510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k042731

B. Purpose for Submission:
New device

C. Measurand:
CA 125

D. Type of Test:
Quantitative, Chemiluminescent Microparticle Immunoassay (CMIA)

E. Applicant:
Fujirebio Diagnostics, Inc.

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

G. Regulatory Information:

1. Regulation section:
   21 CFR § 866.6010, Carcinoembryonic Antigen (CEA) Immunological Test System
   21 CFR § 862.1150, Calibrator
   21 CFR § 862.1660, Quality Control Material (Assayed and Unassayed)
2. Classification:
   Class II, CA 125 assay and Calibrator
   Class I, Quality control material
3. Product code:
   LTK, Test, Epithelial Ovarian Tumor-Associated Antigen (CA 125)
   JIT, Calibrator, Secondary
   JJX, Single (Specified) Analyte Controls (Assayed and Unassayed)
4. Panel:
   Immunology (82), CA 125
   Chemistry (75), Calibrator and Quality control material

H. Intended Use:

1. Intended use(s):
   The ARCHITECT® CA 125™ II assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of CA 125 reactive determinants inhuman serum and plasma on the ARCHITECT *i* System. The ARCHITECT® CA 125™ II assay is to be used as an aid in monitoring response to therapy for patients with epithelial ovarian cancer. Serial testing for patient CA 125 II assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

   The ARCHITECT® CA 125™ II Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of OC 125 defined antigen in human serum and plasma. Refer to the ARCHITECT® CA 125™ II reagent package insert for additional information.

The ARCHITECT® CA 125™ II Controls are for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of OC 125 defined antigen in human serum and plasma. Refer to the ARCHITECT® CA 125™ II reagent package insert for additional information.

2. Indication(s) for use:
   Same as intended use.
3. Special conditions for use statement(s):
   The device is for prescription use only.
4. Special instrument requirements:
   ARCHITECT *i* Systems – ARCHITECT *i* 2000 and ARCHITECT *i* 2000_{SR}. Both systems belong to the ARCHITECT family of instruments. The ARCHITECT *i* 2000_{SR} is similar to the ARCHITECT *i* 2000 but has the following additional features a) STAT sampling hardware and software, b) Auto Retesting software and c) different composition and position of the RV loader.

I. Device Description:

The ARCHITECT® CA 125™ II assay consists of:

1. Microparticles coated with monoclonal mouse anti-CA 125 antibodies in TRIS buffer with bovine protein stabilizers and antimicrobial agent.
2. Acridinium-lableled monoclonal mouse anti-CA 125 antibody conjugate in phosphate buffer with bovine protein stabilizers and antimicrobial agent with a minimum concentration of 0.075 µg/mL.

The following reagents are required but not provided with the ARCHITECT® CA 125™ II assay kit:

The ARCHITECT® CA 125™ II Calibrator Kit consists of:

1. Calibrator A is a TRIS buffer with bovine protein stabilizers and antimicrobial agent
2. Calibrators B to F are preparations of human OC 125 defined antigen in TRIS buffer with bovine protein stabilizers and antimicrobial agent with OC 125 antigen concentrations of 20, 75, 225, 500 and 1000 U/mL.

The ARCHITECT® CA 125 II™ Control Kit consists:

1. Control L with target OC 125 concentration of 40 U/mL (ranges from 28.0-52.0 U/mL)
2. Control M with target OC 125 concentration of 300 U/mL (ranges from 210-390 U/mL)
3. Control H with target OC 125 concentration of 650 U/mL (ranges from 455.0 -845.0 U/mL).

These controls are preparations of human OC 125 defined antigen in TRIS buffer with bovine protein stabilizers and antimicrobial agent.

