FUJIREBIO Diagnostics, Inc.

510(k) SUMMARY

SEP = 1 2011

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K103358

Submitter Information

Address: Fujirebio Diagnostics, Inc.
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Summary preparation date: August 31, 2011

Name of Device

Trade/Proprietary Name: ROMA™ (HE4 EIA + ARCHITECT CA 125 II™)

Common/Usual Name: ROMA
(Risk of Ovarian Malignancy Algorithm)
using HE4 EIA and ARCHITECT CA 125 II

Regulation Number: 21 CFR 866.6050

Regulatory Class: Class II

Product Code: ONX

Predicate Device

OVA1™ Test (K081754)

Intended Use

For In Vitro Diagnostic Use Only.

The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score.

ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.

PRECAUTION: ROMA (HE4 EIA + ARCHITECT CA 125 II) should not be used without an independent clinical /radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of ROMA (HE4 EIA + ARCHITECT CA 125 II) carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

Device Description

The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test in the form of a mathematical function combining the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score.
ROMA was developed in a training set using separate logistic regression equations for premenopausal and postmenopausal women:
Premenopausal woman: Predictive Index (PI) = -12.0 + 2.38*LN[HE4] + 0.0626*LN[CA 125]
Postmenopausal woman: Predictive Index (PI) = -8.09 + 1.04*LN[HE4] + 0.732*LN[CA 125]
ROMA = exp(PI) / [1 + exp(PI)] *10
ROMA is used to stratify women into likelihood groups for finding cancer on surgery. In order to provide a specificity level of 75%, a cut point of ≥ 1.31 was used for premenopausal women and ≥ 2.77 was used for postmenopausal women who present with an ovarian adnexal mass. Women with ROMA results above these cut points is at high likelihood of finding malignancy on surgery.

The test system consists of the assays, reagents, software and instrument used to obtain the ROMA result. The ROMA instructions for use are provided with the HE4 EIA Kit. The HE4 EIA and ARCHITECT CA 125 II are performed according to the manufacturers' directions detailed in each product insert. The immunoassays used in ROMA are:

HE4 EIA	The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum.
ARCHITECT CA 125 II	The ARCHITECT CA 125 II assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of OC 125 defined antigen in human serum and plasma on the ARCHITECT *i* System.

Substantial Equivalence

Similarities		
	ROMA (HE4 EIA + ARCHITECT CA 125 II) (Proposed Device)	**OVA1™ Test (Predicate Device) K081754**
Device Type	*In vitro* diagnostic	*In vitro* diagnostic
Classification	Class II	Class II
Regulation Number	21 CFR 866.6050 Ovarian adnexal mass assessment score test system	21 CFR 866.6050 Ovarian adnexal mass assessment score test system
Product Usage	Clinical and Hospital laboratories	Clinical and Hospital laboratories
Product Code	ONX Serum, algorithm, ovarian cancer assessment test	ONX Serum, algorithm, ovarian cancer assessment test
Panel	Immunology (82)	Immunology (82)
Serum Analyte	CA 125	CA 125
Use	The information provided by the ROMA Test should be used by the physician only as an adjunctive test to complement, not replace, other diagnostic and clinical procedures.	The information provided by the OVA1 Test should be used by the physician only as an adjunctive test to complement, not replace, other diagnostic and clinical procedures.

Differences		
	ROMA (HE4 EIA + ARCHITECT CA 125 II) (Proposed Device)	**OVA1™ Test (Predicate Device) K081754**
Intended Use	For In Vitro Diagnostic Use Only. The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score. ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.	The OVA1™ Test is a qualitative serum test that combines the results of five immunoassays into a single numerical score. It is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. The OVA1 Test is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy. The test is not intended as a screening or stand-alone diagnostic assay.
Measurand	Score based on 2 analytes	Score based on 5 serum analytes
Type of Test	Software algorithm and 2 immunoassays	Software algorithm and 5 immunoassays
Serum Analyte	HE4	Transthyretin, Apolipoprotein A-1, β2-microglobulin, Transferrin

Use of ROMA for the likelihood of malignancy assessment in women presenting with an adnexal mass who will undergo surgical intervention

