510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k080561

B. Purpose for Submission:
New device

C. Measurand:
Cancer Antigen 125 (CA125)

D. Type of Test:
Quantitative, Enzyme Linked Fluorescent assay (ELFA)

E. Applicant:
BioMérieux, Inc.

F. Proprietary and Established Names:
VIDAS® CA 125 II™

G. Regulatory Information:
1. Regulation section:
   21 CFR 866.6010 Tumor-associated antigen immunological test system
2. Classification:
   Class II
3. Product code:
   LTK, Test, Epithelial Ovarian Tumor-Associated Antigen (CA125)
4. Panel:
   Immunology (82)

H. Intended Use:
1. Intended use(s):
   VIDAS® CA 125 II is an automated quantitative test for use on the VIDAS instruments, for the measurement of OC 125 reactive antigenic determinants in human serum using the ELFA technique (Enzyme Linked Fluorescent Assay). The VIDAS CA 125 II is indicated for the serial measurement of OC 125 reactive antigenic determinants as an aid in the monitoring of patients previously diagnosed with ovarian cancer for disease progression or response to therapy. The VIDAS CA 125 II assay can also be used as an aid in the detection of recurrence in previously treated ovarian cancer patients.

2. Indication(s) for use:
   Same as Intended Use
3. Special conditions for use statement(s):
   Prescription use only
4. Special instrument requirements:
   VIDAS and Mini VIDAS instrument systems

I. Device Description:
The device is an *in vitro* diagnostic device using an automated fluorescent immunoassay test principle for the quantitative measurement of CA 125 on VIDAS instruments using human serum specimens. Each VIDAS CA 125 kit contains reagents sufficient for 30 tests. The kit is comprised of 30 CA 125 II strips, 30 CA 125 II SPRs (Solid Phase Receptacle), CA 125 II

control ((2 mL, lyophilized) containing human serum + OC 125 antigenic determinants (human origin) + chemical stabilizers), CA 125 II calibrator ((3 mL lyophilized) containing human serum + OC 125 antigenic determinants (human origin) + chemical stabilizers), CA 125 II diluent ((5 mL, liquid) reagent to use containing bovine serum albumin protein and sodium azide), one MLE (Master Lot Entry) card and one package insert.

J. Substantial Equivalence Information:
  1. Predicate device name(s):
     Tosoh Medical, Inc. ST AIA-Pack CA 125 Enzyme Immunoassay
  2. Predicate 510(k) number(s):
     k023891
  3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	VIDAS CA 125 II Assay	Tosoh ST AIA-Pack CA 125
Technology	Enzyme immunoassay technology using 2 antibodies in a sandwich immunoassay format	Same
Specimen	Serum	Same
Analyte	CA 125	Same
Antibody	Mouse monoclonal anti-CA 125	Same
Assay Principle	Two antibody "sandwich" binding of CA 125 antigen. One antibody is bound to a solid phase and the second antibody is in liquid form and is labeled with fluorescent compound	Same
Automated	Yes	Same

Differences		
Item	Device	Predicate
	VIDAS CA 125 Assay	Tosoh ST AIA-Pack CA 125
Indications for use	The VIDAS CA 125 II is indicated for the serial measurement of OC 125 reactive antigenic determinants as an aid in the monitoring of patients previously diagnosed with ovarian cancer for disease progression or response to therapy. The VIDAS CA 125 II assay can also be used as an aid in the detection of recurrence in	ST AIA-PACK CA 125 is to be used as an aid in monitoring response to therapy for patients with epithelial ovarian cancer. Serial testing for patient CA 125 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer

	previously treated ovarian cancer patients.	
Traceability/ Standardization	Master curve for each kit lot and each calibrator lot are traceable to working standards established by bioMérieux, Inc. and value assigned by the Fujirebio Diagnostics, Inc. radioimmunoassay method	Each calibrator lot are traceable to internal reference standards
Measurement range	4.00 to 600.00 U/mL	2.0 to 1000 U/ml
Assay Technique	Enzyme-linked fluorescent assay (ELFA)	Two-site immunoenzymetric assay
Sample Volume	200 μL	100 μL
Limit of detection	4 U/mL	2.0 U/mL

K. Standard/Guidance Document Referenced (if applicable):
CLSI EP5-A2; Evaluation of Precision Performance of quantitative measurement methods; Approved Guideline – Second Edition. Modifications included 2 lots, 3 sites and 2 calibration cycles within the 20 day period.

