

## 510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY

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

k052000

**B. Purpose for Submission:**

New device.

**C. Measurand:**

CA 19-9

**D. Type of Test:**

Quantitative, Chemiluminescent Microparticle Immunoassay (CMIA)

**E. Applicant:**

Fujirebio Diagnostics, Inc.

**F. Proprietary and Established Names:**

ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> Assay, ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> Calibrator Kit,  
ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> Control Kit

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.6010, Tumor-associated antigen immunological test system

21 CFR 862.1150, Calibrator

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

2. Classification:

Class II, CA 19-9 assay and Calibrator

Class I, Quality control material

3. Product Code:

NIG, System, Test, Carbohydrate antigen (CA 19-9) for monitoring and management of pancreatic cancer;

JIT, Calibrator, Secondary

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

4. Panel:

Immunology (82)

Chemistry (75), Calibrator and Quality control material

**H. Intended Use:**

1. Intended use(s):

The ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of 1116-NS-19-9 reactive determinants in human serum and plasma on the ARCHITECT *i* System. The ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> assay is to be used as an aid in the management of pancreatic cancer patients with a detectable level of Ca 19-9 at some point in their disease process and in conjunction with other clinical methods.

The ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of 1116-19-9 reactive determinants in human serum and plasma. Refer to the

ARCHITECT® CA 19-9™<sub>XR</sub> reagent package insert for additional information.

The ARCHITECT® CA 19-9™<sub>XR</sub> Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT *i* System (reagents, calibrators, and instrument), when used for the quantitative determination of 1116-NS-19-9 reactive determinants in human serum and plasma. Refer to the ARCHITECT® CA 19-9™<sub>XR</sub> reagent package insert for additional information.

2. Indication(s) for use:  
Indicated for the serial measurement of CA 19-9 to aid in the management of patients diagnosed with cancers of the pancreas. Serial testing for patient CA 19-9<sub>XR</sub> assay values is used in conjunction with other clinical methods in the management of pancreatic cancer patients.
3. Special condition for use statement(s):  
Patients known to be genotypically negative for Lewis blood group antigen are unable to produce the CA 19-9 antigen even in the presence of malignant tissue. Phenotyping for the presence of the Lewis blood group antigen may be insufficient to detect true Lewis antigen negative individuals. Even patients who are genotype positive for the Lewis antigen may produce varying levels of CA 19-9 as the result of gene dosage effect.
4. Special instrument Requirements:  
ARCHITECT *i* Systems – ARCHITECT *i* 2000 and ARCHITECT *i* 2000<sub>SR</sub>. Both systems belong to the ARCHITECT family of instruments. The ARCHITECT *i* 2000<sub>SR</sub> 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.

### **Device Description:**

The ARCHITECT® CA 19-9™<sub>XR</sub> assay consists of:

1. Microparticles coated with monoclonal mouse anti-116-NS-19-9 antibodies in citrate buffer with bovine protein stabilizers and antimicrobial agent.
2. Acridinium-labeled monoclonal mouse anti-116-NS-19-9 antibody conjugate in phosphate buffer with bovine protein stabilizers and antimicrobial agent.

The following reagents are required but not provided with the ARCHITECT® CA 19-9™<sub>XR</sub> assay kit:

The ARCHITECT® CA 19-9™<sub>XR</sub> 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 1116-NS-19-9 reactive determinants (human) in TRIS buffer with bovine protein stabilizers and antimicrobial agent with CA 19-9 antigen concentrations of 30, 100, 250, 600 and 1200 U/mL.

The ARCHITECT® CA 19-9™<sub>XR</sub> Control Kit consists:

1. Control L with target CA 19-9 concentration of 40 U/mL (ranges from 26.0-54.0 U/mL)
2. Control M with target CA 19-9 concentration of 150 U/mL (ranges from 102-198 U/mL)
3. Control H with target CA 19-9 concentration of 750 U/mL (ranges from 510 - 990 U/mL).

