

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

A. 510(k) Number:

k080384

B. Purpose for Submission:

New device

C. Measurand:

Cystatin C

D. Type of Test:

Quantitative

E. Applicant:

The Binding Site Ltd.

F. Proprietary and Established Names:

Human Cystatin C Kit for Use on the Modular P

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1225

2. Classification:

Class II

3. Product code:

NDY

4. Panel:

75, Clinical Chemistry

H. Intended Use:

1. Intended use(s):

The Cystatin C kit is intended for the quantitative determination of cystatin C in human serum, lithium heparin plasma and EDTA plasma by turbidimetry using the Roche Modular P analyzer. Cystatin C measurements in serum and plasma are used as an aid in the diagnosis and treatment of renal diseases in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:

This Cystatin C kit is intended for the quantitative determination of Cystatin C in human serum, lithium heparin plasma and EDTA plasma by turbidimetry using the Roche Modular P analyzer. Cystatin C measurements in serum and plasma are used as an aid in the diagnosis and treatment of renal diseases in conjunction with other laboratory and clinical findings.

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Roche Hitachi Modular P analyzer

I. Device Description:

Reagent is comprised of a latex reagent, calibrators, controls and a supplementary reagent:

Latex reagent: Consisting of monospecific sheep antibody coated onto polystyrene latex with preservatives (4.0 mL)

Calibrators and controls: Calibrators and controls are included with the kit. These consist of pooled human serum and are supplied in stabilized liquid form with preservatives. Calibrator is provided as Cystatin C Calibrator Set A-F (6 x 1.0 mL). Controls are provided as Cystatin C Low Control (1 x 1.0 mL) and Cystatin C High Control (1 x 1.0 mL).

Supplementary reagent: Contains 0.999% sodium azide as preservative (17.0 mL)

The sponsor states that all donors of human serum supplied with the kit have been tested and found to be negative for hepatitis C surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV1 and HIV2) and hepatitis C virus.

J. Substantial Equivalence Information:

1. Predicate device name(s):

DakoCytomation Cystatin C kit

2. Predicate K number(s):

k041627

3. Comparison with predicate:

| Similarities | | |
|---------------------|--|---|
| Item | Device | Predicate |
| Intended Use | An <i>in vitro</i> diagnostic assay for the quantitative determination of cystatin C in human serum, heparinized and EDTA plasma. Cystatin C measurements are used as an aid in the diagnosis and treatment of renal diseases. | For in vitro diagnostic use. Cystatin C Immunoparticles are intended for the quantitative determination of cystatin C in human serum, heparinized plasma and EDTA plasma by turbidimetry and nephelometry. Cystatin C measurements are used as an aid in the diagnosis and treatment of renal diseases. |
| Sample type | Human serum, heparin and EDTA plasma | same |

| Differences | | |
|--------------------|---|---|
| Item | Device | Predicate |
| Method | Particle enhanced turbidimetric immunoassay | Particle enhanced turbidimetric or immuno nephelometry |
| Measuring range | 0.4 mg/L – 7.35 mg/L | 0.4 – 7.5 mg/L |
| Reference interval | 0.53 - 1.05 mg/L | 1- 50 years: 0.55 – 1.15 mg/L > 50 years: 0.63 0 1.44 mg/L |
| Antibodies | sheep | rabbit |

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

CLSI EP5-A, Evaluation of Precision Performance of Clinical Chemistry Approved Guideline.

CLSI EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline-Second edition

CLSI EP-17A: Protocol for Determination of Limits Detection and Limits of Quantitation

L. Test Principle:

The determination of soluble antigen concentration by turbidimetric methods involves the reaction with specific antiserum to form insoluble complexes. When light passed through the suspension formed, a portion of the light is transmitted and focused onto a photodiode by an optical lens system. The amount of transmitted light is indirectly proportional to the specific protein concentration of the test sample. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A precision study was conducted according to CLSI, EP5-A Evaluation of Precision Performance of Clinical Chemistry, Approved Guideline. Three different control samples using three different analyzers were run twice a day for 21 days. Total, within-run, between run and between day precision was calculated for the three concentrations: high (75-95% of the upper limit of the measuring range), medium (medical decision level) and low (between 140 and 180% of the lower limit of the measuring range). The studies were performed on the Modular P analyzer. Results are shown in the table below:

| Precision | | | | | | |
|-------------|--------------------------------|------|-----------------------------------|------|---------------------------------|-------|
| | Low control mean 0.552 mg/L | | Medium control mean 0.960 mg/L | | High control mean 6.038 mg/L | |
| | SD | CV% | SD | CV% | SD | CV% |
| Within run | 0.01 | 2.3% | 0.06 | 1.0% | 0.06 | 1.9% |
| Between run | 0.01 | 2.5% | 0.05 | 4.8% | 0.08 | 0.14% |
| Between day | 0.03 | 5.6% | 0.03 | 3.6% | 0.29 | 4.9% |
| Total | 0.04 | 6.6% | 0.06 | 6.2% | 0.31 | 5.2% |

b. *Linearity/assay reportable range:*

A sample with a high value of Cystatin C was diluted to obtain 7 levels with values ranging from 0.13 to 7.76 mg/L. The samples were tested in duplicate. A linear regression of $y = 0.9929 - 0.0144x$ was obtained. An additional linearity study was performed using a different sample with an elevated Cystatin C level. The sample was diluted to obtain 12 levels with values ranging from 0.09 to 6.325 mg/L. A linear regression of $1.0023x + 0.0329$ was obtained. The studies support the analytical measuring range for the assay of 0.4 – 7.35 mg/L.