ROMA takes into account the results of HE4 EIA and the results of ARCHITECT CA 125 II as well as the menopausal status of the woman. The ROMA value is used to aid in assessing whether a woman is at high or low likelihood of finding malignancy on surgery.
The effectiveness of ROMA was determined in a prospective, multi-center, blinded clinical trial for premenopausal and postmenopausal women presenting with an adnexal mass requiring surgical intervention.
A total of 461 women were evaluable in the study. For each patient, an initial cancer risk assessment (ICRA) was completed by a non-gynecological oncologist, providing the assessment of the patient's mass as benign (negative) or malignant (positive) based upon the information available to the non-gynecological oncologist during their work-up of the patient. The corresponding histopathology reports were collected after surgery.
Using a preoperatively collected serum sample, ROMA was determined and the patient was stratified into a low or a high likelihood group for finding malignancy on surgery.
The histopathological classifications of the 461 evaluable patients are summarized below:

Histopathological classification of the multi-center study patients

Histopathological classification	**All**		**Premenopausal**		**Postmenopausal**	
	N	**%**	**N**	**%**	**N**	**%**
Benign Pathology	375	81.3	220	91.7	155	70.1
Low Malignant Potential (LMP) / Borderline	18	3.9	7	2.9	11	5.0
Epithelial Ovarian Cancer	48	10.4	9	3.7	39	17.6
Non-Epithelial Ovarian Cancer	2	0.4	0	0.0	2	0.9
Other Gynecological Cancer	10	2.2	3	1.2	7	3.2
Other Cancer	7	1.5	1	0.4	6	2.7
Metastatic Cancer	1	0.2	0	0.0	1	0.5
Total	**461**	**100.0**	**240**	**23.3**	**221**	**76.7**

Use of ROMA for stratification into low likelihood and high likelihood groups for finding malignancy on surgery

The following cut-points were used in order to provide a specificity level of 75%:

Premenopausal women

ROMA value ≥ 1.31 = High likelihood of finding malignancy

ROMA value < 1.31 = Low likelihood of finding malignancy

Postmenopausal women

ROMA value ≥ 2.77 = High likelihood of finding malignancy

ROMA value < 2.77 = Low likelihood of finding malignancy

The reported result should include both the premenopausal and postmenopausal likelihood result and associated ROMA score on a scale of 0-10.

The stratification of patients presenting with an adnexal mass into high likelihood of harboring malignant disease (epithelial ovarian cancer (EOC), borderline or low malignant potential (LMP) tumors and other gynecological or non-gynecological cancers) using ROMA results above the cut-point ≥ 1.31 for premenopausal and ≥ 2.77 for postmenopausal women by histopathology is shown in the table below:

	Premenopausal n=240	**Postmenopausal n=221**	**All n=461**
All EOC[1]	9/9 (100%)	36/39 (92.3%)	45/48 (93.8%)
EOC Stage I+II	3/3 (100%)	6/9 (66.7%)	9/12 (75%)
EOC Stage III+IV	5/5 (100%)	29/29 (100%)	34/34 (100%)
LMP Tumors	4/7 (57.1%)	9/11 (81.8%)	13/18 (72.2%)
Other cancer[2]	2/4 (50%)	11/16 (68.7%)	13/20 (65.0%)
All cancer & LMP Tumors	15/20 (75%)	56/66 (84.8%)	71/86 (82.6%)

[1] 2 EOC patients were unstaged, [2]non-epithelial ovarian cancer, other gynecologic, and non-gynecologic cancers.

The performance of ROMA for stratification into low likelihood and high likelihood groups for premenopausal and postmenopausal women with epithelial ovarian cancer (EOC) only is shown in the table below:

	Premenopausal (N = 229)			**Postmenopausal (N = 194)**		
	Estimate	**95% CI**		**Estimate**	**95% CI**	
Sensitivity	100.0% (9/9)	66.4%	100%	92.3% (36/39)	79.1%	98.4%
Specificity	74.5% (164/220)	68.3%	80.2%	76.8% (119/155)	69.3%	83.2%
TP – FP[1]	74.5%	68.7%	80.4%	69.1%	58.2%	80.0%
PPV[2]	13.8% (9/65)	6.5%	24.7%	50.0% (36/72)	38.0%	62.0%
NPV[3]	100.0% (164/164)	97.8%	100%	97.5% (119/122)	93.0%	99.5%
Prevalence	3.9% (9/229)			20.1% (39/194)		