These controls are preparations of human CA 19-9 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):  
Fujirebio Diagnostics CA 19-9™ RIA
2. Predicate K number(s):  
k020566
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	ARCHITECT® CA 19-9™ <sub>XR</sub>	Fujirebio CA 19-9 RIA
Intended Use	Quantitative analysis of CA 19-9 in human serum and plasma	Same
Indications for Use	As an aid in management of patients with cancers of the exocrine pancreas	Same
Antibody Type and Source	Monoclonal, mouse	Same

Differences		
Item	Device	Predicate
Methodology	Chemiluminescent Microparticle Immunoassay	Radioimmunoassay
Sample type	Serum and plasma (EDTA, lithium heparin and sodium heparin)	Serum or plasma (Citrate, heparin and EDTA)
Capture	Monoclonal anti-CA 19-9 antibody coated paramagnetic microparticles	Mouse monoclonal anti-CA 19-9 coated polystyrene beads
Conjugate Antibody	Acridinium labeled monoclonal anti-CA 19-9 F(ab') <sub>2</sub> conjugate	<sup>125</sup> I conjugated monoclonal anti-CA 19-9 antibody
Calibrators	6 levels (0 - 1200 U/mL)	6 levels (0-240 U/mL)
Controls	3 levels every 24 hours Low = 40 U/mL	2 levels each run Low = 40 - 50 U/mL

Differences		
Item	Device	Predicate
	Medium = 150 U/mL High = 750 U/mL)	High = 80 - 90 U/mL
Instrument System	ARCHITECT <i>i</i> System	Manual method
Measuring range	0-1200 U/mL	0-240 U/mL
Reaction time	≤ 30 minutes	6 hours
Automated dilution	Yes	No
Calibration frequency	Every 30 days	Every run
Sample size	< 100 µL	200 µL

**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”. CLSI 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 19-9™<sub>XR</sub> assay is a two-step immunoassay to determine the presence of 1116-NS-19-9 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 anti-CA 19-9 coated paramagnetic microparticles are combined. CA 19-9 reactive determinants present in the sample bind to the anti-CA 19-9 coated microparticles. After washing, anti-CA 19-9 acridinium-labeled conjugate is added in the second step. After another wash cycle, 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 quantity of CA 19-9 reactive determinants in the sample and the RLUs detected by the ARCHITECT *i* optical system.

**M. Performance Characteristics (if/when applicable):**1. Analytical performance:i. Precision/Reproducibility:

Precision was evaluated according to CLSI EP5-A2. Two studies were performed:

Study 1 – Six samples (2 serum pools [Panel 1 and 2], 1 CA 19-9 spiked serum pool [Panel 3] and ARCHITECT® CA 19-9™<sub>XR</sub> Controls) were tested in duplicate, two runs per day for 20 nonconsecutive days on two instruments and two lots of ARCHITECT® CA 19-9™<sub>XR</sub> reagents. Results for within-run and total precision are summarized below.

Sample	Reagent Lot	Instrument	N	Mean Conc. (U/mL)	Within-run		Total	
					SD (U/mL)	%CV	SD (U/mL)	%CV
Panel 1	1	1	80	56.52	1.69	3.0	2.19	3.9
	2	2	80	51.20	1.80	3.5	2.10	4.1
Panel 2	1	1	80	311.49	7.22	2.3	10.72	3.4

Sample	Reagent Lot	Instrument	N	Mean Conc. (U/mL)	Within-run		Total	
					SD (U/mL)	%CV	SD (U/mL)	%CV
Panel 3	2	2	80	288.82	9.14	3.2	11.23	3.9
	1	1	80	744.81	27.82	3.7	36.85	5.0
	2	2	80	728.82	42.53	5.8	47.66	6.5
Low Control	1	1	80	45.03	2.59	5.8	2.98	6.6
	2	2	80	42.33	2.94	6.9	3.60	8.5
Med Control	1	1	80	157.66	5.99	3.8	8.52	5.4
	2	2	80	146.93	6.26	4.3	8.14	5.5
High Control	1	1	80	781.68	44.76	5.7	49.87	6.4
	2	2	80	781.42	62.10	8.0	65.28	8.4

Study 2 – Four representative human serum pools spiked with various concentrations of CA 19-9 (50.06, 288.16, 719.38 and 677.26 U/mL) were tested in replicates of four, two runs per day for 13 nonconsecutive days on two instruments with two lots of reagents. The total %CV ranged from 3.7% to 6.2%.

ii. *Linearity/assay reportable range:*

Linearity was evaluated according to CLIS EP6-P2. Aliquots of 10 human serum samples were spiked with CA 19-9 to concentrations within the assay dynamic range. Each sample was automatically diluted by the ARCHITECT instrument with wash buffer. The undiluted and diluted samples were assayed in duplicate and the percent recoveries determined. The expected value was obtained by dividing the undiluted observed value by a dilution factor. The average percent recovery of each sample ranged from 98% to 117% with a mean average of 105%. Acceptance criterion for mean recovery was  $100 \pm 15\%$ .

