DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

Roche Diagnostics
Mr. Angelo Pereira
Regulatory Affairs Program Manager
9115 Hague Road
Indianapolis, IN 46250

June 15, 2016

Re: K153607
Trade/Device Name: Roma Calculation Tool Using Elecsys Assays
Regulation Number: 21 CFR 866.6050
Regulation Name: Ovarian adnexal mass assessment score test system
Regulatory Class: II
Product Code: ONX
Dated: May 13, 2016
Received: May 17, 2016

Dear Mr. Pereira:

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) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. 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); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kelly Oliner -S

For,
Leonthena R. Carrington, MS, MBA, MT(ASCP)
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K153607

Device Name
ROMA Calculation Tool Using Elecsys Assays

Indications for Use *(Describe)*
ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test for serum and plasma (K2-EDTA, K3-EDTA and Li-Heparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score.
RCTUEA 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. RCTUEA 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. RCTUEA 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 electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.

PRECAUTION: RCTUEA 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 RCTUEA carries the risk of unnecessary testing, surgery and/or delayed diagnosis.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

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510(k) Summary

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

Submitter Information

Address	Roche Diagnostics 9115 Hague Rd Indianapolis, IN 46250
Contact Person	Angelo Pereira angelo.pereira@roche.com
Date prepared	June 06, 2016

Device Name

Proprietary names:	ROMA Calculation Tool Using Elecsys Assays
Common names:	ROMA (Risk of Ovarian Malignancy Algorithm)
Product Code:	ONX
Predicate Device:	Fujirebio ROMA (K103358)

Establishment Registration

For the ROMA Calculation Tool Using Elecsys Assays (RCTUEA), the Elecsys HE4 assay and the Elecsys CA 125 II assay the establishment registration numbers for Roche Diagnostics GmbH sites in Mannheim, Germany and Penzberg, Germany are 9610126 and 9610529, respectively. The establishment registration number for Roche Diagnostics, Indianapolis, USA is 1823260

Classification

· The FDA has classified the Ovarian Adnexal Mass Assessment Score Test as a Class II device.

Panel	Product Code	Classification Name	Regulation Citation
Immunology	ONX	Ovarian Adnexal Mass Assessment Score Test System	21 CFR 862.6050

Device Description

ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test for serum and plasma (K_2–EDTA, K_3–EDTA and Li-Heparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score. ROMA was developed using separate logistic regression equations for premenopausal and postmenopausal women:

Pre menopausal:
Predictive Index (PI) = -12.0 + 2.38 x LN[HE4] + 0.0626 x LN[CA 125]
Post menopausal:
Predictive Index (PI) = -8.09 + 1.04 x LN[HE4] + 0.732 x LN[CA 125]
RCTUEA value = exp (PI) / [1 + exp(PI)b)] x 10
RCTUEA is used to stratify women into likelihood groups for finding cancer on surgery. In order to provide a specificity level of 75 %, a cutoff point of ≥ 1.14 was used for premenopausal women and ≥ 2.99 was used for postmenopausal women who present with an ovarian adnexal mass. Women with RCTUEA results above these cutoff points are at high likelihood of finding malignancy on surgery.

The immunoassays used in RCTUEA are:
Elecsys HE4: an electrochemiluminescence immunoassay for the quantitative determination of HE4 in human serum and plasma
Elecsys CA 125 II: an electrochemiluminescence immunoassay for the quantitative determination of OC 125 reactive determinants in human serum and plasma.

Intended Use/ Indications for Use	ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test for serum and plasma K_2–EDTA, K_3–EDTA and Li-Heparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score. RCTUEA 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. RCTUEA 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. RCTUEA 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 electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers. PRECAUTION: RCTUEA 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 the RCTUEA calculation for use with the Elecsys HE4 and Elecsys CA 125 II assays carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.
Substantial Equivalence	The ROMA Calculation Tool Using Elecsys Assays is substantially equivalent to Fujirebio's ROMA (HE4 EIA + ARCHITECT CA 125 II™) (K103358).
Substantial Equivalence Comparison	The following table compares the ROMA Calculation Tool Using Elecsys Assays with the predicate device.