An antigen excess study was conducted to assess the performance of the assay at high Cystatin C concentrations. The study demonstrated that results were not affected by antigen excess up to 17 mg/L for Cystatin C.

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

Kit calibrators and controls are included with the Cystatin C kit. Kit calibrators and controls are manufactured from separate pools of delipidated human serum. Calibrator and control value assignment is controlled during kit production using set target values for initial fluids of pooled serum. An internal reference standard is used to control and validate calibration between batches. The value was assigned to the internal reference standard IR7651 using the DAKO Cystatin C reagents on the Modular P as no internationally recognized reference standard is currently available for cystatin C.

Open vial stability for the calibrators and controls was established in k072166, The Binding Site Human Cystatin C Kit. Open vial stability testing was conducted with three reagent kits, controls and calibrators. The kits were stored and retested at intervals on day 1, 8, 15, 22 and 97. The results obtained at the time points were calculated as % difference against the assigned values. The results support the sponsor's open vial stability of 3 months at 2-8 °C.

d. *Detection limit:*

The assay is designed to only report concentration values above the lowest calibrator (~0.37 mg/L). Samples with absorbance readings between the blank and the lowest calibrator are flagged as below the measurable range and no concentration value is calculated. The limit of detection (LoD) was determined by testing 60 determinations each of the blank, lowest calibrator, and a serum sample with values very close to the value of the lowest calibrator. The LoD was determined to be 0.37 mg/L. The sponsor also conducted a limit of the blank (LoB) study. The limit of blank (LoB) was determined based on the measurement of the 60 blank samples. The LoB was calculated (mean + 3SD) as 0.05 mg/L.

e. *Analytical specificity:*

Interference testing was performed based on CLSI EP7-A2, Interference Testing in Clinical Chemistry. Interference testing was performed using a sample with a very low level of cystatin C (approximately 0.4 mg/L) tested at the minimum sample dilution of 1:2 to demonstrate the maximum effect of interference. The assay uses turbidimetric methodology with the samples diluted on-board before analysis. High concentrations of hemoglobin and bilirubin were added to the test serum sample containing a known concentration of cystatin C. No significant interference was seen for bilirubin up to 200 mg/dL and hemoglobin up to 5 g/L. Interference from lipemia was tested by adding a high concentration of chyle obtained from a commercially available interference check kit to the sample with low concentration of cystatin C. Chyle is a biological fluid consisting of a mixture of lymph and chylomicrons. No interference was found up to a triglyceride equivalent of 240 mg/dL for the chyle fluid. In addition, a sample with a concentration of triglyceride of 840 mg/dL showed no significant interference (1.45%) with the assay. The package insert contains the following statement in the Limitations section: "Turbidimetric assays are not suitable for the measurement of highly lipemic or hemolyzed samples or samples containing high levels of circulating immune complexes due to the unpredictable degree of non-specific scatter these sample types may generate."

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

A correlation study was performed on 66 serum samples (30 normal, 36 from known renal impaired patients) and 57 plasma samples (20 normal, 37 from known renal impaired patients) using this device (y) vs. the predicate device (x) both on the Modular P analyzer. The correlation yielded the following regression equation: $y = 0.96x + 0.02$ (mg/L), $r = 0.996$ based on singlet analysis of the samples. The samples had values ranging from 0.54 to 7.17 mg/L.

b. *Matrix comparison:*

A matrix comparison study was conducted with 38 lithium heparin plasma and serum samples. The samples covered the range of 0.68 to 6.03 mg/L with a linear regression equation of $y = 0.97x + 0.04$, $r = 0.995$.

A matrix comparison study was conducted with 20 EDTA plasma and serum

samples. The samples covered the range of 0.54 to 4.88 mg/L with a linear regression equation of $y = 0.982x - 0.0741$, $r^2 = 0.9984$.

Both studies demonstrated equivalence between sample types.

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:

The sponsor conducted a normal range study using 120 normal sera obtained from healthy adult blood donors. The reference range interval was calculated using non-parametric statistics and represents the central 95% of the population. The following table is in the package insert.

| | Number (n) | Mean (mg/L) | Median (mg/L) | 95 Percentile Range (mg/L) |
|------------|------------|-------------|---------------|----------------------------|
| Cystatin C | 120 | 0.795 | 0.780 | 0.530 -1.050 |

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.