Auto-dilution verification was assessed by assaying aliquots of 10 human serum samples spiked with CA 19-9 to concentrations within the assay dynamic range and manually diluted 1:10 with the wash buffer. The undiluted and diluted samples were tested in replicates of two. The undiluted samples were also tested in replicates of two using the 1:10 auto-dilution protocol of the assay. The percent recoveries of the manual and auto-diluted samples were calculated and compared. The average recovery of the auto-dilution protocol to manual dilution was 93%.

Spike recovery – Aliquots of 10 normal human serum specimens with known endogenous CA 19-9 levels were spiked with various concentrations of CA 19-9 (124.2, 175.7, 629.9 and 884.7 U/mL) and assayed in duplicate. The percent recovery was calculated. The percent recoveries ranged from 94% to 128% and the mean recovery was 105%.

The assay measuring range is from 0 U/mL to 1200 U/mL.

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

There is no known reference standard for CA 19-9. The ARCHITECT® CA 19-9™<sub>XR</sub> Calibrators were standardized against the Fujirebio Diagnostics, Inc. CA 19-9 reference preparation. The ARCHITECT® CA 19-9™<sub>XR</sub> primary calibrators are manufactured gravimetrically by diluting the CA 19-9 antigen stock in Calibrator Standard Matrix and assayed

using the Fujirebio Diagnostics Inc. CA 19-9™ RIA assay. The values were validated by a panel of patient serum samples on two lots of ARCHITECT® CA 19-9™<sub>XR</sub> reagent kit and three ARCHITECT instrument systems. The same panel was also tested on three lots of the Fujirebio Diagnostics Inc. CA 19-9™ RIA kit.

iv. *Detection limit (functional sensitivity):*

The minimal detectable dose (MDD) was determined by testing the ARCHITECT® CA 19-9™<sub>XR</sub> Calibrator A (0 U/mL) in replicates of 10 followed by two replicates of ARCHITECT® CA 19-9™<sub>XR</sub> Calibrator B (30 U/mL), on three instruments using two lots of calibrators and two lots of ARCHITECT® CA 19-9™<sub>XR</sub> reagents. The mean values and the standard deviations (SD) of the 18 sets of Calibrator A and the mean values of the 18 sets of Calibrator B were used to calculate the MDD for each run.  $MDD = [(2 \times SD_{CalA}) \times Conc_{CalB}] / (Mean\ RLU_{CalB} - Mean\ RLU_{CalA})$ . Limit of detection (LOD) is defined as the lowest measurable CA 19-9 concentration that can be distinguish from zero and equal to (MDD + 2SD). The mean LDL claim is  $\leq 2.0$  U/mL.

Number of runs (n)	Mean MDD (U/mL)	MDD SD	MDD Range (U/mL)	LOD (Mean MDD + 2SD)
18	0.48	0.26	0.25 – 1.28	1.00

v. *Analytical specificity:*

Endogenous substances - Interference was determined by spiking a known amount of an interfering substance into serum samples supplemented with CA 19-9. Interfering substances tested included hemoglobin (600 mg/dL), bilirubin (22 mg/dL), triglycerides (5100 mg/dL) and total protein (10 g/dL). Five samples were used for bilirubin, hemoglobin and triglycerides and four samples for total protein. Spiked and non-spiked samples were tested in duplicate and percent recoveries were calculated. Percent mean recoveries ranged from 91% for total protein to 102% for hemoglobin at the levels tested.

