

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

**A. 510(k) Number:**

k100375

**B. Purpose for Submission:**

New device

**C. Measurand:**

CA19-9

**D. Type of Test:**

Quantitative, Sandwich chemiluminescent immunoassay

**E. Applicant:**

Siemens Healthcare Diagnostics Inc.

**F. Proprietary and Established Names:**

Dimension Vista® LOCI CA19-9 Flex® reagent cartridge

Dimension Vista® LOCI 7 Calibrator

**G. Regulatory Information:**

1. Regulation section:

21 CFR § 866.6010, Tumor-Associated antigen immunological test system

21 CFR § 862.1150, Calibrator

2. Classification:

Class II

3. Product code:

NIG - System, Test, Carbohydrate Antigen (CA 19-9) for Monitoring and Management of Pancreatic Cancer

JIT - Calibrator, Secondary

4. Panel:

Immunology (82)

Clinical Chemistry (75)

**H. Intended Use:**

1. Intended use(s):

The LOCI CA19-9 method is an in vitro diagnostic test for the quantitative measurement of the CA 19-9 tumor-associated antigen in human serum and lithium heparin and EDTA plasma on the Dimension Vista® System. Measurements of CA 19-9 are indicated for the serial measurement of CA19-9 to aid in managing patients diagnosed with cancers of the exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who have levels of serum CA 19-9 at some point in their disease process exceeding the median concentration determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined.

The LOCI 7 CAL is an in vitro diagnostic product for the calibration of the Cancer Antigen 19-9 (CA 19-9) method on the Dimension Vista® system.

2. Indication(s) for use:

Same as above

3. Special conditions for use statement(s):  
For Prescription Use Only
4. Special instrument requirements:  
Siemens Dimension Vista® System - device performance was established on the Dimension Vista® 1500 instrument.

**I. Device Description:**

The LOCI CA19-9 method is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated anti-CA 19-9 monoclonal antibody 1116-NS-19-9 fragment. The first bead reagent (Chemibeads) is coated with an anti-CA 19-9 monoclonal antibody (1116-NS-19-9) and contains a chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye.

The LOCI 7 calibrator is a liquid, frozen bovine serum albumin, based product containing CA 19-9 from human cell culture. The kit consists of ten vials, two vials per level (A-E), 2.0 mL per vial.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):  
ADVIA Centaur® CA 19-9 Assay  
ADVIA Centaur® Calibrator 9
2. Predicate 510(k) number(s):  
k031393
3. Comparison with predicate:  
LOCI CA 19-9 Flex® reagent cartridge:

Similarities and differences		
Item	Device	Predicate
Name	LOCI CA 19-9 Flex® reagent cartridge (k100375)	CA 19-9 Assay for the ADVIA Centaur System (k031393)
Intended Use	The LOCI CA 19-9 method is an in vitro diagnostic test for the quantitative measurement of the CA 19-9 tumor-associated antigen in human serum and lithium heparin and EDTA plasma on the Dimension Vista® System. Measurements of CA 19-9 are indicated for the serial measurement of CA 19-9 to aid in managing patients diagnosed with	The ADVIA Centaur CA 19-9 Assay is an in vitro immunoassay for the quantitative measurement of the CA 19-9 tumor-associated antigen, in human serum, using the ADVIA Centaur and ADVIA Centaur XP systems. This assay is indicated for the serial measurement of CA 19-9 to aid in the management of patients diagnosed with cancers of the

<b>Similarities and differences</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
	cancers of the exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who have levels of serum or plasma CA 19-9 at some point in their disease process exceeding the median concentration determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined.	exocrine pancreas. The test is useful as an aid in monitoring of disease status in those patients having confirmed pancreatic cancer who levels of serum CA 19-9 at some point in their disease process exceeding the median concentration determined for the apparently healthy cohort. CA 19-9 values must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined. This assay is not intended for use on any other system.
Sample Type	Serum, lithium heparin plasma and EDTA plasma	Serum
Measuring Range	2-1000 U/mL	1.2-700 U/mL
Sample Size	4 µL	75 µL
Measurement	Chemiluminescent: Homogeneous sandwich immunoassay based on LOCI® technology	Chemiluminescent: Two site sandwich immunoassay using direct chemiluminometric technology

