

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

A. 510(k) Number:

k072965

B. Purpose for Submission:

New device

C. Measurand:

Complement 1 inhibitor (inactivator)

D. Type of Test:

Quantitative immuno-nephelometry

E. Applicant:

Dade Behring Inc.

F. Proprietary and Established Names:

Proprietary Name: Dimension Vista C1IN Flex reagent cartridge, Dimension Vista C1IN CAL, and Dimension Vista C1IN CON

Established name: Complement C1 inhibitor, antigen, antigen, control

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5250 Complement C1 inhibitor (inactivator) immunological test system.

21 CFR§ 862.1150, Calibrator

21 CFR§ 862.1660, Quality Control Material (Assayed and Unassayed)

2. Classification:

Class II – Device and Calibrator

Class I - Quality control material

3. Product code:

DBA, Complement C1 inhibitor (inactivator) antigen, antiserum, control

JIT, Calibrator, secondary

JJX, Single (Specified) Analyte Controls (Assayed and Unassayed)

4. Panel:

Immunology (82), Chemistry (75)

H. Intended Use:

1. Intended use(s):

The C1IN method is an in vitro diagnostic test for the quantitative measurement of C1 inhibitor in human serum and plasma on the Dimension Vista Systems. Measurement of C1 inhibitor aids in the diagnosis of hereditary angioneurotic edema (increased blood vessel permeability causing swelling of tissues) and a rare form of angioedema associated with lymphoma (lymph node cancer).

The C1IN CAL is an in vitro diagnostic product for the calibration of the C1 inhibitor method on the Dimension Vista System.

C1 inhibitor control is an assayed, mid level, intra-laboratory quality control for assessment of precision and analytical bias on the Dimension Vista System in the quantitative determination of C1 inhibitor (C1IN).

2. Indication(s) for use:
Measurement of C1 inhibitor aids in the diagnosis of hereditary angioneurotic edema (increased blood vessel permeability causing swelling of tissues) and a rare form of angioedema associated with lymphoma (lymph node cancer)
3. Special conditions for use statement(s):
Prescription use only
4. Special instrument requirements:
Dimension Vista System (k051087)

I. Device Description:

The device is an in vitro diagnostic measurement system utilizing reagents, calibrators, and controls for use on the Dimension Vista System to measure the presence of complement 1 inhibitor (C1 inhibitor) in human serum and plasma.

The assay reagent consists of a cartridge containing rabbit polyclonal antiserum to C1 inhibitor (concentration 984 g/L) containing sodium azide (an anti-microbial preservative at approximately 0.1% w/v) and a phosphate buffer containing polidocanol (preservative). The reagent cartridge is utilized with the Dimension Vista instrument which performs all specimen and reagent handling, mixing, and processing for a test result. Calibration and assay quality control is performed automatically by the Dimension Vista system.

The C1 inhibitor calibrator consists of 4 vials, 1.0 ml per vial when reconstituted, containing a lyophilized human plasma based product containing C1 inhibitor at a lot-specific defined concentration. The calibrator contains the preservative sodium azide (at approximately 0.1% when reconstituted). The reagent is prepared for use by addition of 1.0 ml of distilled water.

The C1 inhibitor control consists of 4 vials, 1.0 ml per vial when reconstituted, containing lyophilized human plasma based product of C1 inhibitor at a lot-specific defined concentration. The control contains the preservative sodium azide (at approximately 0.1% when reconstituted). The reagent is prepared for use by addition of 1.0 ml of distilled water.

J. Substantial Equivalence Information:

1. Predicate device name(s):
N antisera to human C1 inhibitor
N Protein Standard PY
N/T Protein Control PY
2. Predicate 510(k) number(s):
k960257
k960257
k962407
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use of assay reagent	The C1IN method is an in	In vitro diagnostic reagents

Similarities		
Item	Device	Predicate
	vitro diagnostic test for the quantitative measurement of C1 inhibitor in human serum and plasma on the Dimension Vista Systems. Measurement of C1 inhibitor aids in the diagnosis of hereditary angioneurotic edema (increased blood vessel permeability causing swelling of tissues) and a rare form of angioedema associated with lymphoma (lymph node cancer)	for the quantitative determination of C1 inhibitor (C1-inactivator, C1-esterase inhibitor) in human plasma and serum using the BN Systems
Assay testing principle	Immuno-nephelometry	Same
Assay reagent antibody	Polyclonal rabbit anti-C1 inhibitor antibody	Same
Assay reportable range	0.03 to 0.40 g/L	Same
Calibrator reagent form	Lyophilized human plasma	Same
Control reagent form	Lyophilized human plasma	Same
Control concentration range	1.4 – 3.5 g/L	Same

