510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k071603

B. Purpose for Submission:
New device

C. Measurand:
Carcinoembryonic Antigen (CEA)

D. Type of Test:
Quantitative, homogeneous sandwich chemiluminescence immunoassay

E. Applicant:
Siemens Healthcare Diagnostics Inc. (formerly Dade Behring Inc.)

F. Proprietary and Established Names:
Dimension Vista® Carcinoembryonic Antigen (CEA) Flex® reagent cartridge
Dimension Vista® LOCI 5 Calibrator

G. Regulatory Information:

1. Regulation section:
   866.6010 Tumor-associated antigen immunological test system
   862.1150 Calibrator
2. Classification:
   Class II
3. Product code:
   DHX System, Test, Carcinoembryonic Antigen
   JIX Calibrator, Multi-analyte mixture
4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended use(s):
   Dimension Vista® CEA Method: The CEA method is an *in vitro* diagnostic test for the quantitative measurement of carcinoembryonic antigen in human serum and sodium or lithium heparinized plasma on the Dimension Vista® System. Measurements of carcinoembryonic antigen are used as an aid in the management of cancer patients in whom changing CEA concentrations have been observed.

   Dimension Vista® LOCI 5 Calibrator: For the calibration of the Carcinoembryonic Antigen (CEA) method on the Dimension Vista® System.
2. Indication(s) for use:
   Same as above
3. Special conditions for use statement(s):
   Prescription use only
4. Special instrument requirements:
   Dimension Vista® System

I. Device Description:
The CEA method consists of two synthetic bead reagents and a biotinylated murine-

anti-CEA antibody. The first bead reagent (Chemibeads) is coated with an anti-CEA monoclonal antibody and contains a chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. All are supplied in liquid format in a reagent cartridge.

The LOCI™ 5 Calibrator is a liquid multi-analyte product containing human tissue culture derived CEA. The kit consists of 10 vials, 2 each of 5 levels containing 2 mL per vial.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Beckman Access® CEA Reagents with Calibrators on the Access® Immunoassay System.
2. Predicate 510(k) number(s):
   k031270
3. Comparison with predicate:

CEA Method

Similarities		
Item	Device	Predicate
Intended Use	For the quantitative measurement of carcinoembryonic antigen	Same
Indications for Use	As an aid in the management of cancer patients in whom changing CEA concentrations have been observed	Same
Methodology	Chemiluminescent immunoassay	Same
Capture antibody	Mouse monoclonal	Same

Differences		
Item	Device	Predicate
Measuring Range	0.2– 1000.0 ng/mL	0.1– 1000.0 ng/mL
Sample types	Serum and plasma	Serum
Sample size	2 µL	10 µL
Precision	Repeatability: 1.3 - 2.9 %CV Within Lab: 2.1 – 3.6 %CV	Within Run: 3.01 – 3.97 %CV Total: 3.80 – 4.51 %CV
Instrument platform	Dimension Vista System	Access Immunoassay System
Storage	Store at 2 to 8°C	Store at 2 to 10°C

Calibrator

Similarities		
Item	Device	Predicate
Intended Use	For the calibration of Carcinoembryonic Antigen (CEA) method	Same
Composition	BSA-based matrix	Same
Preparation	Liquid, ready-to-use	Same

Differences		
Item	Device	Predicate
Instrument	Dimension Vista system	Access Immunoassay systems
Calibrator Levels	5 target concentrations: 0, 5, 100, 500 and 1050 ng/mL	6 target concentrations: 0, 10, 100, 500 and 1000 ng/mL
Storage	Store at 2 to 8°C	Store at 2 to 10°C