LOCI 7 Calibrator:

<b>Similarities and differences</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
<b>Feature</b>	<b>LOCI 7 Calibrator (k100375)</b>	<b>ADVIA Centaur® Calibrator 9 (k031393)</b>
Intended Use	For the calibration of the Carbohydrate Antigen 19-9 (CA19-9) method on the Dimension Vista® System.	For calibrating ADVIA® Centaur or ACS:180® 19-9 assays.
Matrix	Bovine serum albumin-based matrix	Same
Preparation	Liquid: ready to use.	Lyophilized

Similarities and differences		
Item	Device	Predicate
Number of Calibrator Levels	5 levels Target Concentrations: CAL A: 0 U/mL CAL B: 30 U/mL CAL C: 131 U/mL CAL D: 525 U/mL CAL E: 1050 U/mL	Same
Storage	Store at -15° to -25°C	Store at 2° to 8°C

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

CLSI EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP06-A, Evaluation of the Linearity of Quantitative Measurement

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline

CLSI EP09-A2- Method Comparison and Bias Estimation Using Patient Samples; Approved Guidelines

CLSI EP17-A version 1 Protocols for Determination of Limits of Detection and Limits of Quantitation published 10/31/2004

**L. Test Principle:**

The LOCI CA19-9 method is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated anti-CA 19-9 monoclonal antibody 116-NS-19-9 fragment. The first bead reagent (Chemibeads) is coated with an anti-CA 19-9 monoclonal antibody (116-NS-19-9) and contains a 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-CA 19-9-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 diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the CA 19-9 concentration in the sample.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

a. *Precision/Reproducibility:*

- i) *Assay-Precision* testing for the CA 19-9 method was performed over twenty days according to CLSI/NCCLS EP5-A2. Data from 2 Flex® lots, 2 calibrator lots and 2 Dimension Vista® 1500 model instruments are included. The test samples consisted of three levels of Bio-Rad Liquichek Tumor Marker control, three serum pools and one to two plasma pools depending on the study site. Two of the serum samples and one of the plasma pools (Lithium heparin) were spiked with CA19-9 antigen. On

each day of testing, each sample was run in duplicate, in two separate runs (N=80). The duplicates were run with two separate sample cups. One site used instrument 41 and reagent lot 09260AD. The second site used instrument 190 and reagent lot 09198AC.

The range of samples tested encompassed the analytical measuring range. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2. This experiment allowed a determination of within-run precision (repeatability), within-day, between days, between runs (within lab) precision for each site and a determination of between site precision.

		Control Level 1 (54.5-57.1 U/mL)	Control Level 2 (159.8-169.4 U/mL)	Control Level 3 (400.6-417.3 U/mL)	Low Normal Serum (11.4-13.1 U/mL)	MDL Spike (40.7-41.2 U/mL)	LiHep Plasma Spike (367.7-380.9 U/mL)	EDTA Plasma (24.9 U/mL)	High Serum Spike (1006.3 U/mL)
Source	N	CV%	CV%	CV%	CV%	CV%	CV%	CV%	CV%
Between-Site plus Between-Lot Reproducibility	160	3.4	4.1	2.9	3.0	3.0	0.6	N/A	N/A
Within Lab (Site 1)	80	3.9	2.8	2.8	8.9	4.2	2.4	N/D	N/D
Within Lab (Site 2)	80	3.3	2.5	2.8	6.4	4.2	2.8	4.0	2.8
Between-day (Site 1)	80	2.2	0.8	1.5	5.1	3.2	1.9	N/D	N/D
Between-day (Site 2)	80	2.3	1.4	1.1	0.0	2.0	0.0	2.9	1.0
Between-run (Site 1)	80	2.2	1.6	1.6	4.4	0.3	1.0	N/D	N/D
Between-run (Site 2)	80	1.4	1.0	1.7	5.0	2.5	2.2	1.5	1.6
Repeatability (Site 1)	80	2.5	2.2	1.7	5.8	2.7	1.1	N/D	N/D
Repeatability (Site 2)	80	1.9	1.7	1.9	4.0	2.7	1.7	2.3	2.1