Differences		
Item	Device	Predicate
Analyzer system	Dimension Vista Systems	BN Systems
Intended Use of Calibrator	The C1IN CAL is an in vitro diagnostic product for the calibration of the C1 inhibitor method on the Dimension Vista System	Establishment of reference curves for the immunochemical determination of fibrinogen, antithrombin III, plasminogen, fibronectin, C1 inhibitor using the BN systems as well as fibronectin by radial immunodiffusion using Partigen plates
Calibrator constituents	C1 inhibitor	Fibrinogen, antithrombin III, plasminogen, fibronectin, and C1 inhibitor
Intended Use of Control reagent	C1 inhibitor control is an assayed, mid level, intralaboratory quality control for assessment of precision and analytical bias on the Dimension Vista System in the quantitative determination of C1	N/T protein control is used for control of accuracy and precision in the immunochemical determination of fibrinogen, antithrombin III, plasminogen, fibronectin, and

Differences		
Item	Device	Predicate
	inhibitor (C1IN)	C1 inhibitor using the BN systems, TurbiTime system and by radial immunodiffusion using Partigen plates
Control constituents	C1 inhibitor	Fibrinogen, antithrombin III, plasminogen, fibronectin, and C1 inhibitor

The Indications for use for the predicate device system and the proposed device system are similar enough that there is no therapeutic or diagnostic effect altering effectiveness. The technological characteristics for the predicate device system and the proposed device system are similar enough that no new safety or effectiveness questions are raised.

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

There are no standard reference preparations or materials for C1 inhibitor. The following guidelines for performance of studies were utilized:

Clinical Laboratory Standards Institute Guideline EP5-A2, "Evaluation of Precision Performance of Quantitative Measurement Methods"

Clinical Laboratory Standards Institute Guideline EP7-A2, "Interference Testing in Clinical Chemistry"

L. Test Principle:

The assay uses the principle of immune precipitation of C1 inhibitor with specific antiserum (nephelometry) as the technological method to measure C1 inhibitor in human plasma or serum. When C1 inhibitor in serum or plasma immunochemically binds with the supplied antiserum, complexes are formed. When a beam of light passes through a solution containing the complexes light is scattered and the intensity of scattered light is proportional to the concentration of C1 inhibitor in the specimen. The amount scattered using samples containing known defined amounts of C1 inhibitor are utilized to create a calibration curve to relate the intensity of scattered light from unknown samples with the intensity of scattered light from the samples with known concentrations of C1 inhibitor. The calibrator system in this device uses 5 different concentrations and has an analytical measurement range of 3.0 to 40.0 mg/dL C1 inhibitor. For a serum or plasma specimen of unknown value, an initial dilution of the specimen of 1:2.5 is performed by the instrument. The Dimension Vista System calculates the concentration of C1 inhibitor in mg/dL under usual calibration conditions. Turbidity and particles in the specimen may interfere with the determination.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Utilizing CLSI guideline EP5, serum and plasma specimens at 2 different concentrations were tested in duplicate twice a day for 20 days. Additionally, the control was tested in a similar manner. Repeatability (within run) and within-lab standard deviations and percent coefficients of variation were calculated using analysis of variance. The data are summarized as follows:

Material	Mean	Repeatability	Within-lab
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	(mg/dL)	%CV	%CV
Positive control	20 mg/dL	2.7%	3.3%
Serum pool	7 mg/dL	2.4%	5.2%
Serum pool	37 mg/dL	2.7%	3.2%
Plasma pool	30 mg/dL	2.5%	3.1%
Plasma pool	37 mg/dL	2.2%	3.0%

Accuracy determination:

As a measure of accuracy highly purified C1 inhibitor at 26 mg/dL was measured in the proposed assay in 5 replicates. The percent recovery (observed concentration divided by known concentration, expressed as a percentage) was calculated for the 5 replicates. The mean percent recovery was 98.8% (ranging from 95.7% to 103.4%). The acceptance criterion was $\pm 15\%$ deviation from the nominal value (%recovery ranging from 85% to 115%). All tested replicates met this acceptance criterion.

b. Linearity/assay reportable range:

Linearity of sample result on dilution was assessed using a single sample with a high C1 inhibitor concentration. The sample was diluted 11 times with system diluent from 41 mg/dL to 3 mg/dL. Each of the 11 dilutions was tested in the proposed assay in 5 replicates. Linearity was assessed using linear regression where the x-axis is the theoretical concentration on dilution and y-axis is the observed mean value of each of 11 dilutions. The acceptance criteria were a slope between 0.9 and 1.1 and a correlation coefficient greater than or equal to 0.95. The slope of the best fit line was 0.981 with a correlation coefficient of 0.98. The acceptance criteria were met.

