510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k062114

B. Purpose for Submission:
New device

C. Measurand:
Ceruloplasmin

D. Type of Test:
Quantitative, immunoturbidimetry

E. Applicant:
Roche Diagnostics Corp.

F. Proprietary and Established Names:
Roche COBAS INTEGRA Ceruloplasmin Model 2055953

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CHN - Immunochemical, Ceruloplasmin	Class II	CFR 866.5210 – Ceruloplasmin Immunological Test System	IM 82

H. Intended Use:
1. Intended use(s):
   The COBAS Ceruloplasmin cassette (CERU) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative immunological determination of human ceruloplasmin in serum and plasma.
2. Indication(s) for use:
   Measurements of ceruloplasmin aid in the diagnosis of copper metabolism disorders.
3. Special conditions for use statement(s):
   Prescription use only
4. Special instrument requirements:
   The COBAS INTEGRA Ceruloplasmin cassette is intended for use with the COBAS INTEGRA 400, 400 plus, 700 and 800 analyzers (k951595) and Roche/Hitachi COBAS c501 analyzer (k060373).

I. Device Description:
The COBAS Ceruloplasmin (CERU) cassette consists of R1 (Accelerator) which is polyethylene glycol in phosphate buffer with preservative and R2 which is anti-ceruloplasmin T antiserum (rabbit) in phosphate buffer with preservative. The reagents are ready for use.

Calibrators and controls are not included with the Ceruloplasmin kit.

Calibrators to be used with the device are Roche Serumproteins T Standards (k954992).

The control set for this new device was submitted in a separate 510(k) for clearance with the control set for Prealbumin (k062379). There are two levels in each set, normal (Precinorm) and abnormal (Precipath). The target values for the Precinorm are 0.217-0.355 g/L for the Roche/Hitachi systems and 0.213-0.345 g/L for the COBAS INTEGRA systems. The target values for the Precipath are 0.49-0.802 g/L for the Roche/Hitachi systems and 0.517-0.841 g/L for the COHAS INTEGRA systems. The controls are lyophilized human sera that have to be reconstituted with distilled water prior to use.

J. Substantial Equivalence Information:

Similarities		
Item	Device	Predicate
	Roche Diagnostics COBAS INTEGRA Ceruloplasmin	**DakoCytomation Polyclonal Rabbit anti-Human Ceruloplasmin Test System (k812486)**
Intended Use/Indications for Use	For the quantitative determination of human ceruloplasmin in serum and plasma. Ceruloplasmin measurements aid in the diagnosis of copper metabolic disorders.	Same
Test principle	Immunoturbidimetry	Same
Antibody	Rabbit anti-human ceruloplasmin (polyclonal)	Same
Sample Matrix	Serum and heparin plasma	Same
Reference standard	IFCC/BCR/CAP reference preparation CRM 470 (RPPHS 91/0619)	Same

Differences		
Item	Device	Predicate
Instrument	COBAS INTEGRA 400, 400 plus, 700 and 800 analyzers and Roche/Hitachi COBAS c501 analyzer	Hitachi 917
Calibration	Roche Serumproteins T Standard diluted to 6 levels (1:4.5, 1:6, 1:15, 1:30, 1:100) by instrument	DakoCytomation Human Serum Protein Calibrator 1 level diluted by instrument
Controls	Roche Serumproteins T Controls (2 levels)	DakoCytomation Human Serum Protein Low and High Controls

Differences		
Item	Device	Predicate
Measuring range	0.03-1.40 g/L Extended range: 0.03-4.20 g/L	0.06-1.50 g/L Extended range: 0.02-1.88 g/L
Detection limit	0.017 g/L	0.015 g/L
Total precision (%CV)	1.97%-5.12%	1.0%-1.6%
Linearity	0.03-1.70 g/L	0.06-0.69 g/L

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

STANDARDS			
Title and Reference Number			
Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-P)			
Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-T2)			
GUIDANCE			
Document Title	**Office**	**Division**	**Web Page**
Format for Traditional and Abbreviated 510(k)s – guidance for Industry and FDA staff	**OIVD**		**http://www.fda.gov/cdrh/ode/ode/guidance/l567.html**