- ii) *Calibrator*-Precision testing for the CA 19-9 calibrators was performed over twenty days according to CLSI/NCCLS EP5-A2. Data from 3 calibrator lots, 2 replicate samples, over 20 days, on 3 Dimension Vista® 1500 model instruments. The test samples consisted of three levels of Bio-Rad Liquichek Tumor Marker control, two serum pools and two plasma pools. One of the serum samples and one of the plasma pools (Lithium heparin) were spiked with CA 19-9 antigen. On each day of testing, each sample was run in duplicate, on three instruments, calibrated from 3 different calibrator lots (N=360). The duplicates were run with two separate sample cups. This experiment used instruments Vista 145, 190, and 238; calibrator lots 9ED082, 9HD099, 9LD092; and reagent lot09260AD.

The range of samples tested covered the analytical measuring range. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2. This experiment allowed a

determination of within-run precision (repeatability), within-day, between days, between runs (within lab) precision for each site and a determination of between site precision.

Material	Mean U/mL	Standard Deviation (%CV)			
		Repeatability	Between-Run	Between-Day	Within-Lab
Control Level 1	54.5	1.34 (2.5)	1.21 (2.2)	1.19 (2.2)	2.15 (3.9)
Control Level 2	159.8	3.50 (2.2)	2.52 (1.6)	1.21 (0.8)	4.48 (2.8)
Control Level 3	400.6	6.97 (1.7)	6.55 (1.6)	5.81 (1.5)	11.19 (2.8)
Low Normal Serum	13.1	0.76 (5.8)	0.58 (4.4)	0.66 (5.1)	1.16 (8.9)
MDL Spike	40.7	1.10 (2.7)	0.13 (0.3)	1.31 (3.2)	1.72 (4.2)
LiHep Spike	377.7	4.32 (1.1)	3.75 (1.0)	7.12 (1.9)	9.13 (2.4)
EDTA	24.9	0.57 (2.3)	0.38 (1.5)	0.73 (2.9)	1.00 (4.0)
High Serum Spike	997.6	11.35 (1.1)	24.03 (2.4)	0.00 (0.0)	26.58 (2.7)

CA19-9 Multi-instrument/ multi-calibrator lot study						
Material	Mean U/mL	Standard Deviation (%CV)				
		Repeatability	Between-Instrument	Between-Calibrator	Between-Day	Total
Control Level 1	54.9	1.52 (2.8)	0.18 (0.3)	1.02 (1.9)	1.60 (2.9)	2.44 (4.4)
Control Level 2	159.1	2.28 (1.4)	0.78 (0.5)	2.91 (1.8)	3.62 (2.3)	5.23 (3.3)
Control Level 3	403.8	4.62 (1.1)	4.53 (1.1)	5.15 (1.3)	10.74 (2.7)	13.55 (3.4)
Sample A	13.9	0.64 (4.6)	0.71 (5.1)	0.30 (2.1)	1.64 (11.8)	1.92 (13.8)
Sample B	27.1	0.76 (2.8)	0.40 (1.5)	0.48 (1.8)	1.49 (5.5)	1.78 (6.6)
Sample C	270.9	2.58 (1.0)	0.48 (0.2)	4.33 (1.6)	6.33(2.3)	8.11 (3.0)
Spiked Serum	698.8	9.87 (1.4)	1.31 (0.2)	4.39 (0.6)	13.47 (1.9)	17.31 (2.5)
EDTA	26.2	0.69 (0.1)	0.54 (0.1)	0.47 (0.1)	1.42 (0.2)	1.74 (0.2)
Data was collected for twenty days, one run per day, two replicates per run, on three separate instruments, using three different calibrator lots on each instrument.						
The data was merged to form one data set for analysis and a variance component analysis using the REML method was performed.						