K. Standard/Guidance Documents referenced (if applicable):

1. NACB: Practice Guidelines and Recommendations for Use of Tumor Markers in the Clinic *Quality Requirements [Section 2]*. National Academy of Clinical Biochemistry Guidelines on Quality Requirements for the Use of Tumor Markers. Catharine Sturgeon, Elizabeth Hammond, Soo-Ling Ch'ng, György Sölétormos, Daniel F Hayes.
2. Clinical and Laboratory Standards Institute/NCCLS. *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fifth Edition.* NCCLS document H3-A5 [ISBN 1-56238-515-1]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2003.
3. Clinical and Laboratory Standards Institute /NCCLS. *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition.* CLSI/NCCLS document EP5-A2 [ISBN 1-56238-542-9]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2004.
4. Clinical and Laboratory Standards Institute/NCCLS. *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition.* CLSI/NCCLS document EP9-A2 [ISBN 1-56238-472-4]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2002.
5. Clinical and Laboratory Standards Institute/NCCLS. *Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition.* CLSI/NCCLS document EP7-A2 [ISBN 1-56238-584-4]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2005.
6. Clinical and Laboratory Standards Institute/NCCLS. *Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline.* CLSI/NCCLS document EP17-A [ISBN 1-56238-551-8]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2004.
7. "Bundling Multiple Devices of Multiple Indications in a Single Submission,"
8. "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable-
9. Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff."

10. CLSI EP9-A2 Approved Guideline Method Comparison and Bias Estimation Using Patient Samples.

L. Test Principle:

The CEA method is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI™ technology. The LOCI™ reagents include two synthetic bead reagents and a biotinylated anti-CEA monoclonal antibody fragment. The first bead reagent (Chemibeads) is coated with an anti-CEA monoclonal antibody and contains chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. Sample is incubated with biotinylated antibody and Chemibeads to form bead-CEA-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffused into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the CEA concentration in the sample.

The LOCI™ 5 Calibrator is a liquid multi-analyte product containing CEA from human tissue culture cells.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The reproducibility testing was conducted in accordance with the CLSI/NCCLS Approved Guideline for Evaluation of Precision Performance of Quantitative Measurement Methods, EP5-A2. Samples (pooled serum, pooled plasma, and controls) were measured in duplicate, two times per day over 20 days. Repeatability, between-run, between day, and within-lab were determined by the analysis of variance method. The repeatability and within-lab data are presented below. Imprecision was less than 3.6% CV at all levels, which was acceptable.

Results:

Material	**Mean ng/mL [µg/L]**	**Standard Deviation (%CV)**	
		Repeatability	**Within-Lab**
Liquichek™ Immunoassay Plus Control			
Level 1	2.1	0.1 (2.9)	0.1 (3.4)
Level 2	26.2	0.6 (2.2)	0.8 (2.9)
Serum pool 1	0.9	0.02 (2.3)	0.02 (2.6)
Serum pool 2	12.8	0.3 (2.6)	0.4 (3.1)
Serum pool 3	67.5	1.3 (1.9)	1.6 (2.4)
Serum pool 4	478.0	6.2 (1.3)	10.1 (2.1)
Serum pool 5	756.4	13.6 (1.8)	24.9 (3.3)
Plasma pool	239.7	5.2 (2.2)	8.6 (3.6)

*Liquichek™ is a trademark of Bio-Rad Laboratories, Irvine, CA 92618.

Between-Lot reproducibility was also evaluated using 6 different samples (3 serum pools and 3 levels of quality control materials) representing the range of the assay (2.4 ng/mL to 486.4 ng/mL) on two different CEA Flex® reagent

lots (with a single calibrator lot). The %CV was less than 3.3% at all levels for both lots, which was acceptable.

Between-Lab/Instrument reproducibility was also evaluated at three different laboratories (New York, Glasgow Scotland and Maryland) on three different instruments using 2 - 3 levels of quality control materials representing the range of the assay (2 ng/mL to 240 ng/mL) on 2 different CEA Flex® reagent lots and two calibrator lots). The %CV was less than 3.4% at all levels, which was acceptable.

b. Linearity/assay reportable range:

Linearity of the reportable range (1.3 – 1207.8 ng/mL) was evaluated by comparing observed vs. expected values using a serially diluted sample pool mixture. Linear regression analysis demonstrated the following results:

Range (ng/mL)	Slope	Intercept ng/mL	Correlation Coefficient	n
1.3 – 1207.8	0.98	15.35	0.999	7

The acceptance criteria of slope between 0.9 and 1.1 and correlation coefficient $\geq$ 0.95 were met.