CLSI EP17-A; Protocols for the determination of limits of detection and limits of quantitation; Approved Guideline. Modifications were the use of 1 blank sample (the zero standard) to determine Limit of Blank (LOB).

CLSI EP7-A2; Interference testing in clinical chemistry

CLSI EP6-A; Evaluation of linearity of quantitative measurement procedures: A statistical approach; Approved Guideline

L. Test Principle:
The assay principle combines a 2-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA).

The Solid Phase Receptacle (SPR®) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times. The sample is cycled in and out of the SPR several times. This operation enables the monoclonal M11 antibody fixed onto the interior wall of the SPR to capture the reactive antigenic determinants present in the sample. Unbound components are eliminated during the washing steps. Alkaline phosphatase labeled monoclonal OC 125 antibody (conjugate) is then incubated in the SPR where it binds with the OC 125 reactive antigenic determinants. Unbound conjugate is then eliminated during the washing steps. During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the

concentration of OC 125 reactive antigenic determinants present in the sample. At the end of the assay, results are automatically calculated by the instrument in relation to the calibration curve stored in memory, and then printed out.

M. Performance Characteristics (if/when applicable):
1. Analytical performance:
   a. *Precision/Reproducibility:*
   Three serum samples were tested in duplicate in 40 different runs (2 runs per day over 20 sequential days) with 2 reagent lots using one instrument at each of three sites (N = 480). The between-site precision, between-lot precision, between-recalibration precision, between-day precision, between-run precision, repeatability (within-run precision) and total precision (within-run, between-run, between-day, between-recalibration, between-lot and between-site) were calculated using a modified (2 lots, 3 sites and 2 calibration cycles within the 20 day period) protocol, which was based on the recommendations of CLSI® EP5-A2:

Source	N	Pool A (389 U/mL)	Pool B (75.3 U /mL)	Pool C (18.9 U /mL)
		CV (%)	CV (%)	CV (%)
Between-site	480	4.15	2.13	2.43
Between-lot	480	1.01	0.00	0.79
Between-recalibration	480	1.87	2.26	1.96
Between-day	480	0.00	1.08	0.74
Between-run	480	0.99	2.00	1.79
Within-run	480	3.40	3.50	3.35
Total	480	5.85	5.20	5.03

   b. *Linearity/assay reportable range:*
   The VIDAS® CA 125 II kit linearity and recovery after dilution were studied according to a protocol based on the recommendations of the document CLSI® EP06-A [17].

   Linearity range: two natural serum samples, one with a low concentration (5 U/mL) and one with a high concentration (~700 U/mL), were mixed in varying proportions distributed over the measurement range. Each dilution was tested in duplicate. VIDAS CA 125 II was linear over the entire measurement range.

   Dilution: Using the kit diluent, four patient samples (three > 600 U/mL and one close to 50 U/mL) were diluted up to 1/20. Each dilution was tested in duplicate. VIDAS CA 125 II assay was linear over the entire measurement range.

   Hook Effect: Specimens were prepared by spiking serum with CA 125 antigen from 50 to 200,000 U/mL. The samples represented a large measurement range and four were within the measurement range. The specimens were tested with two lots of

VIDAS CA 125 kits. No hook effect was observed for CA 125 concentrations up to 200,000 U/mL.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceability. Assay calibrators are traceable to working standards established by bioMérieux with values assigned by Fujirebio Diagnostic Inc. radioimmunoassay method.