*b. Linearity/assay reportable range:*

- i) The linear range was determined according to CLSI EP06-A. Based on the results of this testing and that from the Limit of Detection Study, the analytical measuring range was established in serum. A study covering the whole assay range was performed using two natural serum samples. One sample with a low concentration (3.9 U/mL) and one with a high concentration (1198.3 U/mL), were mixed in varying proportions distributed over the measurement range. Each dilution was tested 5 times. Dimension Vista Flex assay data showed good correlation ( $R^2 > 0.999$ ) to sample concentration when evaluated using a weighted linear regression model. It was linear over the measured range, showing little constant or proportional bias, with linear regression analysis giving

$$y=1.026x +0.9$$

Additional patient samples within the assay range with CA 19-9 concentrations of 188 U/mL and 102 U/mL were diluted to evaluate low end linearity. Based upon measuring 5 replicates of the 188 U/mL sample diluted with water, the data provide a linear regression line of  $y=1.026x+1.1$  and  $R^2=0.997$  with 95% CI for the slope of 1.006 to 1.046 and for the intercept of -0.1 to 2.2.

ii) Spiking and Dilutional Recovery Studies

- a. Spiking Recovery: Known amounts of CA19-9, approximately 37, 73, 165, 620 and 970 U/mL, were added to serum samples with baseline CA19-9 values of 6.7 U/mL or 49.3 U/mL) and to plasma samples with baseline CA19-9 values of 2.8 U/mL (EDTA) or 3.3 U/mL (LiHeparin). The CA19-9 concentrations were measured and the percent recovery ranged from 92-114.3% for serum, 91.8-105.8 for EDTA plasma, and 99.3-115.5% for LiHeparin plasma. The highest biases in recovered values for LiHeparin Plasma were observed for measurements near the cut-off value.

**Dimension Vista® LOCI CA 19-9  
Value Recovery Following Spiking of Samples**

<b>Serum (49.3 U/mL)</b>			
<b>CA19-9 Spiked In U/mL</b>	<b>Expected U/mL</b>	<b>Recovered U/mL</b>	<b>% Recovery</b>
0.0	44.4	40.9	92.0
37.0	81.4	87.8	107.8
72.9	117.3	127.1	108.3
165.6	210.0	212.8	101.4
621.8	666.2	690.3	103.6
970.9	1015.3	1014.9	100.0

<b>Serum (6.7 U/mL)</b>			
<b>CA19-9 Spiked In U/mL</b>	<b>Expected U/mL</b>	<b>Recovered U/mL</b>	<b>% Recovery</b>
0.0	6.0	5.5	92.2
37.0	43.0	47.1	109.4
72.9	78.9	90.2	114.3
165.6	171.6	172.9	100.8
621.8	627.8	650.3	103.6
970.9	977.0	989.1	101.2

<b>EDTA (2.8 U/mL)</b>			
<b>CA19-9 Spiked In U/mL</b>	<b>Expected U/mL</b>	<b>Recovered U/mL</b>	<b>% Recovery</b>
0.0	2.5	2.6	102.5
37.0	39.6	39.7	100.4
72.9	75.5	79.9	105.8
165.6	168.1	155.9	92.7
621.8	624.3	581.6	93.2
970.9	973.5	893.9	91.8

<b>Lithium Heparin (3.3 U/mL)</b>			
<b>CA19-9 Spiked In U/mL</b>	<b>Expected U/mL</b>	<b>Recovered U/mL</b>	<b>% Recovery</b>
0.0	3.0	3.3	110.4
37.0	40.0	45.6	113.8
72.9	75.9	87.7	115.5
165.6	168.6	167.3	99.3
621.8	624.8	639.3	102.3
970.9	973.9	995.4	102.2

- b. Dilution recovery: Two serum samples with CA19-9 values of 1759.6 or 188.3 U/mL were diluted manually at 9:1, 4:1, 3:2, 1:1, 2:3, 1:4, 1:9, or 1:19 with reagent grade water and assayed for recovery. The recoveries ranged from 97.0-105.1% for the high sample and 99.8-102.3% for the low sample

**Dimension Vista® LOCI CA 19-9 Value Recovery Following Dilution of Samples**

<b>Sample</b>	<b>Dilution</b>	<b>Expected (U/mL)</b>	<b>Observed (U/mL)</b>	<b>% Recovery</b>
S1-1	neat	1759.6	1715.3	97.5%
S1-2	9:1	1583.6	1537.7	97.1%
S1-3	4:1	1407.7	1392.7	98.9%
S1-4	3:2	1055.8	1026.2	97.2%
S1-5	1:1	879.8	886.4	100.8%
S1-6	2:3	703.8	722.1	102.6%
S1-7	1:4	351.9	362.7	103.1%
S1-8	1:9	176.0	174.4	99.1%
S1-9	1:19	88.0	88.0	100.0%
S2-1	neat	188.3	188.3	100.0%
S2-2	9:1	169.5	169.2	99.8%
S2-3	4:1	150.6	152.6	101.3%
S2-4	3:2	113.0	113.9	100.8%
S2-5	1:1	94.2	95.8	101.7%
S2-6	2:3	75.3	77.1	102.3%
S2-7	1:4	37.7	38.4	102.1%