Spiking recovery: A spiking recovery study was performed by adding known amounts of CEA (~5, 15, 75, and 500 ng/mL) to a human serum pool with a baseline CEA value of 3.4 ng/mL. The sample concentrations were measured and the percent recovery ranged from 94.0% to 100.4% with a mean recovery of 97.1%.

Dilution recovery: A dilution recovery study was performed by diluting 5 serum samples with CEA values from 157.5 ng/mL to 751.5 ng/mL with Reagent grade water. The samples were diluted 1:2, 1:3, 1:4, 1:5, and 1:10 and assayed for recovery. The recoveries ranged from 98.0% to 109% with a mean of 102.9%.

Antigen Excess (Hook Effect): The effect of antigen excess was evaluated using a serum sample above the assay range. The CEA method generated signal high enough to trigger the Above Assay Range flag and thus did not hook back to generate falsely low value with CEA up to 225,000 ng/mL. The declared analytical measurement range for this assay is 0.2 – 1000.0 ng/mL. The data provided in the submission and summarized above support this choice of measurement range.

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

No information provided on traceability to any reference standard. The predicate device, Beckman Coulter™ Access® CEA is used to assign values to the Dimension Vista CEA calibrators.

Calibrator stability claims in the IFU were supported by stability protocols

and data.

Specimen stability claims were supported by protocols employing freeze-thaw and stress testing up to 7 days at 4°C or stored at -20°C and -70°C for 30 days. Results were within 7% of the control sample demonstrating that the specimen was stable at recommended temperatures.

d. Detection limit:

The Limit of Blank (LoB) and the Limit of Detection (LoD) were evaluated according to CLSI EP17-A "Protocols for Determination of Limits of Detection and Limits of Quantitation." The LoD defined as the lowest concentration that can be detected reliably) was determined to be 0.2 ng/mL with proportions of false positives (α) less than 5% and false negatives (β) less than 5%; based on 15 determinations, with 4 blank and 4 low level samples. The LoB is the highest concentration that is likely to be observed for a blank sample and was determined to be 0.12 ng/mL.

e. Analytical specificity:

i. Interference Studies: Interference testing was performed according to CLSI Approved Guideline for Interference Testing in Clinical Chemistry EP7-A2, to determine the effect of various substances on the Dimension Vista® CEA assay at two concentrations of CEA (5 ng/mL and 500 ng/mL). The following interferents were tested for their effect on test samples and compared to a control sample without interferent; bias exceeding 10% was considered interference: bilirubin (conjugated and unconjugated, 60 mg/dL), hemoglobin (1000 mg/dL), Intralipid 3000 mg/dL, albumin (6 g/dL), total protein (8 g/dL), urea (500 mg/dL), uric acid (20 mg/dL) and rheumatoid factor (500 IU/mL). Acceptance criteria were met. Additionally, 53 potentially interfering drugs were also assayed on serum and plasma samples containing 1.3 and 541 ng/mL CEA and shown to exhibit minimal interference (<10%).

ii. HAMA: Interference by human anti-murine antibodies was evaluated by mixing a sample with a high CEA level into three different heterophilic human samples containing HAMA and comparing the results to the CEA specimen before mixing. The percent bias at 500 ng/mL CEA was calculated and shown to be less than -8.9% which meets the acceptance criteria of 10%. The standard limitation for possible interference from heterophilic antibodies is included in the package insert.

iii. Cross Reactivity: NCA (nonspecific crossreactive antigen) and NCA-2 were evaluated for cross-reactivity with the CEA method when present in serum in the amounts indicated. Systematic inaccuracies (bias) due to these substances are less than 10 % at a CEA concentration of 5 ng/mL.