Stability. Lyophilized calibrator and control stability is 12 months when stored at 2-8ºC. Reconstituted calibrator and control stability is 2 weeks when stored at 2-8ºC or 7 months when stored at -25 ± 6ºC. The frozen calibrator was demonstrated to be able to undergo up to five freeze/thaw cycles. One lot of control and calibrator was tested. The acceptance criterion was target concentration plus 3 standard deviations. Values of Calibrators and controls. The values for each kit lot are indicated on the Master Lot Entry (MLE) card included in each kit lot.

d. *Detection limit:*
Limits of blank, detection, and quantitation were determined using 2 kit lots on 2 instruments (one per lot) using CLSI protocol EP17-A. Five low CA 125 samples were tested using two lots on two VIDAS instruments. Tested CA 125 values ranged from approximately 0.0 to 0.3 U/mL. Samples ranging from 0.2 to 0.3 U/mL were used to estimate the limit of detection. Acceptance criteria for the limit of blank, detection, and quantitation were described as follows:
- Limit of blank (LOB) – highest measurement result which has a 95% probability to be observed for a blank sample. It is the 95th percentile of a blank distribution
- Limit of detection (LOD) – lowest amount of analyte that can be detected with 95% probability, though not quantified at an exact value.
- Limit of quantitation (LOQ) – lowest actual amount of analyte that can be reliably detected and at which total error meets lab requirements for accuracy.

The results are noted to support a claim for LOB, LOD and LOQ of less than 4 U/mL. Therefore, the lowest value for the range of the assay is 4 U/mL.

e. *Analytical specificity:*
Hemoglobin, triglyceride, bilirubin, human albumin, rheumatoid factor, HAMA, and 27 drug interferents were evaluated for interference when added to a human serum pool containing approximately 75.29 ± 20.64 U/mL of CA 125.

Three samples, one of low CA125 concentration and two positive CA 125 (spiked into a low sample) samples were prepared and split into 2 aliquots each. One aliquot was spiked with hemoglobin, triglyceride, or bilirubin and the other with a corresponding volume of buffer. Five intermediate CA 125 concentrations, derived from the highest and lowest CA 125 concentrations, were prepared by mixing varying amounts of the two aliquots. Hemoglobin concentrations ranged from 0 to 312

Umol/L. Triglyceride concentrations ranged from 0 to 30 g/L. Bilirubin concentrations ranged from 0 to 513 Umol/L. Aliquots of each concentration were tested in single replicates in 2 runs. The linear regression line coefficients were calculated for the mean CA 125 concentration at each interfering substance concentration. The hypothesis that the slope of the best fit line was zero was tested. If the slope is not equivalent with 0 with a probability < 0.05 then there is interference in the assay from the tested substance and testing must be repeated with lower concentrations of interfering substance. As acceptance criteria, there must be no effect from hemoglobin for concentrations less than 300 Umol/L, no effect from triglycerides for concentrations less than 30 g/L, and no effect from bilirubin at concentrations less than 364 Umol/L.

For hemoglobin concentrations ranging from 0 to 312 Umol/L, three different CA 125 concentrations were within the CA 125 specification range in the presence and absence of hemoglobin. The 95% confidence intervals of the slope of the best fit line of CA 125 concentration and hemoglobin concentration all included zero in the confidence interval

For triglyceride concentrations ranging from 0 to 30 g/L, three different CA 125 concentrations were within the CA 125 specification range in the presence and absence of triglyceride. Additionally, the 95% confidence intervals of the slope of the best fit line of CA 125 concentration and triglyceride concentration all included zero in the confidence interval with one exception.