[1]TP-FP = True Positive rate – False Positive rate, [2]PPV = Positive Predictive Value, [3]NPV = Negative Predictive Value

Adjunctive use of ROMA with Initial Cancer Risk Assessment (ICRA) for stratification into low likelihood and high likelihood groups of harboring malignancy

The performance for the adjunctive use of ROMA with ICRA (ROMA and/or ICRA being positive for high likelihood of finding malignancy on surgery) was evaluated by calculating sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value). Adding ROMA to ICRA produced a statistically significant improvement in the negative predictive value. The NPV for correctly classifying benign patients into the low likelihood group increased from 93.2 to 96.2%, making the adjunctive use of ROMA with ICRA effective in ruling out cancer.

Total counts for premenopausal and postmenopausal women combined

Malignancy by Pathology[1]					No Malignancy by Pathology[1]				
		ICRA					ICRA		
		Positive (High Likelihood)	Negative (Low Likelihood)	Total			Positive (High Likelihood)	Negative (Low Likelihood)	Total
ROMA	Positive (High Likelihood)	58	13	71	ROMA	Positive (High Likelihood)	28	64	92
	Negative (Low Likelihood)	5	10	15		Negative (Low Likelihood)	31	252	283
	Total	63	23	86		Total	59	316	375

[1]All malignancies found including EOC, LMP, non-epithelial ovarian cancer, other gynecologic, and non-gynecologic cancers

Performance for premenopausal and postmenopausal women combined with 95% Confidence Intervals (CI)

	ICRA			ROMA			Adjunctive		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Sensitivity	73.3%	63.1%	81.4%	82.6%	73.2%	89.1%	88.4%	79.9%	93.5%
Specificity	84.3%	80.2%	87.6%	75.5%	70.9%	79.5%	67.2%	62.3%	71.8%
TP-FP[1]	57.5%	47.3%	67.8%	58.0%	48.7%	67.3%	55.6%	47.1%	64.0%
PPV[2]	51.6%	42.9%	60.3%	43.6%	36.2%	51.2%	38.2%	31.7%	45.1%
NPV[3]	93.2%	90.0%	95.4%	95.0%	91.9%	96.9%	96.2%	93.1%	97.9%
Prevalence	18.7%								

[1]TP-FP = True Positive rate – False Positive rate, [2]PPV = Positive Predictive Value, [3]NPV = Negative Predictive Value

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food & Drug Administration
10903 New Hampshire Avenue
Building 66
Silver Spring, MD 20993

Fujirebio Diagnostics, Inc.
c/o Ms. Diana L. Dickson
Manager, Regulatory Affairs
201 Great Valley Parkway
Malvern, PA 19355

SEP 0 1 2011

Re: k103358
Trade/Device Name: ROMA™ (HE4 EIA +ARCHITECT CA 125 II™)
Regulation Number: 21 CFR §866.6050
Regulation Name: Ovarian adnexal mass assessment score test system
Regulatory Class: Class II
Product Codes: ONX
Dated: August 29, 2011
Received: August 30, 2011

Dear Ms. Dickson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act and the limitations described below. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

The Office of *In Vitro* Diagnostic Device Evaluation and Safety has determined that there is a reasonable likelihood that this device will be used for an intended use not identified in the proposed labeling and that such use could cause harm. Therefore, in accordance with Section 513(i)(1)(E) of the Act, the following limitation must appear in the device's labeling:

PRECAUTION: ROMA (HE4 EIA + ARCHITECT CA 125 II) should not be used without an independent clinical /radiological evaluation and is **not** intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of ROMA (HE4 EIA + ARCHITECT CA 125 II) carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

Please note that the above labeling limitations are required by Section 513(i)(1)(E) of the Act. Therefore, a new 510(k) is required before these limitations are modified in any way or removed from the device's labeling.

The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market. This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification if the limitation statement described above is added to your labeling.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Alberto Gutierrez, Ph.D.
Director
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication for Use

510(k) Number (if known): K103358

Device Name: ROMA™ (HE4 EIA + ARCHITECT CA 125 II™)

Indication For Use:

For In Vitro Diagnostic Use Only.
The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score.
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Prescription Use ___√___ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K103358