ARCHITECT *i* Pre-Trigger Solution
ARCHITECT *i* Trigger Solution
ARCHITECT *i* Wash Buffer
ARCHITECT *i* Multi-Assay Manual Diluent.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Abbott Laboratories AxSYM® CA 125™ Assay
2. Predicate 510(k) number(s):
   k964020
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	ARCHITECT® CA 125™ II Assay	**AxSYM® CA 125™ Assay**
Intended Use	For the quantitative determination of CA 125	Same
Indications for Use	Use 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 for monitoring ovarian cancer	Same

Differences		
Item	Device	Predicate
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Microparticle Enzyme Immunoassay (MEIA)
Sample matrix	Serum and plasma (EDTA, lithium heparin and sodium heparin)	Serum
Capture Antibody	Mouse monoclonal anti-OC 125	Sheep anti-CA 125 polyclonal
Conjugate antibody	Mouse monoclonal M11	Mouse monoclonal anti-OC 125
Conjugate label	Acridinium	Alkaline phosphatase
Measuring range	0-1000 U/mL	0-600 U/mL
Sample volume	75 µL	150 µL
Calibrators	6 levels (0-1000 U/mL)	6 levels (0-600 U/mL) or 2 levels (0 and 50 U/mL)
Controls	3 levels Low = 40 U/mL Medium = 300 U/mL High = 650 U/mL	3 levels Low = 30 U/mL Medium = 80 U/mL High = 200 U/mL
Instrument System	ARCHITECT *i* Systems	AxSYM

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

Special guidance "Guidance Document for the Submission of Tumor Associated Antigen premarket Notifications (510(k)s) to FDA". NCCLS guidelines include EP5-A (Evaluation of Precision Performance of Clinical Chemistry Devices), EP7-A (Interference Testing in Clinical Chemistry Devices), EP9-A2 (Method Comparison and Bias Estimation Using Patient Samples), EP6-P2 (Evaluation of the Linearity of Quantitative Analytical Methods – Proposed Guideline), C28-A2 (How to Define and Determine reference Intervals in the Clinical Laboratory) and EP14-A (Evaluation of Matrix Effects).

L. Test Principle:

The ARCHITECT® CA 125 II™ assay is a two-step immunoassay to determine the presence of ovarian cancer (OC) 125 reactive determinants in human serum or plasma, using CMIA technology with flexible assay protocols, referred to as Chemiflex™. In the first step of the assay, sample and OA 125 coated paramagnetic microparticles are combined. CA 125 reactive determinants present in the sample bind to the OA 125 coated microparticles. After washing, M11 acridinium-labeled conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of CA 125 reactive determinants in the sample and the RLUs detected by the ARCHITECT™ *i* optical system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Two precision studies were performed according to NCCLS Guideline EP5-A.

Study 1 - Three defibrinated plasma panel samples were tested in duplicate twice per day for 20 days on 2 separate instruments and two lots of reagents. Each reagent lot used a single calibration curve throughout the study. Results supported the claim ≤10% for total precision (see below).

Panel	Reagent Lot	Instrument	N	Mean Conc. (U/mL)	Within-Run		Total	
					SD	%CV	SD	%CV
1	1	1	80	43.5	1.1	2.4	1.7	3.9
	2	2	80	49.7	0.8	1.5	0.8	1.7
2	1	1	80	303.3	9.8	3.2	11.9	3.9
	2	2	80	340.7	5.6	1.7	6.7	2.0
3	1	1	80	598.0	18.8	3.1	25.8	4.3
	2	2	80	678.3	12.4	1.8	13.5	2.0

Study 2 - Three defibrinated plasma panel samples were tested in replicates of four twice per day for 13 days on 3 separate instruments and 3 lots of reagents and a single calibration per reagent lot per instrument. Results supported the claim ≤10% for total precision (see below).