For bilirubin concentrations ranging from <2 to 513 Umol/L, three different CA 125 concentrations were within the CA 125 specification range in the presence and absence of bilirubin. Additionally, the 95% confidence intervals of the slope of the best fit line of CA 125 concentration and bilirubin concentration all included zero in the confidence interval Interference with human albumin, rheumatoid factor, and human anti-mouse antibodies (HAMA) was evaluated at a separate site during clinical study testing for precision. A modified variation of CLSI document EP7-A2 was used. The 3 interferents were added to a human serum pool containing known CA 125 concentration (75.29 $\pm$ 20.64 U/mL of CA 125.). The acceptance criterion was no interference if the test sample (%recovery was within the range 90% to 110% (i.e. $\pm$ 10% of 100% recovery). No interference was seen with human albumin or HAMA, or rheumatoid factor at 100.5 IU/mL.

For human albumin and HAMA, no interfering effect was seen up to 150 mg/mL albumin and up to 100.4 IU/mL HAMA. **Interference was seen with RF at 2400 IU/ml. The limitations section of the labeling will reflect this interference.** Interference with various chemotherapeutic drugs was evaluated at a separate site during clinical study testing for precision. A modified variation of CLSI document EP7-A2 was used. Twenty-seven drug interferents were added to a human serum pool containing a known CA 125 concentration (75.29 $\pm$ 20.64 U/mL of CA 125.) and tested in three assay runs. The drugs tested represent drugs typically used in treatment and over-the-counter (OTC) drugs.

The following drugs were tested:

Tested interfering drugs

5-fluorouracil	Acetaminophen
N-acetyl-L-cysteine	Acetylsalicylic acid
Ampicillin	Ascorbic acid
Bleomycin	Carboplatin
Cefoxitin	Cisplatin
Cyclophosphamide	Cyclosporine
Dactinomycin	Doxicycline
Doxorubicin	Etoposide
Ibuprofen	Levodopa
Methotrexate	Metronidazole
Mitomycin C	Naprosyn
Paclitaxel	Phenylbutazone
Rifampicin	Vinblastine
Vincristine	

The acceptance criterion is a ratio of test sample to control between 0.9 and 1.10. No significant interference was noted for other tested drugs. All %recoveries were between 0.9 and 1.1 with the exception of Cisplatin. Cisplatin showed no significant interference at a concentration of 0.1 mg/mL.

Cross-reactivity with beta-HCG, AFP, CEA, CA19-9, CA 15-3, Prostate-specific antigen (PSA), was assessed using samples serving as calibrators in respective TOSOH assays at its designated concentration. A human serum-based diluent served as a blank. The samples and concentrations tested are:

- Beta-HCG - 206 mIU/mL
- AFP - 201 ng/mL
- CEA -49.6 ng/mL
- CA19-9 - 423 U/mL
- PSA - 52 ng/mL
- CA 15-3 (453.6 U/mL)

All samples gave no CA 125 value, which was the acceptance criterion for this analysis.

f. *Assay cut-off:*

The sponsor defined a $\geq$10.25% percentage change in CA 125 values as significant. This significant change is 2.5 times the total imprecision of the CA125 assay across sites, lots, and concentration (expressed as %CV = 4.10%). The sponsor chose this value to ensure that the change in CA 125 value is not attributed to assay variation. To test this cutoff choice, 333 samples from 77 evaluable serial sets collected from women with confirmed ovarian cancer were tested. The ethnic variation of the evaluable women consisted of Caucasian (86%), Hispanic (10%), and Asian (4%). The average age of women at the time of diagnosis was 56 years (median: 56.0 years, SD = 14.1 years). The distribution of stage disease at time of diagnosis was approximately; 10% at Stage I, 3% at Stage II, 67% at Stage III, and 20% at Stage IV.

Disease progression was determined by the subject's physician based on any or a composite of all of the following:

(1) Examination of the patient for clinical signs and symptoms, including the results of laboratory tests that are current standard of care for the assessment of ovarian cancer disease status.

(2) Examination of radiographic findings (imaging) ordered as standard of care that can be used for the assessment of ovarian cancer disease status. Radiographic findings include results from CAT scans, PET scans, MRI and x-Ray images as well as Ultrasound.

(3) Interviews with the subjects as to how she felt and any symptoms she experienced, how the subject felt compared to previous time intervals, etc.