Hook effect

The possibility of a hook effect was evaluated using a single sample with a value above the assay range in the proposed and predicate assay. A sample with a value of 108 mg/dL on the predicate assay was tested using the proposed assay. The resulting value in the proposed assay was > 4 mg/dL, above the assay range of the proposed assay.

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

No standard reference material for C1 inhibitor is available at present. A concentrated pool of human plasma containing C1 inhibitor is designated a Master Calibrator. It is assigned a value by the assay using highly purified C1 inhibitor protein preparation as a calibrator. A commercial calibrator lot preparation is prepared by dilution to a target concentration. The commercial lot is assigned a value by the assay in multiple replicates of multiple runs on at least 2 instruments using the Master Calibrator to generate several calibration curves. The commercial lot is vialled, labeled, and packaged for shipment.

d. Detection limit:

Three samples with 3 mg/dL (the lower limit of the reportable range) were measured in triplicate in 5 runs in one day to validate the limit of quantitation for the assay. The mean, standard deviation, %coefficient of variation, and percent bias were calculated for the 15 replicates. The acceptance criterion of $\pm 30\%$ bias was met.

e. Analytical specificity:

Interferences were assessed using CLSI document EP7 to determine the effect of endogenous and exogenous substances on the assay. For all interfering substances, except rheumatoid factor, the acceptance criterion for percent bias was $\pm 10\%$.

Interference was assessed by testing a control sample with or without addition of the interfering substance. Bias was calculated as the percentage of concentration in the presence of substance to the concentration in the absence of substance. To assess interference from rheumatoid factor samples with concentrations greater than 470 IU/ml were mixed in equal volume with samples without rheumatoid factor. The samples were tested in the assay and percent recovery of C1 inhibitor was calculated. The acceptance criterion of $\pm 10\%$ deviation was used. For the substances tested no significant interference was detected in the proposed assay. The complete list of tested interfering substances is listed in the labeling. The labeling states that at the concentrations of interfering substances tested, there is less than 10% interference at C1 inhibitor concentrations of 23 to 38.7 mg/dL.

f. Assay cut-off:

As described in the labeling, the range of values expected from normal donors is 21 – 39 mg/dL [0.21 – 0.39 g/L]. Samples from 370 healthy Central European donors were used to establish this reference interval. It represents the range from the 2.5th to 97.5th percentile determined using the predicate device.

2. Comparison studies:

a. Method comparison with predicate device:

Assay results of the proposed assay were compared with results of the predicate assay (N antisera on the BN Prospec system) using 67 serum and 129 plasma samples ranging from 3 to 39 mg/dL. Passing-Bablok regression analysis was performed on results of the two assays. The slope of the best fit regression line was 0.915 (95% confidence interval 0.903 to 0.928). The intercept of the best fit line was 0.006 (95% confidence interval 0.3 to 0.8 mg/dL). The Pearson correlation coefficient was 0.993.

b. Matrix comparison:

A comparison of test results using three specimen types (serum, lithium heparin plasma, and sodium heparin plasma) was performed on 10 matched specimens. Linear regression analysis was performed to show agreement of values between serum and plasma samples. The range of C1 inhibitor concentrations in the 10 samples was 3 to 33 mg/dL. The slope of the best fit line of sodium heparin plasma and lithium heparin plasma vs. serum was 0.94 (95% confidence interval for lithium heparin vs. serum 0.931 to 0.96; 95% confidence interval for sodium heparin vs. serum 0.917 to 0.97). The correlation coefficient was 1.0 and 0.998 for lithium and sodium heparin, respectively vs. serum. The standard error in value in lithium or sodium plasma for a given serum value was 1 and 0.0 mg/dL, respectively.

3. Clinical studies:

a. Clinical Sensitivity:

None determined

b. Clinical specificity:

None determined

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

None determined

5. Expected values/Reference range:

The concentration of C1 inhibitor expected in a normal healthy population is 21 – 39 mg/dL when using this assay system. Each laboratory should verify or establish its own expected range of values using this assay system.

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.