Substance	**Concentration**
Cancer Marker NCA	500 ng/mL
Cancer marker NCA-2	100 ng/mL

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
A split serum sample method comparison study was performed according to CLSI document EP9-A2; "Guideline for Method Comparison and Bias Estimation using Patient Samples." A total of 141 serum samples spanning the assay range (0.8 to 974.0 ng/mL) were evaluated on both the Dimension® Vista and the Beckman Coulter™ Access® methods. Linear regression of singlicate measurements yielded the following statistics:

Comparative Method	n	CEA concentration range ng/mL [µg/L]	Slope	Intercept ng/mL [µg/L]	Correlation Coefficient
ACCESS® CEA	141	0.8-974	1.01	9.01	0.989
	46	0.8-17.1	1.04	0.44	0.970

b. Matrix comparison:
Recommended sample types are serum and plasma (lithium and sodium heparin). A matched sample method comparison study was performed. A total of 54 paired serum and plasma samples spanning the assay range (1.2 to 992.6 ng/mL) were evaluated on the Dimension® Vista System. Linear regression of singlicate measurements yielded the following statistics:

Sample Comparison	Slope	Intercept ng/mL [µg/L]	Correlation Coefficient	N
Lithium heparin vs. Serum	1.00	1.45	0.997	54
Sodium heparin vs. serum	0.99	2.55	0.998	54

No clinically significant difference was observed between serum and plasma samples.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:
Not applicable.

b. Other clinical supportive data (when a .is not applicable):
A clinical evaluation was performed to assess the Dimension Vista® CEA method for the purpose of obtaining FDA premarket clearance for monitoring cancer patients. Seventy-five (75) retrospective serial serum sample sets (with a minimum of 3 blood draws for each patient) with colorectal cancer clinical data were tested. Inclusion and exclusion criteria for the samples were provided. One patient was excluded from statistical analysis when it was determined that they did not meet the protocol inclusion criteria. Samples were characterized by sex, age (range 36.1 year old to 86.2 years old; average age 63 years old), ethnicity, smoking history, treatment, and stage of disease (stage I through IV).

A longitudinal analysis of serial draws from 74 patients was performed. All patients were categorized as Active/Progressive, Responding, Stable, or No Evidence of Disease (NED). Disease progression was determined by the patient physician based on either or all of the following:

- Physical examination of clinical signs and symptoms, including results of laboratory tests.
- Radiographic findings used in the assessment of cancer status (CAT Scans, MRI, X-rays, or colonoscopy, sigmoidoscopy or ultrasound images.
- Surgical procedures including biopsy, esophagogastroduoden-oscopy, laparotomy or resection.

The Reference Change Value (RCV) was used to determine if a significant change in CEA occurred. For this calculation, the RCV for each assay (the Dimension Vista CEA method and predicate) was derived by taking into account the published biological variation for CEA and the total imprecision of the assay. The formula for this calculation is $RCV = 2^{1/2} * Z * (CV_A^2 + CV_I^2)^{1/2}$, where Z is the z-score, CV_A is the analytical variation, and CV_I is the biological variation (Fraser, Callum G. Biological Variation: From Principles to Practice, Washington, DC: AACC Press, 2001). The within-subject biological variation (12.7%) was obtained from the literature (Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." Scand J Clin Lab Invest 1999;59:491-500) and used for both the new assay and the predicate. The RCV for the Vista CEA method was calculated to be 36.2% and that of the predicate to be 36.7%.

Per Visit analysis:
Changes in CEA concentrations and in disease status were analyzed on a per visit basis. Patients were categorized as Active/Progressive, Responding, Stable or No Evidence of Disease (NED) by the attending physician based on the clinical information. All 74 patients were analyzed to determine the change of disease status per sequential pair (n=217). The table below shows the distribution of results when compared to the disease status:

Per Visit Vista® CEA Value vs. Disease States

	Change in Disease State				
Change in CEA	Responding n (%)	Stable n (%)	No Evidence of Disease n (%)	Progression n(%)	Total
>36.2% increase	6 (2.8%)	14 (6.5%)	6 (2.8%)	32 (14.8%)	58 (26.7%)
No significant Change	12 (5.5%)	33 (15.2%)	62 (28.6%)	22 (10.1%)	129 (59.5%)
>36.2% decrease	5 (2.3%)	15 (6.9%)	6 (2.8%)	4 (1.8%)	30 (13.8%)
Total	23 (10.6%)	62 (28.6%)	74 (34.1%)	58 (26.7%)	217 (100.0%)

