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

Fujirebio Diagnostics, Inc.
Ms. Diana Dickson
Director, Clinical and Regulatory Science
201 Great Valley Parkway
Malvern, PA 19355

May 2, 2016

Re: K151502
Trade/Device Name: ARCHITECT ROMA
Regulation Number: 21 CFR 866.6050
Regulation Name: Ovarian adnexal mass assessment score test system
Regulatory Class: II
Product Code: ONX
Dated: April 18, 2016
Received: April 19, 2016

Dear Ms. Dickson:

This letter corrects our substantially equivalent letter of April 28, 2016.

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)*
k151502

Device Name
ARCHITECT ROMA

Indications for Use *(Describe)*

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

ARCHITECT 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. ARCHITECT 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. ARCHITECT 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: ARCHITECT ROMA 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 ARCHITECT ROMA 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)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

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

A. 510(k) Number:

k151502

B. Purpose for Submission:

New device

C. Measurand:

ROMA (Risk of Ovarian Malignancy Algorithm) – Ovarian adnexal mass assessment score based on 2 serum analytes

D. Type of Test:

Software algorithm and 2 immunoassays

E. Applicant:

Address: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact person: Diana Dickson
(610) 240-3917
dicksond@fdi.com

Summary preparation date**: April 18, 2016**

F. Proprietary and Established Names:

ARCHITECT ROMA

G. Regulatory Information:

1. Regulation section:
   21 CFR §866.6050 – Ovarian adnexal mass assessment score test system

2. Classification:
   Class II

3. Product code:
   ONX; Ovarian adnexal mass assessment score test system

4. Panel:
   82, Immunology

H. Intended Use:

1. Intended use(s):
   For In Vitro Diagnostic Use Only.

   ARCHITECT Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of ARCHITECT HE4, ARCHITECT CA 125 II™ and menopausal status into a numerical score.
   ARCHITECT 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. ARCHITECT 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. ARCHITECT 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: ARCHITECT ROMA 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 ARCHITECT ROMA carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

2. Indication(s) for use:
   Same as Intended Use.

3. Special conditions for use statement(s):
   Prescription use only

4. Special instrument requirements:
   ARCHITECT *i*2000SR system

I. Device Description:

ARCHITECT ROMA is a qualitative serum test that combines the results of 2 analytes, HE4 (ARCHITECT HE4) and CA125 (ARCHITECT CA 125 II) and menopausal status into a numerical score between 0.0 and 10.0. The premenopausal or postmenopausal status must be based on ovarian function determined with information available from clinical evaluation and medical history.

The test system consists of the ARCHITECT HE4 assay, the ARCHITECT CA 125 II assay and the ARCHITECT *i*2000SR. The ARCHITECT *i*2000SR is capable of calculating the ROMA score. The immunoassays are performed according to the directions detailed in each product insert.

Both ARCHITECT HE4 and ARCHITECT CA 125 II are previously 510(k) cleared Class II devices (k093957 and k042731 respectively). The ARCHITECT HE4 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of HE4 antigen in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring

ovarian cancer. ARCHITECT CA 125 II assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of CA125 reactive determinants in human serum and plasma on the ARCHITECT *i* System and was previously cleared as an aid in monitoring response to therapy for patients with epithelial ovarian cancer.

Using an algorithm and the value of the 2 analytes, ARCHITECT ROMA scores (numerical score from 0.0-10.0) for both premenopausal and postmenopausal will be calculated and indicate a low likelihood or high likelihood for finding malignancy on surgery.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ROMA™ (HE4 EIA + ARCHITECT CA 125 II)

2. Predicate 510(k) number(s):
   K103358

3. Comparison with predicate:

Similarities		
	ARCHITECT ROMA (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
Device Type	*In vitro* diagnostic	*In vitro* diagnostic
Classification	Class II	Class II
Regulation Number	21CFR § 866.6050 Ovarian adnexal mass assessment score test system	21CFR § 866.6050 Ovarian adnexal mass assessment score test system
Product Usage	Clinical and Hospital laboratories	Clinical and Hospital laboratories
Intended Use	ARCHITECT Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of ARCHITECT HE4, ARCHITECT CA 125 II™ and menopausal status into a numerical score. ARCHITECT 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. ARCHITECT 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. ARCHITECT 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 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.
Black box warning (PRECAUTION)	Should not be used without an independent clinical /radiological evaluation and is	Should not be used without an independent clinical /radiological evaluation and is