An analysis of the choice of cutoff (as defined in terms of percent change between 2 successive Vidas CA125 II results) was performed using 256 evaluable visit pairs. The percent change as cutoff is informative when the lower bound of the 95 % confidence interval of the sum of positive and negative percent agreement exceeds 100%. Presented below is a table of several percent changes and their corresponding Positive and Negative Percent Agreements from the analysis as examples of what might be expected with using different criteria to assess change based on the CA125 II results.

Percent Change Between Two Consecutive Visits	Positive Percent Agreement	Negative Percent Agreement	The Lower Bound of the 95% Confidence Interval of the Sum of Positive and Negative Percent Agreement
$\geq$3.0%	70.65%	62.80%	121.6
$\geq$10.25%	70.65%	68.00%	126.7
$\geq$25.2%	67.39%	71.34%	127
$\geq$68.6%	55.43%	80.49%	123.9

As can be seen in the above table, the chosen cutoff of $\geq$10.25% is very near the maximum lower bound of the 95% confidence interval of the sum of positive and negative percent agreement. This means that this cutoff gives very near to maximal positive plus negative agreement.

2. Comparison studies:
   a. *Method comparison with predicate device:*
      Study Design. One serum sample randomly chosen from each of the 77 women with ovarian cancer tested for the monitoring of the disease status (77 samples) and for the expected values (133 samples) using the VIDAS® CA 125 II (Y) assay were compared with another commercially available CA 125 II assay (X). The results obtained are presented below (Deming). The equation represents the relationship between the two techniques.

      n = 210

      Y = 0.93X – 58.10

      95% Confidence interval for the intercept: -169.15 to 52.95

      95% Confidence interval for the slope: 0.61 to 1.25

Range of samples: 4.0 – 31801 U/mL (VIDAS); 2.0 – 29940 U/mL (another commercially available assay).

b. *Matrix comparison:*
Not applicable since only serum specimens are utilized.

3. Clinical studies:

a. *Clinical Sensitivity and Specificity:*
In a study of 77 subjects with at least 3 serum samples collected during the course of follow-up surveillance for ovarian cancer progression, 333 visits were cross-tabulated with a change in VIDAS CA 125 II concentration of ≥10.25% at each surveillance visit. At each visit, any or a composite of physical signs/symptoms, results of lab tests for colorectal cancer, radiographic findings (CAT scans, PET scans, MRI, x-ray, or ultrasound), or patient reported symptoms were utilized by a physician to determine disease status. Using a cut-off of ≥10.25% rise in CA125 II value, 70.65% of subject visits (95% confidence interval 60.87% to 79.35%) had a rise in CA 125 II value when the patient's disease status was classified as progression. This value represents the positive percent agreement of CA 125 II rise with a progression disease status.

Using a cut-off of a ≥10.25% rise in CA125 II value, 67.68% of subject visits (95% confidence interval 60.36% to 75.0%) had no rise in CA 125 II value when the patient's disease status was classified as no progression. The sponsor stated that this value represents the negative percent agreement of CA 125 II rises with a progressive disease status.

b. *Other clinical supportive data (when a. is not applicable):*
Samples utilized in this study were obtained from retrospective sample banks at M.D. Anderson Cancer Center. Specimens for the study were from subjects with ovarian cancer. Serial sets must include a minimum of 3 draws (4 draws or more desired) per subject. Samples were blood draws performed at or after diagnosis throughout as much of the clinical course as possible. Clinical information detailing the disease status for each sample and information on types of therapy, if any, received with dates of administration was collected. Three hundred and thirty-three (333) specimens from 77 subjects were collected. There were 256 evaluable observation pairs. The mean number of serial specimens per subject was 4.32. Of the serial samples from 77 subjects, 31.2% of subjects had 3 visits, 32.5% had 4 visits, 20.8% had 5 visits, 10.4% had 6 visits, 3.9% had 8 visits and 1.3% had 9 visits. The mean age at diagnosis was 56 years. Eighty-six percent of subjects were Caucasian, 4% Asian, and 10% Hispanic. Approximately 88% were stage III and IV subjects. Stage I, and II represented the remainder. Localized stage is stage I and II. Regional stage corresponds to stage III, and distant stage corresponds to stage IV.

