 251 mg/dL. Samples in both series were diluted with saline. Ceruloplasmin values were measured and the recovered value was compared to the theoretical value. Diluted samples were run in triplicate with median measured values reported. The theoretical values were generated by applying the dilution factors to the undiluted patient sample concentration. The acceptance criteria for linearity are measured recovery $\pm 5\%$ of theoretical values for samples 10-140 mg/dL and $\pm 2SD$ for samples up to 10 mg/dL. The regression equations of the two series are as follows:

Passing-Bablok

Series 1 (low) $y = 1.00x + 0.00$ (95%CI for slope 0.988 to 1.009 and for intercept -0.126 to 0.242)

Series 2 (high) $y = 0.96x + 2.70$ (95% CI for slope 0.92 to 0.98 and for intercept 0.75 to 7.77)

Linear regression:

Series 1 (low) $y = 0.993x + 0.357$ (95% CI for slope 0.973 to 1.012 and for intercept -0.172 to 0.885)

Series 2 (high) $y = 0.999x + 0.303$ (95% CI for slope 0.975 to 1.022 and for intercept -1.46 to 2.067)

The recommended measuring range is defined as the limit of detection to the upper limit of linearity. The recommended measuring range is 3-140 mg/dL.

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Calibration method has been standardized against the reference preparation CRM 470 (RPPHS – Reference Preparation for Proteins in Human Serum). All calibrators and controls have been previously cleared. The C.f.a.s. PAC calibrator was cleared in k040245. The Prealbumin/Ceruloplasmin Control set was cleared in k062379. The adjusted concentration of the control components are usually in the normal range or at the normal/pathological threshold.

Unopened kit components are stable up to the expiration date at 2-8°C. Reagents R1 and R2 are both stable for 90 days opened and refrigerated on the analyzer.

- d. *Detection limit:*
The limit of blank (LoB) and limit of detection (LoD) of the Tina-Quant Ceruloplasmin on the Roche/Hitachi 917 were determined in accordance with the CLSI EP17-A requirements. For LoB, one analyte free sample was analyzed in five-fold determinations over three days, two runs per day, for a total of n=60. For LoD, five human serum samples with low analyte concentration were analyzed in one-fold determination over three days, two runs per day. Two lots of reagents were used for testing.

The LoB is 2 mg/dL and the LoD is 3 mg/dL.

- e. *Analytical specificity:*
Effect on quantitation of analyte in the presence of endogenous interfering substances using the Tina-Quant Ceruloplasmin assay on the Roche/Hitachi 917 was determined by using pooled human serum samples spiked with varying levels of interferent, including bilirubin (conjugated and unconjugated), hemoglobin, lipemia, and rheumatoid factors. The resulting sample series (ten dilution steps per sample) were tested in triplicate and the median values were used to calculate recovery. The specifications were $\leq \pm 3$ mg/dL or $\leq \pm 10\%$ for I index (bilirubin) ≤ 60 ; $\leq \pm 3$ mg/dL or $\leq \pm 10\%$ for L index (intralipid) ≤ 400 ; $\leq \pm 3$ mg/dL or $\leq \pm 10\%$ for H index (hemoglobin) ≤ 350 ; and < 76 IU/mL ($< +0.03$ g/L or $< +10\%$) for rheumatoid factor.

The assay is unaffected by:

- Bilirubin: approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL
- Hemoglobin: approximate hemoglobin concentration: 350 mg/dL
- Intralipid: 400 mg/dL
- Rheumatoid Factors: < 76 IU/mL

Eighteen commonly used pharmaceuticals were added to native patient samples and tested for interference on the Roche/Hitachi 917. Significant interference was defined as a $\pm 10\%$ deviation from the reference value. No pharmaceuticals tested showed significant interference.

Hook effect:

No hook effect was detected up to 5 g/L.

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

A method comparison study was performed to compare the Roche Tina-Quant Ceruloplasmin on the Roche/Hitachi 917 and Roche Ceruloplasmin assay on cobas c501. Eighty-two native human samples from multiple donors including hospitalized patients and healthy blood donors were analyzed. In a second study, an additional 15 samples were included to fully span the measuring range. Sample concentrations were between 4.7-138 mg/dL. In all, n=97 and the following correlation was obtained using Passing/Bablok:

$$y=1.012x-1.04$$

95% CI Slope: 0.99 to 1.03

95% CI Intercept: -1.79 to -0.44

$\tau=0.945$

b. *Matrix comparison:*

To validate the use of the lithium heparin sample type on the Tina-Quant Ceruloplasmin assay on the Roche/Hitachi 917, parallel samples were collected in serum and lithium heparin plasma for 58 samples. Each plasma sample was compared to the respective serum sample result and percent recovery was determined. The acceptance criteria were that plasma results =had to be within $\pm 10\%$ of the serum result or for serum results of ≤ 30.0 mg/dL, a recovery of $\leq \pm 3.0$ mg/dL. The experiment allowed for 20% of samples to be within 10% and 15% recovery. Later, four additional lithium heparin plasma samples were tested to fully span the measuring range. The data have been combined for n=62, and all recoveries except one were within 10% or ± 3.0 mg/dL (as applicable). The following correlation was obtained using Passing/Bablok:

$$y=0.99x+0.144$$

95% CI Slope: 0.97 to 1.00

95% CI Intercept: -0.54 to 0.81

$\tau=0.937$

3. Clinical studies:

a. *Clinical sensitivity and specificity:*

Not applicable

b. *Other clinical supportive data (when a. is not applicable):*

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

A Roche reference interval study was performed to obtain this data. Reference ranges were determined in Germany from 249 males and 251 females (n=500 total) who were resting, fasting, healthy volunteers between 20-70 years old.

Male: 15-30 mg/dL

Female: 16-45 mg/dL

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.