L. Test Principle:

The COBAS INTEGRA Ceruloplasmin cassette is an immunoturbidimetic assay. A sample is mixed with the antibody solution (R2). If ceruloplasmin is present in the sample, it will form a precipitate with the specific antiserum which is determined turbidimetrically at 340 nm. The signal generated is proportional to the concentration of ceruloplasmin in the sample. The concentration of ceruloplasmin is determined from a standard curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. *Precision/Reproducibility:*
      Precision was evaluated according to CLSI EP5-T2. Five samples were assayed in duplicate in the morning and in the afternoon for 20 days on the COBAS INTEGRA 700 using a single reagent lot. The samples consisted of two commercial controls (Roche Serumproteins T and DakoCytomation Human Serum Protein) and two serum pools with different concentrations of ceruloplasmin (0.204-0.594 g/L). For each sample, the mean, standard deviation (SD) and coefficient of variation (CV) was calculated for within-run, day-to-day and total precision. The acceptable criteria for within-run and day-to-day %CV are ≤ 4% and ≤ 6% respectively. Precision results are summarized below.

Sample	Within-run			Run-to-Run		Day-to-Day		Total	
	Mean g/L	SD g/L	CV %	SD g/L	CV %	SD g/L	CV %	SD g/L	CV %
Precinorm Protein	0.217	0.0093	4.27	0.0061	2.81	0.0007	0.31	0.0111	5.12
Precipath Protein	0.594	0.0053	0.9	0.0098	1.64	0.0038	0.63	0.0117	1.97
Human Serum Pool 1	0.204	0.0073	3.59	0.0027	1.30	0.0014	0.69	0.0079	3.88
Human Serum Pool 2	0.347	0.0082	2.37	0.0010	0.28	0.0041	1.17	0.0092	2.66

A second precision study was performed to evaluate samples in the low and high end of the measuring range. The samples consisted of 1 calibrator, 2 controls (Precinorm and Precipath) and 6 human serum samples (ceruloplasmin concentrations of 0.092, 0.099, 0.181, 0.297, 1.337 and 1.461 g/L). The samples were assayed three times a day for 10 days. The %CV for between-day ranged from 0.51% to 4.25% and for total precision 0.89% to 5.67%.

b. *Linearity/assay reportable range:*
   The assay reportable range is 0.03 g/L to 1.40 g/L. The extended measuring range with a recommended dilution factor of 3 is 0.03 g/L to 4.20 g/L. Values outside of the reportable range are flagged by the instrument. Users can select an automatic rerun with dilution if they use COBAS INTEGRA 800, 700, 400/400 Plus or 800 CTS. The recommended dilution factor is 3.

   Linearity was determined by assaying serial dilutions of 4 human serum pool spiked with different concentrations of human ceruloplasmin on the COBAS INTEGRA 700. The ceruloplasmin concentrations for Pool A, B, C and D were 1.71, 0.654, 0.312 and 0.21 g/L respectively. For Pool A the serial dilutions were from 1.71 to 0.156 g/L, Pool B from 0.654 to 0.067 g/L, Pool C 0.312 to 0.031 g/L and Pool D, 0.21 to 0.044 g/L. Each dilution was assayed in quadruplicate except for those of Pool A which were run in duplicate. The acceptance criterion is 5% from the regression line. Results showed assay is linear in the range of 0.03-1.70 g/L.

   High-Dose Hook Effect
   For this study19 serially diluted samples of DAKO Human Serum Protein High Control were analyzed in duplicate without sample predilution. Results showed that no high dose effect up to 13.23 g/L.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
   The calibrator and controls are traceable to the IFCC/BCR/CAP reference preparation CRM 470 (RPPHS 91/0619).

d. *Detection limit/analytical sensitivity:*
   The detection limit is the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value three standard deviations (SD) above the mean value of 30 replicates of the zero calibrator (water) assayed on a COBAS INTEGRA 400 analyzer. The mean value was 0.011 g/L with a SD of 0.002 g/L. The detection limit is therefore, 0.017 g/L.

e. *Analytical specificity:*

<u>Endogenous substances</u>: Interference studies were performed according to CLSI document EP7-P. Three human serum pools containing ceruloplasmin (0.16 – 0.494 g/L) were spiked with varying concentrations of each of the following interferents: hemoglobin, conjugated and unconjugated bilirubin and triglycerides. Each interferent concentration was tested in quadruplicate. The spiked and unspiked samples were analyzed on the COBAS INTEGRA 700 analyzer. Percent recovery was calculated. Results were within the acceptable limit of ≥ 90% recovery and supported the claims that no interference was found for the interferent concentrations tested (hemoglobin up to 10 g/L, conjugated and unconjugated bilirubin up to 600 mg/L and triglycerides up to 25 g/L).