Panel	Reagent Lot	Instrument	N	Mean Conc. (U/mL)	Within-Run		Total	
					SD	%CV	SD	%CV
1	1	1	104	43.3	0.8	1.9	1.7	3.9
		2	104	45.0	0.1	0.2	1.2	2.6
		3	104	43.8	0.4	0.8	1.5	3.4
	2	1	104	43.3	0.0	0.0	1.8	4.2
		2	104	43.3	0.1	0.2	1.2	2.7
		3	104	41.7	0.0	0.0	1.5	3.7
	3	1	104	43.4	0.0	0.0	2.3	5.2
		2	104	43.5	0.0	0.0	1.2	2.7
		3	104	43.0	0.5	1.2	1.4	3.2
2	1	1	104	307.9	3.7	1.2	11.7	3.8
		2	104	303.9	0.0	0.0	7.9	2.6
		3	104	298.9	3.6	1.2	9.65	3.2
	2	1	104	300.3	3.6	1.2	12.9	4.3
		2	104	308.5	1.2	0.4	9.3	3.0
		3	104	301.4	2.4	0.8	9.9	3.3
	3	1	104	322.5	0.0	0.0	15.5	4.8
		2	104	301.3	0.0	0.0	8.1	2.7
		3	104	298.4	0.9	0.3	11.0	3.7
3	1	1	104	597.7	4.2	0.7	20.9	3.5
		2	104	601.8	3.6	0.6	16.2	2.7
		3	104	587.1	5.9	1.0	22.3	3.8
	2	1	104	600.4	7.8	1.3	30.6	5.1
		2	104	601.4	3.0	0.5	13.8	2.3
		3	104	592.6	0.0	0.0	17.2	2.9
	3	1	104	623.3	10.6	1.7	34.3	5.5
		2	104	594.0	5.9	1.0	16.0	2.7
		3	104	584.0	2.3	0.4	20.4	3.5

Assay precision on the ARCHITECT *i* 2000 and the ARCHITECT *i* 2000_{SR} was also evaluated by testing 80 replicates of each of three defibrinated plasma panels (two replicates per run, two runs per day, 20 nonconsecutive days) on each instrument. The acceptance criterion was a total %CV of <10% for each panel. Percent CV for the ARCHITECT *i* 2000 ranged from 3.9% to 4.3% and for the ARCHITECT *i* 2000_{SR}, 1.7% to 2.0%.

b. Linearity/assay reportable range:

Linearity – Linearity was determined using the NCCLS protocol EP6-P2. Aliquots of 10 human serum specimens were supplemented with CA 125 antigen to concentrations within the assay dynamic range. These samples were diluted serially with the ARCHITECT Multi-Assay Manual Diluent. The undiluted and diluted samples were analyzed in duplicate and the percent recovery was calculated. The average percent recovery of each sample ranges from 100.3% to 108.6%.

Auto-dilution - Dilution linearity using the auto-dilution protocol was assessed. Aliquots of 10 human serum specimens supplemented with CA 125 antigen to concentration within the assay dynamic range were diluted manually 1:10 with ARCHITECT Multi-Assay Manual Diluent. The undiluted and diluted samples were analyzed in duplicate. The undiluted

samples were also tested in duplicate using the 1:10 auto-dilution protocol. The percent recovery of the auto-dilution protocol was compared to that of the manual dilutions and was found to be 103% (ranged from 100% to 109%).

Spike recovery - A study was performed to verify that CA 125 spiked into human serum could be accurately recovered by the ARCHITECT® CA 125™ II assay. Aliquots of 10 normal human serum specimens with known endogenous levels of CA 125 were supplemented with CA 125 concentrations of 65, 165, 465 and 715 U/mL. The mean recovery ranged from 89% to 92% and supported the percent recovery claim of 100±15% (see table).

Number of Samples	CA 125 Added (U/mL)	Average % Recovery
10	65	92
10	165	91
10	465	89
10	715	90

Spike recovery experiments were performed on the ARCHITECT *i* 2000 and the ARCHITECT *i* 2000_{SR} instruments. A set of ten normal human serum samples each supplemented with four different concentration of CA 125 antigen at 65, 165, 465 and 715 U/mL were tested on each platform. Each sample was assayed in duplicate. Percent recovery was calculated by comparing the concentration of each spiked sample with the expected concentration. The acceptance criterion was a mean % recover across all four concentration and all ten samples of 100±15% (85% to 115%). The percent recovery on the ARCHITECT *i* 2000 instrument was 91% and for the ARCHITECT *i* 2000_{SR} was 102% (see table below).

	Spike Recovery				
CA 125 Spiked-in concentration	65 U/mL	165 U/mL	465 U/mL	715 U/mL	Overall Mean
ARCHITECT *I* 2000	92%	91%	89%	90%	91%
ARCHITECT *I* 2000_{SR}	105%	108%	98%	97%	102%

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):* No reference material and method available.