The outcome of interest was defined as progression of disease from time point i (clinical visit i, $i=1$ to n-1) to a succeeding time point j (clinical visit j, $j=i+1$ to n). The number of clinical visits for which samples and data are available is defined as n. The visit number made by a study subject is at the time of diagnosis or after diagnosis

and prior to death, loss to follow-up or remission of disease. The sponsor statistically defines w_{ij} as a variable representing disease progression and has 2 values as follows:

1 if there is disease progression from visit i to visit j

0 if no progression (stable disease, response to therapy) from visit i to visit j

Disease progression is determined by the subject's physician and is based on any or a composite of physical signs/symptoms, results of lab tests for colorectal cancer, radiographic findings (CAT scans, PET scans, MRI, x-ray, or ultrasound), or patient reported symptoms.

The sponsor defines the variable v_{ij} as 1 if the difference in value of the test assay at visit i (x_i) and value of the test assay at a later visit j (x_j) is greater than or equal to 12.2% (i.e. $v_{ij} = 1$ if $(x_j - x_i) \geq 12.2\%$). The variable v_{ij} is 0 if the difference is otherwise (i.e. $v_{ij} = 0$ if $(x_j - x_i) < 12.2\%$). The sponsor chose this value to ensure that the change in CA125 value is not attributed to assay variation and is statistically significant. In the same way, the percentage change in the predicate device was defined as 2.5 times the %CV of total imprecision as stated in the predicate package insert. This value was 2.5 x 4% = 10% change.

To determine an association between the variables w (disease progression) and v (change in CA 125 value) a 2 x 2 contingency table can be constructed to find an association between variables. Items in each of the 4 cells represent pairs of v and w (1 and/or 0) for visits for all subjects (or for subjects only). The total concordance from the 2 x 2 contingency table (equivalent with total agreement), positive concordance, and negative concordance can be calculated. In each situation, it is assumed that agreement is with physician determined disease progression or no progression. No specification for concordance values was present. A similar definition and association will be sought for the predicate device for comparison purposes.

The table and calculation of agreement values for the association of the proposed test with disease state across all patient visits for all subjects is the following:

VIDAS CA 125 II	Change in disease state (variable w) to		
Change in CA 125 (variable v)	Progression	No progression	Total
$\geq 10.25\%$	65	53	118
$< 10.25\%$	27	111	138
Total	92	164	256

Positive percent agreement measures the percent of visits when a percent change in VIDAS CA 125 value exceeds $\geq 10.25\%$ relative to same measurement at previous visit and there is a corresponding patient disease status of progression at this visit. The Positive percent agreement is 70.6% (65/92) with a 95% CI: 60.87% to 79.35%.

Negative percent agreement measures the percent of visits when a percent change in VIDAS CA 125 value is less than 10.25% relative to the same measurement at

previous visit and there is a corresponding patient disease status of "No Progression" (Responding or Stable) at this visit. The negative percent agreement is 67.68% (111/164) with a 95% CI: 60.36% to 75.0%.

Similar data was available for the predicate device at the cutoff chosen using the same criteria as for the VIDAS test.

Predicate	Change in disease state (variable w) to		
Change in CA 125 (variable v)	Progression	No progression	Total
>11.25%	62	57	119
≤ 11.25%	30	107	137
Total	92	164	256

Positive percent agreement measures the percent of visits when a percent change in VIDAS CA 125 value exceeds 11.25% relative to same measurement at previous visit and there is a corresponding patient disease status of progression at this visit. The positive percent agreement is 67.4% (62/92) with a 95% CI: 59.0% to 76.0%.