Pharmaceutical compounds – Interference was determined by spiking the following pharmaceutical compounds into serum samples and assayed: Leucovorin (11.4 mg/dL), Gemzar/Gemcitabine HCl (38.2 mg/dL), Streptozotocin/Zanosar (28 mg/dL), Doxorubicin (4 mg/dL), Cyclophosphamide/Cytosan (37.5 mg/dL), Cisplatin (5.7 mg/dL), 5-Fluorouracil/Adrucil (39 mg/dL), Methotrexate/Amethopterin-Hydrate (91 mg/dL), Tamoxifen (2.28 µg/dL), Cytarabine (3 mg/dL) and Paclitaxel/Taxol (6.7 mg/dL). Spiked and non-spiked samples were tested in replicates and percent recoveries were calculated. At the concentrations tested, the percent mean recoveries ranged from 97% to 104%.

Human anti-mouse antibody (HAMA) - To assess interference due to HAMA, five HAMA positive samples and one normal sample were studied. Each sample was split into three aliquots. One aliquot was

spiked with CA 19-9 antigen to achieve 35 U/mL while the second aliquot was spiked with the same volume of antigen to achieve 250 U/mL. The third aliquot was spiked with an equivalent volume of antigen free matrix and served as the control. All aliquots were run in duplicate in the same run. Percent recoveries were calculated and for the HAMA samples with 35 U/mL CA 19-9, the % recovery ranged from 84% to 95% (mean = 91%) and for samples with 250 U/mL CA 19-9, the % recovery ranged from 74% to 104% (mean = 94%).

Rheumatoid factor (RF) - To assess interference due to RF, five RF positive samples and one normal sample were tested. Each sample was split into three aliquots. One aliquot was spiked with CA 19-9 antigen to achieve 35 U/mL while the second aliquot was spiked with the same volume of antigen to achieve 250 U/mL. The third aliquot was spiked with an equivalent volume of antigen free matrix and served the control. All aliquots were run in duplicate in the same run. Percent recoveries were calculated and recoveries for samples with 35 U/mL CA 19-9 ranged from 82% to 95% (mean = 88%) and for samples with 250 U/mL CA 19-9, % recovery ranged from 74% to 104% (mean = 99%).

Cross-reactivity

No data provided.

- vi. *Assay cut-off:*  
See Expected Value.

2. Comparison studies:

- i. *Method comparison with predicate device:*

Two hundred fifty nine serum samples were tested on the ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> assay and the Fujirebio CA 19-9<sup>TM</sup> RIA Assay. All samples with values outside the dynamic range of either assay were diluted per package inserts. Excluded from analysis were 41 samples with values below the limit of detection (< 2.0 U/mL) and 23 samples with values above the dynamic range even after auto dilution (> 12,000 U/mL) of the ARCHITECT® CA 19-9<sup>TM</sup><sub>XR</sub> assay. In addition, one sample with discrepant results on both assays and one with an invalid CV in the Fujirebio assay were excluded. The remaining 193 samples were analyzed by Passing-Bablok linear regression analysis. The CA 19-9 concentrations of the specimen as determined by the Fujirebio CA 19-9<sup>TM</sup> RIA ranged from 1.17 to 10,782 U/mL. The Passing-Bablok linear regression analysis yielded a slope of 1.2 (99% CI 1.08, 1.37) and y-axis intercept of -5.1 U/mL (99% CI -7.4, -3.4) with a Spearman Correlation coefficient of 0.96.

In addition to regression analysis, samples were also evaluated to the percent agreement with the predicate device (see table below):

		CA 19-9 RIA		Total
		≤ 37 U/mL	> 37 U/mL	
Architect CA 19-9	≤ 37 U/mL	151	4	155
	> 37 U/mL	3	76	79

	Total	154	80	234
Percent positive agreement		95% (76/80)		
Percent negative agreement		98% (151/154)		
Percent total agreement		97% (227/234) (95% CI: 93.9, 98.8)		

#### Comparison of ARCHITECT CA 19-9<sub>XR</sub> i2000 and i2000<sub>SR</sub>

*Analytical sensitivity* – Ten replicates of calibrator A and two replicates of calibrator B were tested per run for six runs on one i2000<sub>SR</sub> instrument using one calibrator lot and two reagent lots. Analytical sensitivity was 0.60 U/mL. The same samples were also assayed on two i2000 instruments for 12 runs. The analytical sensitivity for the i2000 was 1.14 U/mL. Analytical sensitivity for both instrument met the acceptance criterion of  $\leq 2.0$  U/mL.