Value assignment for the ARCHITECT® CA 125 II™ primary calibrators – The ARCHITECT® CA 125 II™ Calibrators are manufactured volumetrically and since there is no recognized for this analyte, the calibrators are referenced to a standard prepared by Fujirebio Diagnostic, Inc. A stock antigen solution was assigned a value using the Fujirebio Diagnostics, Inc. CA 125 II RIA. Based on this value, the calibrator levels were prepared and the antigen concentrations were determined by assaying with the Fujirebio Diagnostics Inc. CA 125 II RIA using three kit lots. To standardize the product, 161 serum samples were assayed in triplicate on two AxSYM and two

ARCHITECT instrument systems using two reagent lots for each platform. The sample values determined on the ARCHITECT system with the RIA value assigned calibrators were correlated with the sample values determined on the AxSYM instruments. The Passing-Bablock analysis showed that the correlation between the ARCHITECT and AxSYM was non-linear with y = 0.83x - 4.57. The difference between the sample values derived from each instrument system was then plotted against the value determined using the AxSYM system. The ten sample running average was calculated and the upper bracketed values were estimated at the concentrations of the calibrator. The calibrator concentrations were re-evaluated and the samples re-correlated (Passing-Bablock regression equation: y = 0.978x - 0.426). The back-calculated values were assigned to the calibrators and the sample values were re-calculated. The correlation was repeated and found to be the same and these values were used for adjusting the calibrators. The adjusted calibrators were assayed to establish new standard curves to re-evaluate the ARCHITECT samples values using the original sample RLU values. The new correlation between the two assays was y = 1.015x + 0.815 and was within the slope of 1±2% (0.98 to 1.02). To verify the appropriateness of the value assignment, an independent correlation study was performed using 106 serum samples assayed singly on one AxSYM and one ARCHITECT system using one reagent lot. The Passing-Bablock regression equation was y = 1.033x + 4.653.

d. Detection limit:

The analytical sensitivity or Limit of Detection (LOD) is defined as the concentration at two standard deviations (SD) above the mean minimum detectable dose (MDD) and the lowest measurable CA 125 concentration that can be distinguished from zero. LOD was determined by testing the ARCHITECT CA 125 II Calibrator A (0 U/mL) in replicates of 10 followed by two replicates of ARCHITECT CA 125 II Calibrator B (20 IU/mL) on each of three instruments using two lots of reagents and calibrators for 24 runs. The mean values and the standard deviations (SD) of the 24 sets of Calibrator A and Calibrator B were used to calculate the MDD using the following formula - $MDD = [(2 \times SD_{Cal\ A}) \times Conc_{Cal\ B}]/(Mean\ RLU_{Cal\ B} - Mean\ RLU_{Cal\ A})$. Results are summarized below:

Number (n)	Mean MDD (U/mL)	MDD SD (U/mL)	MDD Range (U/mL)	LOD (Mean MDD + 2SD)
24	0.33	0.157	0.12 - 0.70	0.64

The LOD was determined to be 0.64 U/mL which supported the claim of ≤1.0 U/mL.

Analytical sensitivity was determined on ARCHITECT *i* 2000 and ARCHITECT *i* 2000_{SR} by testing ten replicates of Calibrator A and two replicates of Calibrator B per run. Nine runs were performed on one ARCHITECT *i* 2000_{SR} instrument and 15 runs on two different ARCHITECT *i* 2000 instruments with three different combinations of two calibrator lots and

two reagent lots. Analytical sensitivity was 0.76 U/mL on the ARCHITECT *i* 2000_{SR} instrument (mean = 0.40 U/mL, SD = 0.179 U/mL) and 0.55 U/mL on the ARCHITECT *i* 2000 instrument (mean = 0.28 U/mL, SD = 0.136 U/mL).

e. Analytical specificity:

Endogenous substances - Interference was assessed by adding high concentrations of triglycerides (3 g/dL), hemoglobin (500 mg/dL), bilirubin (20 mg/dL) and total protein (12 g/dL) to aliquots of a sample spiked-with a known concentration of CA 125. The percentage recovery was calculated by comparing the supplemented aliquots to the non-supplemented aliquots. All assays were performed in duplicate. The study demonstrates that less than 12% interference (ranged from 92% for triglycerides to 111% for total protein) was observed at the stated concentrations.