Continued on next page

Assay Comparison		
Feature	**Fujirebio ROMA**	**ROMA Calculation Tool Using Elecsys Assays**
General Assay Features		
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	ONX
Panel	Immunology (82)	Immunology (82)
Intended Use/ Indications 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. 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.	ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test for serum and plasma (K_2EDTA, K_3EDTA and LiHeparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score. RCTUEA 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. RCTUEA 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. RCTUEA 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 **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Assay Comparison		
Feature	**Fujirebio ROMA**	**ROMA Calculation Tool Using Elecsys Assays**
General Assay Features		
Precautions (ROMA)	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.	Precaution: RCTUEA 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 RCTUEA carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.
Assay	Quantitative enzyme linked immunosorbent assay	Both Elecsys HE4 and Elecsys CA 125 are quantitative sandwich immunoassays
Analytes	HE4 and CA 125 II	HE4 and CA 125 II
Sample types	Serum	Serum and plasma
Detection Protocol	EIA (HE4) and CMIA (CA 125 II)	ECLIA for CA125 II and HE4
Type of Test	Software algorithm and 2 immunoassays	Software algorithm and 2 immunoassays

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

RCTUEA takes into account the results of Elecsys HE4 and Elecsys CA 125 II as well as the menopausal status of woman. The RCTUEA value is used to aid in assessing whether a woman is at high or low likelihood of finding malignancy on surgery.
The effectiveness of RCTUEA 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 455 women were evaluable in the study. For each patient, an initial cancer risk assessment (ICRA) was completed by a nurse practitioner, physician assistant or a non-gynecological oncologist who provided the assessment of the patient's mass as benign or malignant based on the information available during their work-up of the patient. The corresponding histopathology reports were collected after surgery.
The histopathological classifications of the patients are given in the table below:

Histopathological classification of the multi-center study patients

	All		**Premenopausal**		**Postmenopausal**	
Histopathological classification	**N**	**%**	**N**	**%**	**N**	**%**
Benign Pathology	371	81.5	228	91.6	143	69.4
Borderline/ LMP	18	3.9	7	2.8	11	5.3
Epithelial Ovarian Cancer	47	10.3	9	3.6	38	18.4
Non-Epithelial O. C.	2	0.4	0	0	2	1.0
Sex Cord Stroma	2	0.4	0	0	2	1.0
Other Gynecologic Cancer	9	2.0	3	1.2	6	2.9
Endometrial	8	1.802.	3	1.2	5	2.5
Leiomyosarcoma	1	1.5	0	0	1	0.4
Other Cancer	7	0.4	1	0.4	6	2.9
Peritoneal Mesothelioma	2	0.2	0	0	2	1.0
Appendix	1	0.2	1	0.4	0	0
Carcinoid Tumor	1	0.2	0	0	1	0.5
Colon	1	0.2	0	0	1	0.5
Malignant Lymphoma	1	0.2	0	0	1	0.5
Pseudomyxoma Peritonel	1	0.2	0	0	1	0.5
Metastatic Cancer	1	0.2	1	0.4	0	0
Pancreatic	1	0.2	1	0.4	0	0
Total	455	100	249	100	206	100

Use of RCTUEA for stratification into low and high likelihood groups for finding malignancy on surgery
Using a preoperatively collected serum sample, RCTUEA was determined and the patient was stratified into a low or high likelihood group for finding malignancy on surgery. Samples were tested on the Elecsys e411 analyzer at three US testing sites.

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

RCTUEA values ≥ 1.14 = High likelihood of finding malignancy
RCTUEA values < 1.14 = Low likelihood of finding malignancy
Postmenopausal women
RCTUEA values ≥ 2.99 = High likelihood of finding malignancy
RCTUEA values < 2.99 = Low likelihood of finding malignancy

The reported results include the likelihood and associated RCTUEA score on a scale of 0-10 for premenopausal and postmenopausal women.