*Precision* – Three serum panels and three assay controls (low, medium and high) were tested in duplicate per run, two runs per day for 20 nonconsecutive days on one i2000 and one i2000<sub>SR</sub> instrument. Results are summarized below and both systems met the acceptance criterion of total CV of  $\leq 10\%$ .

Sample	Total CV (%)	
	i2000	i2000 <sub>SR</sub>
Control L	6.6	8.5
Control M	5.4	5.5
Control H	6.4	8.4
Panel 1	3.9	4.1
Panel 2	3.4	3.9
Panel 3	4.9	6.5

*Spike recovery* – Ten normal human serum samples each spiked with four different concentrations of CA 19-9 (125, 175, 650 and 900 U/mL) were tested. Five of the samples were tested on one i2000 instrument and the other five samples on one i2000<sub>SR</sub> instrument. Each sample was assayed in duplicate. The mean percent recovery across all concentrations and all samples on the i2000 instrument was 98% as compared to 111% on the i2000<sub>SR</sub> instrument. Both instruments met the acceptance criterion of  $100 \pm 15\%$ .

*Correlation* – One hundred twenty samples were assayed on both instruments. The acceptance criteria were a slope of  $1.0 \pm 0.2$  for samples with CA 19-9 values between 0-100 U/mL and a r-value of  $\geq 0.90$  for samples with CA 19-9 values of 0-1200 U/mL. Regression results are summarized in table below.

CA 19-9 (U/mL)	N	R	Least Squares		Passing-Bablok	
			Slope	Intercept	Slope	Intercept
0-100	92	0.98	0.95	1.36	0.99	0.54



0-1200	120	0.99	0.98	-0.79	0.95	0.65
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ii. *Matrix comparison:*

Matched human serum and plasma samples were collected in the following tube types: serum clot, serum separator tube (SST), EDTA, lithium heparin and sodium heparin. Twenty-six sample sets were assayed unchanged. Twenty-four sample sets were subdivided into 4 groups and each group was spiked with CA 19-9 to achieve concentrations of 50, 100, 200 or 650 U/mL. All samples were tested in duplicate and within 36 hours of sample draw. Results of the average recovery for each anticoagulant are summarized below.

CA 19-9 (U/mL)	Average % Recovery			
	SST	EDTA	Sodium Heparin	Lithium Heparin
50	102	96	103	102
100	99	101	101	102
200	101	98	99	95
650	103	101	101	102
Total % and (SD)*	100 (5)	98 (5)	100 (6)	100 (7)
CA 19-9 (U/mL)	Average U/mL Recovery and (SD)			
<24	0.7 (1.4)	0 (0.8)	0 (0.9)	0 (0.9)

\*Includes samples between 24 to 50 U/mL

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):*

Serial Monitoring Analysis

Two hundred and sixty one serum samples from 74 patients with confirmed pancreatic cancer collected and banked at two US clinical sites were analyzed. The average number of sample pairs per patient was 3.5 (see table below)

Number in Series	Number of Observation Pairs	Frequency	Percent
3	2	36	48.6
4	3	37	50.0
5	4	1	1.4

The average age of the patients at the time of diagnosis was 61.8 years ranging from 41 to 85 years. Fifty-five percent were males and forty-five percent females. Majority of the patients (80%) were Caucasians, the remaining 20% consisted of African-Americans (11%), Hispanics (8%) and Asians (1%). Only 9% of the patients were current smokers, 51% were past smokers and 38% nonsmokers (smoking status of one patient was unknown). At the time of diagnosis, 30% of the patients had diabetes and 27% had other medical conditions. Of the diabetic patient subset, 64% were males.

Sixty-nine of the 74 patients had disease stage information: 4.34% were Stage I, 7.25% Stage II, 44.9% Stage III, and 43.5% stage IV. Ninety-five percent of the pancreatic tumors were adenocarcinomas with 65% involving the head of the pancreas. In addition, histology stratification showed that 13.51% were as well differentiated, 22.97% moderately differentiated, 5.41% poor to moderately differentiated, 12.16% poorly differentiated and 45.95% as other.

Changes in CA 19-9 concentrations and changes in disease state were analyzed on a per-visit basis. A significant change in CA 19-9 was defined as greater than 14% (2.5 times the total precision %CV). The following tables show the association between CA 19-9 concentrations and disease status for the 187 evaluable observation pairs. The 95% confidence intervals for the concordance statistics were based on General Estimable Equations and calculated using the GENMOD procedure of SAS.