Chemotherapeutic agents - Interferences from Cisplatin (165 µg/mL), Cyclophosphamide (500 µg/mL), Doxorubicin (1.16 µg/mL), Carboplatin (500 µg/mL), Clotrimazole (0.3 µg/mL), Dexamethasone (10 µg/mL), methotrexate (45 µg/mL), Leucovorin (2.65 µg/mL), Melphalan (2.8 µg/mL) and Paclitaxel (3.5 µg/mL) were also determined. These substances were added to a sample spiked with a known concentration of CA 125. The percentage recovery was calculated by comparing the chemotherapeutic agent supplemented aliquots to aliquots supplemented with the solvent for each chemotherapeutic agent. All assays were performed in duplicate. The study demonstrates that less than 12% interference (ranged from 99% to 108%) was observed at the stated concentrations.

Human anti-mouse antibodies (HAMA) - Each of 5 HAMA positive samples (HAMA concentrations 45, 92, 159, 217 and 1494 ng/mL) and one normal sample was divided into 3 aliquots each. One aliquot served as control with no CA 125 antigen added. The other two was supplemented with the same volume of CA 125 antigen to achieve 35 U/mL and 250 U/mL respectively. All three aliquots for each sample were assayed in duplicate within the same run using the ARCHITECT® CA 125™ II assay. Results are summarized in table below:

		CA 125 II (U/mL)			% Recovery	
Sample	HAMA (ng/mL)	Neat	35 U/mL Spike	250 U/mL Spike	35U/mL Spike	250 U/mL Spike
1	1494	19.1	53.5	259.0	86%	89%
2	92	8.7	48.4	286.0	99%	103%
3	159	12.2	50.9	295.0	97%	105%
4	217	15.6	55.3	291.0	99%	102%
5	45	6.7	42.1	247.0	89%	89%
Normal	0	4.9	44.8	274.0		
				Average % Recovery	94%	98%

For samples with 35 U/mL and 250 U/mL CA 125, average % interference was 6% and 2% respectively.

Rheumatoid factor (RF) - Each of 5 RF positive samples (HAMA concentrations 24, 46, 71, 146 and 179 IU/mL) and one normal sample was divided into 3 aliquots each. One aliquot served as control with no CA 125 antigen added. The other two was supplemented with the same volume of CA 125 antigen to achieve 35 U/mL and 250 U/mL respectively. All three aliquots for each sample were assayed in duplicate within the same run using the ARCHITECT® CA 125™ II assay. Results are summarized in table below:

		CA 125 II (U/mL)			% Recovery	
Sample	RF (IU/mL)	Neat	35 U/mL Spike	250 U/mL Spike	35U/mL Spike	250 U/mL Spike
1	24	21.5	61.2	286.5	98%	94%
2	46	13.4	56.6	284.7	107%	96%
3	71	26.8	68.1	308.1	102%	99%
4	179	14.6	56.4	299.5	103%	101%
5	146	44.3	75.4	297.6	77%	90%
Normal	0	4.6	45.0	287.4		
				Average % Recovery	97%	96%

For samples with 35 U/mL and 250 U/mL CA 125, average % interference was 3% and 4% respectively.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Correlation study was performed on 280 serum samples with 120 samples from patients with ovarian cancer using the ARCHITECT® CA 125™ II assay and the AxSYM CA 125 assay. The CA 125 concentrations as determined by the ARCHITECT® CA 125™ II assay ranged from 4.5 to 4085.9 U/mL. The same samples determined by the AxSYM CA 125 assay gave CA 125 concentrations of 2.7 U/mL to 3436.1 U/mL. Seven samples gave values above the AxSYM assay dynamic range and six of these seven samples were also above the ARCHITECT dynamic range. These samples were diluted and rerun on both instruments. One sample was discordant (3014.4 U/mL on the ARCHITECT and 240.17 on the AxSYM) and was retested with and without centrifugation. The retest results were similar to the original result with the ARCHITECT. The sample was excluded from the analysis. Passing-Bablock regression analysis on 279 samples yielded a correlation coefficient of 0.985, a slope of 1.06 (99% CI: 1.03, 1.11) and y-axis intercept of 4.0 U/mL (99% CI: 2.0, 4.9). For the 167 samples with CA 125 values ranging from 4.5 to 110.5 U/mL on the ARCHITECT® CA 125™ II assay, Passing-Bablock regression analysis yielded a correlation coefficient of 0.967, a slope of 1.23 (99% CI: 1.16, 1.30) and y-axis intercept of 0.4 U/mL (99% CI: -0.9, 1.8).