Negative percent agreement measures the percent of visits when a percent change in VIDAS CA 125 value is less than 11.25% relative to the same measurement at previous visit and there is a corresponding patient disease status of No Progression (Responding or Stable) at this visit. The Negative percent agreement is 65.2% (107/164) with a 95% CI: 56.9% to 73.2%.

As can be seen, both the VIDAS test and the predicate obtained performance characteristics compared to the reference clinical outcome that were substantially equivalent (overlapping 95% confidence intervals.)

4. Clinical cut-off:
The sponsor defines a ≥10.25% percentage change in CA 125 II values as significant. The significant change is 2.5 times the total imprecision of the CA 125 II assay across sites, lots, and concentration (expressed as %CV = 4.10%). The sponsor chose this value to ensure that the change in CA 125 II value is not attributed to assay variation.

An analysis of the choice of cutoff (as defined in terms of percent change between two successive Vidas CA125 II results) was performed using the above-mentioned 256 evaluable visit pairs. The percent change as cutoff is informative when the lower bound of the 95 % confidence interval of the sum of positive and negative percent agreement exceeds 100%. Presented below is a table of several percent changes and their corresponding Positive and Negative Percent Agreements from the analysis as examples of what might be expected with using different criteria to assess change based on the CA125 II results. Users may examine this table in the package insert to decide if they prefer the VIDAS-recommended cutoff or another with different performance characteristics.

Percent Change Between Two Consecutive Visits	Positive Percent Agreement	Negative Percent Agreement	The Lower Bound of the 95% Confidence Interval of the Sum of Positive and Negative Percent Agreement
≥3.0%	70.65%	62.80%	121.6
≥10.25%	70.65%	68.00%	126.7
≥25.2%	67.39%	71.34%	127
≥68.6%	55.43%	80.49%	123.9

Note from the table that at higher positive percent agreement there is lower negative percent agreement. Note that the sponsor's chosen cutoff of ≥10.25% is close to the maximum lower bound of the 95% confidence interval of the sum of positive and negative agreement.

5. Expected values/Reference range:
   Estimation and empirical distributions of CA 125 II values in various populations of subjects was performed. An apparently healthy population of 187 ambulatory females aged 18-55 years of age, who were apparently healthy (by self report) and were not sick on the day of serum sampling, were tested using the proposed CA 125 II assay. One hundred thirty-one (131) were 50 years of age or younger, while the remaining 56 were over age 50 and presumed to be post-menopausal. The results for these normal healthy subjects were as follows:

Normal Healthy Females	Number of subjects	Percentage (%) of the population according to the range of values in U/mL				95th percentile (U/mL)	95% CI
		≤ 35.00	35.01 - 65.00	65.01 - 100.00	> 100.00		
Pre-menopausal*	131	97.71	1.53	0.76	0.00	20.88	16.62 – 32.32
Post-menopausal**	56	100.00	0.00	0.00	0.00	13.88	9.64 – 17.06
Total	187	98.40	1.07	0.53	0.00	20.15	15.38 – 25.74

* Age 50 or less

** Over age 50.

The following benign disease cohort of 146 women was collected for analysis of the CA 125 II distribution:

Non malignant disease	Number of subjects	Percentage (%) of the population according to the range of values in U/mL				95th percentile (U/mL)	95% CI
		< 35.00	35.01 - 65.00	65.01 -100.00	> 100.00		
Benign Genito/Urinary	28	96.43	0.00	3.57	0.00	25.99	17.29 – 94.59
Benign Gastrointestinal	22	95.45	4.55	0.00	0.00	24.81	21.91 – 63.80
Diabetes	28	96.43	0.00	3.57	0.00	25.34	14.52 – 70.57
HTN/Heart/Liver Disease	13	92.31	7.69	0.00	0.00	36.86	8.18 – 36.86
Benign Breast Disease	55	98.18	1.82	0.00	0.00	20.63	15.89 – 39.92
Total	146	96.58	2.05	1.37	0.00	25.34	18.17 – 70.57

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.