- iii) High Dose Hook Effect: Specimens were prepared by diluting two high CA19-9 human serum patient sample with deionized water to concentrations ranging from 95 to 1,230,509.5 U/mL for 1 sample and 89.1-1,152,955.2 U/mL for the second. The samples represented a large measurement range. The specimens were tested with one lot each of flex reagents on two different Vista instruments. No hook effect was observed for CA19-9 concentrations up to 1,230,509.5 U/mL.
- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
- i) Traceability  
There is no recognized standard for CA19-9.
  - ii) Calibrator  
The Dimension Vista® LOCI 7 Calibrator (KC605) is a frozen multi-analyte liquid containing Cancer Antigen19-9 purified from human colon adenocarcinoma tissue culture in 6% bovine albumin with buffer and preservatives. There are five levels (A-E) with target values of 0, 30, 131, 525 and 1050 U/mL.
    - a) Value assignment  
An anchor pool of purified CA19-9 is prepared and a value is assigned by comparing to patient samples assayed by the predicate device. The anchor pool is then diluted into a series of 5 Master pools whose values are determined on the Dimension Vista® system. The Master pool materials are then aliquoted into the commercial product whose values are confirmed using the Dimension Vista® System. The 5-level calibrators are then used to calibrate the Flex CA19-9 method.
    - b) Stability  
Frozen liquid calibrator stability is 12 months from the date of manufacture when stored unopened at -20°C. Thawed liquid calibrator stability is 30 days when stored unopened at 2-8°C. Once the vial stopper is punctured, the assigned calibrator values are stable for 30 days on board the Dimension Vista System. LOCI 7 calibrators should not be used on board the instrument once the cap is removed. One lot of control calibrator (reference material stored at -70°C) and three production lots of calibrator were tested. The acceptance criterion was <5% deviation from reference concentration for levels B-E.
  - iii) Kit Stability  
Shelf-life stability (expiration) dating assignment at commercialization reflects the real time stability data on file at Siemens Healthcare Diagnostics.
- d. *Detection limit:*  
Limits of blank (LOB) and limit of detection (LOD) were determined using 2 kit lots on 2 instruments (one per lot) using CLSI protocol EP17-A. Five low CA19-9 samples were tested using two lots on two Vista instruments. CA19-9 values in tested blank samples ranged from approximately -1.2 to 1.6 U/mL and standard deviation (SD) of 0.634. Samples with CA19-9 values ranging from 0.1.4 to 4.6

U/mL were used to estimate the limit of detection. Acceptance criteria for the LOB, LOD, and limit of quantitation (LOQ) were described as follows:

**LOB** – highest measurement result which has a 95% probability to be observed for a blank sample. It is the 95<sup>th</sup> percentile of a blank distribution. Where blank values are negative, this is estimated as  $1.645 \times \text{SD}$  of blank values. The data generated here give  $\text{LoB} = 1.645 \times 0.589 = 0.968$  which was rounded to  $\text{LoB} = 1.0 \text{ U/mL}$ .

**LOD** – lowest amount of analyte that can be detected with 95% probability, though not quantified at an exact value.  $\text{LoD} = \text{LoB} + \text{SD} \times \text{Cp}$  or  $1.00 + 0.589 \times 1.653 = 1.974$  which was rounded to  $\text{LoD} = 2.0 \text{ U/mL}$

**LOQ** – lowest actual amount of analyte that can be reliably detected and at which total error meets lab requirements for accuracy. LOQ was not claimed for the Dimension Vista CA19-9 assay.