Similarities		
	ARCHITECT ROMA (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
	not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use carries the risk of unnecessary testing, surgery, and/or delayed diagnosis	**not** intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use carries the risk of unnecessary testing, surgery, and/or delayed diagnosis
Specimen Collection Method	Routine Phlebotomy Techniques	Routine Phlebotomy Techniques
Type of Specimen	Human Serum	Human Serum
Serum Analyte	HE4 and CA125	HE4 and CA125
Device Type	Algorithm (Qualitative, numeric)	Algorithm (Qualitative, numeric)
Equation used for test	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	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
Clinical Cut-off	Premenopausal: ARCHITECT ROMA score ≥ 1.31 = High likelihood of finding malignancy ARCHITECT ROMA score < 1.31= Low likelihood of finding malignancy Postmenopausal: ARCHITECT ROMA score ≥ 2.77 = High likelihood of finding malignancy ARCHITECT ROMA score < 2.77 = Low likelihood of finding malignancy	Premenopausal: ROMA score ≥ 1.31 = High likelihood of finding malignancy ROMA score < 1.31= Low likelihood of finding malignancy Postmenopausal: ROMA score ≥ 2.77 = High likelihood of finding malignancy ROMA score < 2.77 = Low likelihood of finding malignancy

Differences		
	ARCHITECT ROMA (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
Instrument System	ARCHITECT *i*2000SR Only	Manual ELISA for HE4 and ARCHITECT *i*2000SR fro CA125
Assay Format	Same immunoassay platform for the detection of HE4 and CA125 in a single sample	Separate immunoassay platforms for the detection of HE4 and CA125 in a single sample
HE4 Measuring Range	The measuring interval of the ARCHITECT HE4 assay is 20.0 pmol/L to 1500.0 pmol/L.	The measuring interval of the HE4 EIA is between 15 and 900 pM.
Software	Provided on the ARCHITECT *i*2000SR for automated entry of assay values to obtain result	Provided as separate CD-ROM for manual entry of assay values to obtain result
Sample Volume	75µL per reportable HE4 test result (singlicate) 75µL per reportable CA125 test result (singlicate)	50µL per reportable HE4 test result (duplicate) 75µL per reportable CA125 test result (singlicate)
Software	ARCHITECT *i*2000SR will have the capability to produce the ROMA result	Manual entry of assay values using software on a Personal Computer (PC) to produce the ROMA result

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

- CLSI EP5-A2 - Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition
- CLSI EP7-A2 - Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition
- CLSI C28-A3c - Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition
- CLSI EP9-A3 – Measurement Procedure Comparison and Bias Estimation Using Patient Samples; approved Guideline – Third Edition
- Guidance document entitled “Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System”
- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff
- FDA Guidance Document - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005)

L. Test Principle:

The ARCHITECT HE4 assay is a two-step immunoassay for the quantitative determination of HE4 antigen in human serum using chemiluminescent microparticle immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample and anti-HE4 coated paramagnetic microparticles are combined. HE4 antigen present in the sample binds to the anti-HE4 coated microparticles. After washing, acridinium-labeled anti-HE4 conjugate is added. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of HE4 antigen in the sample and the RLUs detected by the ARCHITECT *i* System optics.

The ARCHITECT CA 125 II assay is a two-step sandwich technique immunoassay to determine the presence of OC 125 defined antigen in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex. In the first step of the assay, sample and antibody (mouse monoclonal anti-OC 125) coated paramagnetic microparticles are combined. CA125 reactive determinants present in the sample bind to the antibody coated microparticles. After washing, a second acridinium-labeled antibody 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 CA125 reactive determinants in the sample and the RLUs detected by the ARCHITECT™ *i* optical system.

The ARCHITECT *i*2000SR is capable of calculating the ROMA score. Using and the value of the 2 analytes, ARCHITECT ROMA scores (numerical score from 0.0-10.0) for both premenopausal and postmenopausal will be calculated and will indicate whether a woman is at low likelihood or high likelihood for finding malignancy on surgery. Both premenopausal and postmenopausal ARCHITECT ROMA results will be reported to the ordering physician who will decide which result to use based on patient's menopausal status.