	Change in Disease State		
Changes in CA 19-9	Progression	No Progression	Total
≥14%	16	56	72
< 14%	17	98	115
Total	33	154	187

Positive concordance = 0.485 (16/33) (95% CI: 0.318, 0.655)

Negative concordance = 0.636 (98/154) (95% CI: 0.560, 0.706)

Total concordance = 0.61 (114/187) (95% CI: 0.543, 0.673)

Fujirebio RIA	Change in Disease State		
Changes in CA 19-9	Progression	No Progression	Total
≥ 20%	15	51	66
< 20%	18	103	121
Total	33	154	187

Positive concordance = 0.455 (15/33) (95% CI: 0.284, 0.637)

Negative concordance = 0.669 (103/154) (95% CI: 0.585, 0.743)

Total concordance = 0.631 (118/187) (95% CI: 0.554, 0.702)

Serial monitoring results were also analyzed on a per-patient basis as shown below. Concordances and 95% CI were determined. Confidence intervals for these estimates were determined using binomial distribution.

	Change in Disease State		
Changes in CA 19-9	Progression	No Progression	Total
≥ 14%	15	16	31
< 14%	7	36	43
Total	22	52	74

Positive concordance = 0.682 (15/22) (95% CI: 0.451, 0.861)

Negative concordance = 0.692 (36/52) (95% CI: 0.549, 0.813)

Total concordance = 0.689 (51/74) (95% CI: 0.571, 0.792)

Fujirebio RIA	Change in Disease State		
Changes in CA 19-9	Progression	No Progression	Total
≥ 20%	14	18	32
< 20%	8	34	42
Total	22	52	74

Positive concordance = 0.636 (14/22) (95% CI: 0.407, 0.828)

Negative concordance = 0.654 (34/52) (95% CI: 0.509, 0.780)

Total concordance = 0.649 (48/74) (95% CI: 0.529, 0.756)

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

The normal reference range was established by testing serum samples from 360 apparently healthy subjects consisted of 180 females and 180 males. Of the 180 female subjects, 56 were post-menopausal and 124 premenopausal. No age or ethnicity information was provided. No analysis was performed according to age, gender or ethnicity. A cumulative distribution was established and the 99<sup>th</sup> percentile was determined to be 64.39 U/mL and the 95<sup>th</sup> percentile was 37.83 U/mL. The table below shows the distribution of CA 19-9 results.

# subjects	Percent (%)				
	0-37.0 U/mL	37.1-100 U/mL	100.1-500 U/mL	500.1-1200 U/mL	>1200 U/mL
360	94.4	5.6	0.0	0.0	0.0

In addition to the normal cohort, 441 serum samples from patients with benign conditions and 537 from patients with malignant diseases were tested. The following table summarizes the sample distribution, diseases/conditions and distribution of CA 19-9 results.

Cohort	# Subjects	Distribution of CA 19-9 Values (%)				
Nonmalignant Disease		0-37.0 U/mL	37.1-100 U/mL	100.1-500 U/mL	500.1-1200 U/mL	>1200 U/mL
Rectal Polys	33	97	3	0	0	0
Pancreatitis	3	100	0	0	0	0
Gall bladder	21	95.2	0	0	0	4.8
Diabetes	38	94.7	5.3	0	0	0
Pulmonary	40	100	0	0	0	0
Cirrhosis	153	92.8	4.6	0.7	0.7	1.3
Hepatitis	68	92.6	7.4	0	0	0
Renal	34	91.2	8.8	0	0	0
Other	51	96.1	3.9	0	0	0
Malignant Disease						
Colorectal	169	81.1	7.7	5.3	1.2	4.7
Pancreatic	66	43.9	6.1	12.1	10.6	27.3
Gastric	69	66.7	11.6	10.1	2.9	8.7
Hepatocellular	30	63.3	16.7	3.3	10.0	6.7
Pulmonary	70	84.3	5.7	4.3	1.4	4.3
Mammary	102	86.3	10.8	2.0	1.0	0
Ovarian	31	87.1	6.5	3.2	3.2	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.