The results are noted to support a claim for LOB of less than 1.0 U/mL and of LOD of less than 2.0 U/mL. Therefore, the lowest value for the range of the assay is 2.0 U/mL.

e. *Analytical specificity:*

Interference testing was performed according to CLSI/NCCLS EP7-A2 to determine the effect of various endogenous and exogenous substances on the Dimension Vista® CA19-9 assays. For all interferents the percent bias was determined by testing a control serum sample without the interferent and compared to the value obtained from a test sample to which the potential interferent had been added.

i) Endogenous Substance Interference

Testing was performed at two CA19-9 concentrations: 40 U/mL and 110 U/mL with two lots of Flex® reagents. Bias exceeding 10% is considered interference. Results for hemoglobin, triglyceride, bilirubin and intralipid are summarized below:

Substance tested	Substance concentration	LOCI CA19-9 U/mL	Bias %
Hemoglobin (hemolysate)	Hemoglobin (monomer) 600 mg/dL [0.369 mmol/L]	41.4- 42.1	<10
		101-102.3	<10
Bilirubin (unconjugated)	20 mg/dL [342 µmol/L]	43.0 -44.2	<10
		106.6-106.9	<10
Bilirubin (conjugated)	20 mg/dL [342 µmol/L]	43.4-43.7	<10
		106.9-107.3	<10
Lipemia (Intralipid)	3000 mg/dL [33.9 mmol/L]	40.8-41.6	<10
		101.8-105.5	<10
Triglycerides	1134 mg/dL [12.8 mmol/L]	47.1-49.0	<10
		114.8-115.7	<10

Eight additional endogenous substances include serum proteins were also tested with bias <10%.

- ii) Exogenous Substance Interference  
62 exogenous substances were tested for interference including common over-the-counter drugs and cancer drugs. All recorded biases were less than the 10% acceptance criteria.
- iii) HAMA interference  
A number of optimized concentrations of HAMA blockers are employed in the reaction, as well as reagents designed to minimize non-specific binding (NSB) interference. Interference from HAMA was evaluated by testing commercially available sera (three replicates) containing up to 327.1 mg/mL HAMA. All of the CA19-9 results from the 10 samples evaluated were within 10% of control values or showed <1 U/mL difference from control.
- iv) Method Cross-Reactivity  
Five tumor-marker proteins were added to two human serum samples containing 38 or 100 U/mL CA19-9.

Substance	[Test] Mg/dL	[Test] S.I. Units	Bias (%) at 38 U/mL	Bias (%) at 100 U/mL
CA125	1000 U/mL	1000 U/mL	3.8%	0.6%
CA15-3	100 U/mL	100 U/mL	10.0%	0.8%
CEA	1000 µg/L	1000 µg/L	9.0%	1.9%
AFP	300 µg/L	300 µg/L	0.7%	-1.4%
PSA	100 µg/L	100 µg/L	1.4%	0.4%

*f. Assay cut-off:*

For the Dimension Vista® LOCI CA 19-9 assay, the reference change value (RCV) was used to determine if a significant change occurred. The RCV was chosen to ensure that the change in CA19-9 value is not attributed to assay variation or normal biological variation. The RCV value also considers a z value for significant change (p,0.05), so that assay results that change by more than the RCV should be within the 95% confidence interval of significant changes in CA19-9 levels.

The RCV was derived by taking into account the published biological variation<sup>19</sup> and total imprecision for the Dimension Vista® LOCI CA 19-9 assay. In determining the RCV, the analytical variation used was 13.8% (which is the reported total variability (Within laboratory Total %CV) at 13.9 U/mL). The within-subject biological variation (27.2%) was obtained from the literature. The RCV for the Dimension Vista® LOCI CA 19-9 method was calculated to be 84.7%.

2. Comparison studies:

a. *Method comparison with predicate device:*

One serum sample randomly chosen from each of the 75 men and women with pancreatic cancer who were tested for the monitoring of their disease status were

combined with 218 excess de-identified serum samples containing measureable CA19-9. Each sample was assayed for the observed values (293 samples) using the Dimension Vista® CA 19-9 (Y) assay and compared with the expected values using the Advia Centaur® CA19-9 (X). The results obtained are presented below (Passing & Bablock). The equation represents the relationship between the two techniques.

n = 293

Y = 1.12X -5.71, R<sup>2</sup>=0.787

95% Confidence interval for the intercept: -6.79 to -4.73

95% Confidence interval for the slope: 1.08 to 1.16

Range of samples: 2.0 - 836.3 U/mL (Dimension Vista);  
3.3 - 672 U/mL (Advia Centaur)