The following two tables show per visit clinical performance results for the

Dimension Vista CEA test and predicate device analyzed as "Progression" and "No Progression" with "No Progression" consisting of responding, stable, and no evidence of disease:

Per Visit Vista CEA RCV vs. Disease States

	Progression	**No-Progression**	**Total**
>36.2% increase	**32**	26	58
≤36.2% increase	26	**133**	159
Total	58	159	217

	Estimate	***Exact 95% Confidence Interval***
%Overall Agreement	76.0%	(69.8% - 81.6%)
% Sensitivity	55.2%	(41.5% - 68.3%)
% Specificity	83.6%%	(77.0% - 89.0 %)

Per Visit Predicate CEA RCV vs. Disease States

	Progression	**No-Progression**	**Total**
>36.7% increase	**32**	32	64
≤36.7% increase	26	**127**	153
Total	58	159	217

	Estimate	***Exact 95% Confidence Interval***
%Overall Agreement	73.3%	(66.9% - 79.0%)
% Sensitivity	55.2%	(41.5% - 68.3%)
% Specificity	79.9%	(72.8% - 85.8%)

The per visit concordances were pooled by taking the correlation structure within each patient series into consideration as recommended by B. Emir, S. Wieand, John Q.S., and S. Cha, Statistics in Medicine, 17, 2563-2578 (1998). Efficacy is demonstrated when the sum of sensitivity and specificity is greater than one. Non-parametric estimates for the 95% confidence intervals were derived using a bootstrap resampling technique with 2000 iterations. For the Dimension Vista CEA method the bootstrap 95% CI was 1.2416 to 1.5227 for the sum of Sensitivity + Specificity, and for the comparative method the bootstrap 95% CI for the sum of the Sensitivity + Specificity was 1.2180 to 1.4771. This demonstrated that both tests are effective.

Concordance between Dimension Vista CEA and predicate:

All specimens were analyzed for percent agreement between the two assays using their RCVs. Results are shown below:

Vista CEA Comparison to Predicate CEA Assay (on a per visit basis)

	Access CEA		
Vista CEA	>36.7% increase	≤36.7% increase	**Total**
>36.2% increase	**55**	3	58
≤36.2% increase	9	**150**	159
Total	64	153	217

	Estimate	***Exact 95% Confidence Interval***
% Overall Agreement	94.5% (205/217)	(90.5% - 97.11%)
% Positive Agreement	85.9% (55/64)	(75.0% - 93.4%)
% Negative Agreement	98.0% (150/153)	(94.4% - 99.6%)

4. Clinical cut-off**:**
   Not applicable for serial monitoring assay that looks for a significant rise.
5. Expected values/Reference range:
   The distribution of CEA values was determined using the Dimension Vista System in 347 specimens from normal individuals (smokers and non-smokers) and patients with colorectal cancer. In this study 96.4% of the healthy subjects had CEA levels less than 5.0 ng/mL.

Expected Values: Non- smokers: 0.0 – 3.0 ng/mL [µg/L]
Smokers: 0.0 – 5.0 ng/mL [µg/L]

The expected values were calculated non-parametrically and represent results determined from a population of healthy adults (n= 347); 198 (96%) non-smokers and 149 (96.6 %) smokers).

Cohorts	**N**	**Distribution of CEA results**			
		0.0-3.0 (%)	**3.1-5.0 (%)**	**5.1-10.0 (%)**	**>10.0 (%)**
Non-Smokers	198	190 (96.0)	8 (4.0)	0 (0.0)	0 (0.0)
Smokers	149	113 (75.8)	31 (20.8)	5 (3.4)	0 (0.0)
Total	347	303 (87.2)	39 (11.2)	5 (1.4)	0 (0.0)
Colorectal cancer	74*	48 (64.9)	6 (8.1)	7 (9.4)	13 (17.6)

*The 74 colorectal cancer samples were the first samples available for each serial patient. These were not baseline samples.

Each laboratory should establish its own expected values for CEA as performed on the Dimension Vista® 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.