<u>Rheumatoid factor</u>: Rheumatoid factor interference was determined by testing two patient samples with a medium and high ceruloplasmin concentration (0.289 g/L and 0.452 g/L) spiked with increasing concentrations of RF (IgM). Spiked and unspiked samples were analyzed on a COBAS INTEGRA. No significant interference was observed up to a RF concentration of 400 IU/mL.

    f. Assay cut-off:
    Not applicable.
2. <u>Comparison studies:</u>
    a. Method comparison with predicate device:
    The predicate device is the DakoCytomation Polyclonal Rabbit Anti-Human Ceruloplasmin Test System. A total of 97 retrospective archived serum samples with ceruloplasmin concentrations ranging from 0.11 g/L to 0.59 g/L were tested. The samples were measured in duplicate. The new device was run on the Roche/INTEGRA 700 analyzer and the predicate device on COBAS MIRA Plus. All testing were performed at Roche GmbH. Results were analyzed by linear regression and Passing-Bablok analysis. Linear regression analysis gave a slope of 1.034, a y-intercept of 0.012 and correlation coefficient (r) of 0.987. Passing-Bablok analysis gave a slope of 1.00 (95% CI: 1.00, 1.053), intercept of 0.00 (95%CI: -0.019, 0.00) and r of 0.978.

Since this study only evaluated samples with ceruloplasmin concentration in the reference range, the sponsor was requested to provide additional data for samples above 0.59 g/L and below 0.11 g/L. A second comparison study was performed using the Dade Behring Ceruloplasmin assay on the BN II (k053074) because the DakoCytomation Polyclonal Rabbit Anti-Human Ceruloplasmin Test System is unavailable. The Dade Behring Ceruloplasmin assay on the BN II is an immunonephelometric assay and not a turbidimetric assay. A total of 57 samples with ceruloplasmin concentration ranged from 0.051 g/L to 1.15 g/L were tested. Linear regression analysis yielded a slope of 0.999 (95% CI: 0.953, 1.045) and a y-intercept of -0.0125 (95%CI: -0.0292, 0.0043). Passing-Bablok analysis gave a slope of 0.915 (95% CI: 0.877, 0.966), intercept of 0.014 (95%CI: -0.0028, 0.0208) and r of 0.986.

Platform comparison

For this study, 91 serum samples with ceruloplasmin concentration ranging from 0.152 g/L to 1.016 g/L were assayed on the COBAS c501 and the COBAS INTEGRA 700 instrument systems. Linear regression analysis yielded a slope of 0.97 (95%CI: 0.95, 1.00) and y-intercept of 0.0195 (95%CI: 0.0098, 0.0293). Passing-Bablok analysis yielded a slope of o.98 (95%CI: 0.96, 1.01) and a y-intercept of 0.0211 (95%CI: 0.0113, 0.0301).

b. *Matrix comparison:*

For this study, 46 serum/lithium heparin plasma paired samples with ceruloplasmin concentrations covering the reference range were assayed on the COBAS c501. Percent recoveries ranged from 89% to 105%. Linear regression analysis yielded a slope of 0.98 (95%CI: 0.92, 1.03) and a y-intercept of -0.0195 (95% CI: -0.168, 0.0164). Passing-Bablok analysis gave a slope of 0.98 and an intercept of 0.021.

3. Clinical studies:
   a. *Clinical Sensitivity:*
      Not provided
   b. *Clinical specificity:*
      Not provided.
   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:
   The normal range ranges from 0.20 to 0.60 g/L according to published literature.

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 sufficient to support a substantial equivalence decision.