Comparative Method	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient	n
Dimension Vista® CA 19-9 To Advia Centaur® CA19-9	1.12 (1.08 to 1.16)	-5.71 (-6.79 to -4.73)	0.787	293

- b. *Matrix comparison:* The Dimension Vista Flex Assay for CA19-9 was evaluated in serum, LiHeparin plasma, and EDTA plasma.
- i. Serum samples were evaluated with matched samples of Lithium Heparin plasma. The two matrices were evaluated with 60 samples over the measuring range of the device (linear regression line  $y=1.013x - 1.649$  and  $R^2=0.989$ ).
  - ii. Serum samples were evaluated with matched samples of EDTA plasma. The two matrices were evaluated with 63 samples over the measuring range of the device (linear regression line  $y=0.9754x + 0.4812$  and  $R^2=0.997$ ).
3. Clinical studies:  
For the clinical evaluation, thirty eight (38) retrospective and thirty four (34) prospectively collected serial serum sample sets from pancreatic cancer patients purchased from two sample banks, were tested. Samples were selected for age (range 45.4 years old to 69.5 years old), ethnicity and stage of disease (stage 1 through IV). For each patient, at least 3 serum samples were collected during the course of follow-up surveillance for pancreatic cancer progression. Clinical information that details the status of the subject's disease was required for inclusion of samples in the study.  
Changes in CA 19-9 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 (medical imaging, physical examination, and other clinical investigations). All 72 patient sets were analyzed to determine the change in disease status per sequential pair (n = 189). Table below shows the distribution of results when compared to the disease status.

**Disease State Frequency using the  
Dimension Vista® LOCI CA 19-9 Method**

Change in CA19-9	Change in Disease State				Total
	Responding N (%T)	Stable N (%T)	No Evidence of Disease N (%T)	Progression N (%T)	
>84.7% increase	3 (1.6%)	10(5.3%)	0 (0.0%)	14(7.4%)	27 (14.3%)
No significant Change	44(23.3%)	50(26.5%)	8(4.2%)	59(31.2%)	161 (81.5%)
>84.7% decrease	0(0.0%)	0(0.0%)	1(0.5%)	0(0.0%)	1 (3.2%)
<b>Total</b>	<b>47 (24.9%)</b>	<b>60 (31.8%)</b>	<b>9 (4.7%)</b>	<b>73 (38.6%)</b>	<b>189 (100.0%)</b>

For the Dimension Vista® LOCI CA 19-9 assay, the reference change value (RCV) was used to determine if a significant change occurred. A change of 15% was considered to be significant for the predicate method (ADVIA Centaur® CA19-9 assay). This value was obtained from the manufacturer’s published insert sheet.

Per patient visit clinical performance results for the Dimension Vista® LOCI CA 19-9 test and predicate devices are given in the following two tables. In this evaluation, disease status was classified as “Progression” and “No Progression” with “No Progression” consisting of responding, stable, and no evidence of disease. Using a cut-off of  $\geq 84.7\%$  rise in CA19-9 value, 19.2% of subject visits (95% confidence interval 10.9% to 30.1%) had a rise in CA19-9 value when the patient’s disease status was classified as progression. This value represents the positive percent agreement of significant CA19-9 rise with a clinical disease status classified as progression. Using a cut-off of a  $\geq 84.7\%$  rise in CA19-9 value, 88.8% of subject visits (95% confidence interval 81.6% to 93.6%) had no rise in CA19-9 value when the patient’s disease status was classified as no progression. This value represents the negative percent agreement of CA19-9 rises with a progressive disease status.

**Dimension Vista® LOCI CA 19-9 Value vs. Disease Progression**

	<b>Progression</b>	<b>No-Progression</b>	<b>Total</b>
<b>&gt;84.7% increase</b>	<b>14</b>	13	27
<b><math>\leq 84.7\%</math> increase</b>	59	<b>103</b>	162
<b>Total</b>	73	116	<b>189</b>
		<i>Estimate</i>	<i>Exact 95% Confidence Limits</i>
<b>Total Concordance</b>		61.9%	(54.6% - 68.9%)
<b>Positive Concordance</b>		19.2%	(10.9% - 30.1%)
<b>Negative Concordance</b>		88.8%	(81.6% - 93.9%)