The stratification of patients presenting with an adnexal mass into high likelihood of malignant disease (epithelial ovarian cancer), borderline or low malignant potential (LMP) tumors and other gynecological and non-gynecological cancers, using RCTUEA results above the cut-points of ≥ 1.14 for premenopausal and ≥ 2.99 for postmenopausal women by histopathology is shown in the table below:

	Premenopausal n=249	**Postmenopausal n=206**	**All n=455**
All EOC	9/9[1] (100%)	34/38[1] (89.5%)	43/47 (91.5%)
EOC Stage I+II	3/3 (100%)	5/9 (55.6%)	8/12 (66.7%)
EOC Stage III+IV	5/5 (100%)	28/28 (100%)	33/33 (100%)
LMP Tumors	4/7 (57.1%)	9/11 (81.8%)	13/18 (72.2%)
Other Cancers[2]	2/5 (40%)	9/14 (64.2%)	11/19 (57.9%)
All cancers &LMP Tumors	15/21 (71.4%)	52/63 (82.5%)	67/84 (79.8%)

[1] One EOC patient was unstaged [2] non-epithelial cancer, other gynecologic and non-gynecologic cancers

The performance of RCTUEA 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=237)		**Postmenopausal (N=181)**	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Sensitivity	100% (9/9)	66.4% 100%	89.5% (34/38)	75.2% 97.1%
Specificity	77.6% (177/228)	71.7% 82.9%	82.5% (118/143)	75.3% 88.4%
TP-FP[1]	77.6%	72.1% 83.2%	72.0%	60.2% 83.8%
PPV[2]	15.0% (9/60)	7.1% 26.6%	57.6% (34/59)	44.1% 70.4%
NPV[3]	100.0% (177/177)	97.9% 100%	96.7% (118/122)	91.8% 99.1%
Prevalence	3.8% (9/237)		21.0% (38/181)	

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

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

The performance for the adjunctive use of RCTUEA with ICRA (ICRA and/or RCTUEA being positive for high likelihood of finding malignancy on surgery) for

diagnosis of EOC including LMP, sensitivity for malignancy increased from 76.9% to 90.8%. Specificity for malignancy decreased from 84.4% to 70.4%. PPV for adjunctive use of ICRA and RCTUEA decreased from 46.3% to 34.9% due to the increase in the number of false positive tests. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 95.4% to 97.8%. This observed increase in NPV was statistically significant, (P=0.0000) supporting the adjunctive use of RCTUEA with ICRA effective in ruling out cancer.

Performance of RCTUEA versus ICRA for Malignant and Non-Malignant cohorts as determined by Pathology

Malignancy by Pathology[1]						**No Malignancy by Pathology[1]**				
		ICRA						**ICRA**		
		Pos	**Neg**	**Total**				**Pos**	**Neg**	**Total**
RCTUEA	**Pos**	47	9	56		**RCTUEA**	**Pos**	24	52	76
	Neg	3	6	9			**Neg**	34	261	295
	Total	50	15	65			**Total**	58	313	371

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

Performance of RCTUEA for Diagnosis of EOC including LMP

	ICRA			**RCTUEA**			**Adjunctive**		
	Estimate	**95% CI**		**Estimate**	**95% CI**		**Estimate**	**95% CI**	
Sensitivity	76.9% 50/65	64.8%	86.5%	86.2% 56/65	75.3%	93.5%	90.8% 59/65	81.0%	96.5%
Specificity	84.4% 313/371	80.3%	87.9%	79.5% 295/371	75.0%	83.5%	70.4% 261/371	65.4%	75.0%
PPV	46.3% 50/108	36.7%	56.2%	42.4% 56/132	33.9%	51.3%	34.9% 59/169	27.8%	42.6%
NPV	95.4% 313/328	92.6%	97.4%	97.0% 295/304	94.5%	98.6%	97.8% 261/267	95.2%	99.2%
TP-FP[a]	61.3%	50.2%	72.4%	65.7%	56.1%	75.2%	61.1%	52.5%	69.7%
PLR[b]	4.92	3.75	6.45	4.21	3.37	5.26	3.06	2.57	3.65
NLR[c]	0.27	0.18	0.43	0.17	0.09	0.32	0.13	0.06	0.28
Prevalence	14.9% (65/436)								

[a] TP-True Positive; FP-False Positive[b] PLR-Positive Likelihood Ratio[c] NLR-Negative Likelihood Ratio

Standard/ Guidance Document Reference	In addition to FDA guidance regarding 510(k) submissions, the following standards were used for the performance studies. · Evaluation of Precision Performance of Quantitative Measurement Methods; CLSI document EP5-A2, August 2004. · Method Comparison and Bias Estimation Using Patient Samples, CLSI document EP9-A2-IR, July 2010.