When samples were categorized into ≤35 U/mL and >35 U/mL, the total agreement between the new device and the predicate device was 91.8%

(256/279) with a positive agreement of 98.5% (167/169) and a negative agreement of 80.9% (89/110). Results are summarized below.

		AxSYM CA 125		
		>35 U/mL	≤35 U/mL	Total
ARCHITECT CA 125 II	>35 U/mL	167	21	188
	≤35 U/mL	2	89	91
	Total	169	110	279

Correlation between the ARCHITECT *i* 2000 and ARCHITECT *i* 2000_{SR} instruments was also assessed by testing 104 specimens (CA 125 concentrations ranged from 7.8 U/mL to 863 U/mL) on each of three ARCHITECT *i* 2000 instruments and one ARCHITECT *i* 2000_{SR} instrument. The acceptance criterion was a slope of 1.00±0.10 for each ARCHITECT *i* 2000 and ARCHITECT *i* 2000_{SR} instrument comparison. Results of Passing-Bablock linear regression analyses are summarized below.

ARCHITECT *i* 2000_{SR} vs.	Correlation ®	Slope	Intercept
ARCHITECT *i* 2000 #1	0.999	1.023	0.5
ARCHITECT *i* 2000 #2	0.999	1.063	0.2
ARCHITECT *i* 2000#3	1.000	0.991	-0.1

b. Matrix comparison:

A study was performed to evaluate the use of different types of anticoagulants. From each subject 5 specimens were collected in the following tube types: serum clot tube, serum separator (SST), EDTA, sodium heparin and lithium heparin. A total of 40 sample sets were collected and analyzed. Twenty sample sets were supplemented with various concentrations of CA 125 antigen (five samples each for CA 125 concentrations of 50, 100, 200 and 400 U/mL) and the remaining 20 sets were not supplemented. All samples within a set were assayed together within 36 hours of sample draw. All specimens were tested in duplicate. The mean concentration value of each sample with a sample set was compared to the mean concentration of the corresponding serum sample. The percent recovery for SST, EDTA, lithium heparin and sodium heparin was 102% when compared to that of serum. Linear regression analysis yielded the following results:

SST = 1.04 (Serum) + 0.38
EDTA = 1.04 (Serum) + 0.05
Li Hep = 1.04 (Serum) + 0.15
Na Hep = 1.03 (Serum) + 1.08

3. Clinical studies:
   a. Clinical Sensitivity:
   Not applicable.
   b. Clinical specificity:
   Not applicable.
   c. Other clinical supportive data (when a. and b. are not applicable):

To support the monitoring claim, serial serum samples from 63 diagnosed ovarian cancer patients were analyzed. These samples were retrospective banked samples obtained from one clinical site. Testing was performed at Fujirebio Diagnostics, Inc. There were a total of 306 evaluable observations and the average number of 4.9 observations per patient (see breakdown of series below).

# of visits	# observation pairs	Frequency	%	Cumulative %
2	1	1	2	2
3	2	10	16	18
4	3	13	21	39
5	4	17	27	66
6	5	17	27	93
7	6	5	8	100

The average age of the subjects at time of diagnosis was 56 years (Exact 95% CI: 52.0, 59.4). Ninety-three percent of the cohort was post-menopausal at time of diagnosis. Staging was available for 60 of the 63 patients and 67.7% were stage III whereas 6.7% and 21.7% were stage I and IV respectively.

The outcome measure was the determination of progression of disease from one clinical visit to a succeeding clinical visit made by a patient after diagnosis of ovarian cancer and prior to death, low to follow-up or remission of disease. Disease progression from visit to visit was determined by the patient's physician based on either or both of the following: 1) examination of patient for clinical signs and symptoms, including results of laboratory tests that are currently standard of care for assessment of ovarian cancer disease status; and/or 2) examination of radiographic findings (imaging) that were used for the assessment of ovarian cancer disease status. Radiographic findings include results from CAT scans, PET scans, MRI, x-ray and ultrasound. Second look surgery results were used when available.