The positive and negative agreement for the FLEX CA19-9 method, when taken together, show similar performance to the predicate method (below):

**Predicate CA 19-9 Value vs. Disease Progression**

	<b>Progression</b>	<b>No-Progression</b>	<b>Total</b>
<b>&gt;15% increase</b>	<b>29</b>	35	64
<b>≤15% increase</b>	44	<b>81</b>	125
<b>Total</b>	73	116	<b>189</b>
		<i>Estimate</i>	<b>Exact 95% Confidence Limits</b>
<b>Total Concordance</b>		58.2%	(50.8% - 65.3%)
<b>Positive Concordance</b>		39.7%	(28.5% - 51.9%)
<b>Negative Concordance</b>		69.8%	(60.6% - 78.0%)

4. Clinical cut-off:

Clinical Cut-off is based upon a 84.7% reference change value (RCV). When the measurement of CA19-9 varies by >84.7% of the baseline measurement (either positive or negative) the change is considered significant. The RCV was used to ensure that the change in CA19-9 value is not attributed to assay variation or biological variation. This percent variation represents values within the 95% confidence interval for real alteration in CA19-9 values above system noise.

5. Expected values/Reference range:

The distribution of CA19-9 values was determined in specimens from healthy individuals (n= 300; males and females) and from patients with nonmalignant or malignant diseases. 98.7 % of 300 samples from apparently healthy adults (age 45.4 to 69.5 years) had CA19-9 levels less than or equal to 37 U/mL. Each laboratory should establish its own reference values for healthy patients' CA19-9 levels as performed on the Dimension Vista® System.

Expected values of CA19-9 measurements are dependent upon the individual patient's baseline reading for CA19-9. Decreases from baseline value of 84.7% or more in subsequent repeated measurements are indicative of response to therapy or remission. Increases of 84.7% or more suggest no response to therapy and are weakly correlated with progression of disease.

Estimation and empirical distributions of CA19-9 values in various populations of subjects was performed. The distribution of CA19-9 values in 300 apparently healthy individuals, 200 patients with nonmalignant and 398 patients with malignant disease is shown in the tables below.

<b>Non-malignant Disease and Healthy Normal: # of Patients (%Patients) with CA19-9 level U/mL</b>							
<b>Sample Category</b>	<b>n</b>	<b>0 - 37 (%)</b>	<b>37.1 - 60 (%)</b>	<b>60.1 - 120 (%)</b>	<b>120.1 - 500 (%)</b>	<b>500.1 - 1000 (%)</b>	<b>&gt;1000 (%)</b>
Healthy Normal	300	296 (98.7)	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Healthy Normal are Males and Females							
<b>Non-malignant Diseases</b>							
Breast	30	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polycystic Ovaries	15	15 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cervix / Uterus	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GI Tract	20	18 (90.0)	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
Ovarian Cyst	15	14 (93.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
UTI	30	29 (96.7)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
Pancreas	27	20 (74.1)	0 (0.0)	4 (14.8)	3 (11.1)	0 (0.0)	0 (0.0)
Colon	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congestive Heart Failure	20	19 (95.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Malignant Diseases</b>							
Breast	31	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian	54	40 (74.1)	2 (3.7)	5 (9.3)	4 (7.4)	0 (0.0)	3 (5.6)
Cervix / Uterus	41	38 (92.7)	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver*	23	11 (47.8)	1 (4.3)	3 (13.0)	0 (0.0)	4 (17.4)	4 (17.4)
Colorectal	41	38 (92.7)	0 (0.0)	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic	105	32 (30.5)	7 (6.7)	5 (4.8)	19 (18.1)	8 (7.6)	34 (32.4)
Lung	30	22 (73.3)	1 (3.3)	1 (3.3)	4 (13.3)	0 (0.0)	2 (6.7)
Lymphoma	30	24 (80.0)	0 (0.0)	1 (3.3)	3 (10.0)	2 (6.7)	0 (0.0)
Prostate/Testicle	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper GI*	13	9 (69.2)	2 (15.4)	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)
Renal	2	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Liver\* = Gall Bladder, Bile Duct

Upper GI\* = Oral, Larynx, Esophagus, Stomach

**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.