A significant change in a patient's CA 125 value was defined as an increase that was at least 2.5 times greater than the assay's total %CV (4.3%) which was equivalent to 10.75%. The following 2x2 table showed the association between change in CA 125 value and disease progression per observation pairs. Of the 243 observation pairs, 68% of the paired samples correlated with changes in disease status.

	Change in Disease Status per Observation Pair		
Change in CA 125	Progression	No Progression	Total
≥10.75%	85	51	136
<10.75%	26	81	107
Total	111	132	243

Positive concordance = 76.6% (85/111) (95% CI: 68.1, 83.3)
Negative concordance = 61.4% (81/132) (95%CI: 52.5, 69.9)

Total concordance = 68.3% (166/243) (95% CI: 62.2, 73.9)

Analysis on a per-patient basis showed 83% of patients correlated with change in disease status (see table below).

	Change in Disease Status per Patient		
Change in CA 125	Progression	No Progression	Total
≥10.75%	46	10	56
<10.75%	1	6	7
Total	47	16	63

Positive concordance = 97.9% (46/47) (95% CI: 88.7, 99.9)
Negative concordance = 37.5% (10/16) (95%CI: 15.3, 64.5)
Total concordance = 82.5% (52/63) (95% CI: 70.9, 91.0)

4. Clinical cut-off**:**
   Not applicable.
5. Expected values/Reference range:
   Sera from 199 apparently healthy women (100 post-menopausal and 99 premenopausal) were tested with the ARCHITECT® CA 125 II™ Assay. Three subjects in the post menopausal cohort were considered outliers because their CA 125 values (52.9, 46.2 and 63.3 U/mL) were more than 3 SD from the mean and twice the interquartile range above the 75th percentile value and were excluded from the data analysis. Results showed that 94.4% (95% CI: 96.9, 100) of healthy female subjects had CA 125 concentrations ≤35 U/mL. Sample statistics of the age and CA 125 values are summarized below.

Menopausal Status	N	Age (Years)						CA 125 Concentration (U/mL)					
		Mean	SD	95%CI	Median	95%CI	Range	Mean	SD	95%CI	Median	95%CI	Range
Pre	99	38.3	6.3	3.7-49.5	37	34-40	31-50	19.4	16.3	16.1-22.6	15.1	11.4-16.8	4.0-87.5
Post	97	49.3	4.8	4.8-50.2	49	48-50	36-64	13.3	7.2	11.8-14.8	12.1	10.7-14.0	3.3-41.2
Overall	196	43.8	7.9	42.7-44.9	45	45-46	31-64	16.9	13.7	15-18	13.1	11.5-15.2	3.3-87.5

Distribution of CA 125 values in these subjects are shown in the following table:

	# subjects	Percent			
		0-35 U/mL	35.0-165 U/mL	65.1-100 U/mL	>100 U/mL
Pre-menopausal	99	89.9	6.1	4.0	0.0
Post-menopausal	97	99.0	1.0	0.0	0.0

Distribution of CA 125 concentrations was also determined in 615 patients with other malignant and non-malignant conditions. Results are summarized below:

	# subjects	Percent			
		0-35 U/mL	35.0-165 U/mL	65.1-100 U/mL	>100 U/mL
Malignant conditions					
Breast Cancer	50	80.0	20.0	0.0	0.0
Ovarian Cancer	166	49.9	14.3	4.8	32.8
Colorectal Cancer	50	84.0	4.0	10.0	2.0
Endometrial Cancer	25	96.0	4.0	0.0	0.0
Lung Cancer	50	60.0	18.0	10.0	12.0
Non-Malignant conditions					
Ovarian Disease	100	90.0	9.0	1.0	0.0
Urogenital Disease	49	83.7	14.3	2.0	0.0
Hypertension/CHD	100	88.0	11.0	0.0	1.0
Benign Endometrial	25	84.0	8.0	4.0	4.0

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.