M. Performance Characteristics (if/when applicable):

Both ARCHITECT HE4 and ARCHITECT CA 125 II are previously cleared devices. Analytical performance for ARCHITECT HE4 and ARCHITECT CA 125 II were validated in k093957 and k042731 respectively. There has been no modification of assay methods for ARCHITECT HE4 and ARCHITECT CA 125 II since the original clearance for each assay. Since there have been no modifications of either assay, there is no increased potential for carry-over contamination

Data were generated using the ARCHITECT *i*2000SR System.

1. Analytical performance:

   a. *Precision/Reproducibility:*

Lot-to-Lot Precision
A study was performed as described per the National Committee for Clinical Laboratory Standards NCCLS (CLSI) guideline EP5-A2. A panel of five serum samples was tested and evaluated using both premenopausal and postmenopausal forms of the ROMA equation, using three lots of ARCHITECT HE4 Reagent Kits and Calibrators and three lots of ARCHITECT CA 125 II Reagent Kits and Calibrators, evaluating two measurements of each panel, at two separate times per day for 10 days. Data from this study is summarized in the following tables.

Summary for the Lot-to-Lot Variability for the Combined Data for Premenopausal ROMA Score (N=160 for each panel)

Sample	Mean	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Panel 1	0.6721	0.0459	6.84	0.0152	2.26	0.0204	3.04	0.0269	4.01	0.0590	8.78
Panel 2	1.4404	0.0890	6.18	0.0380	2.64	0.0244	1.69	0.0506	3.51	0.1118	7.76
Panel 3	3.1073	0.1440	4.63	0.0569	1.83	0.0000	0.00	0.1040	3.35	0.1865	6.00
Panel 4	1.1066	0.0679	6.13	0.0153	1.39	0.0154	1.39	0.0531	4.80	0.0889	8.03
Panel 5	8.8753	0.0595	0.67	0.0243	0.27	0.0000	0.00	0.0783	0.88	0.1013	1.14

Summary for the Lot-to-Lot Variability for the Combined Data for Postmenopausal ROMA Score (N=160 for each panel)

Sample	Mean	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Panel 1	1.0614	0.0436	4.10	0.0154	1.45	0.0072	0.68	0.0222	2.09	0.0517	4.88
Panel 2	2.5897	0.0752	2.90	0.0238	0.92	0.0214	0.83	0.0552	2.13	0.0986	3.81
Panel 3	4.9463	0.0911	1.84	0.0295	0.60	0.0154	0.31	0.1341	2.71	0.1655	3.35
Panel 4	2.6272	0.0726	2.76	0.0243	0.92	0.0000	0.00	0.0692	2.63	0.1032	3.93
Panel 5	8.8011	0.0370	0.42	0.0141	0.16	0.0000	0.00	0.0901	1.02	0.0984	1.12

Reproducibility

A study was performed as described per the National Committee for Clinical Laboratory Standards NCCLS (CLSI) guideline EP5-A2. A panel of five serum samples was tested and evaluated using both premenopausal and postmenopausal forms of the ROMA equation, using two lots of ARCHITECT HE4 Reagent Kits and two lots of ARCHITECT CA 125 II Reagent Kits, at three sites, evaluating two measurements of each panel, at two separate times per day for 10 days. Data from this study is summarized in the following tables.

Summary for the Site-to-Site Variability for the Combined Data for Premenopausal ROMA Score (N=120 for each panel)

Sample	Mean	Within-Run		Between-Run		Between-Day		Between-Site		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Panel 1	0.6280	0.0368	5.86	0.0222	3.54	0.0227	3.61	0.0408	6.50	0.0635	10.11
Panel 2	1.3702	0.0931	6.80	0.0775	5.65	0.0000	0.00	0.0476	3.47	0.1301	9.50
Panel 3	2.9969	0.1412	4.71	0.0770	2.57	0.0000	0.00	0.0741	2.47	0.1771	5.91
Panel 4	1.0451	0.0612	5.86	0.0170	1.62	0.0264	2.53	0.0293	2.81	0.0748	7.16
Panel 5	8.8501	0.0701	0.79	0.0000	0.00	0.0279	0.32	0.0104	0.12	0.0762	0.86

Summary for the Site-to-Site Variability for the Combined Data for Postmenopausal ROMA Score (N=120 for each panel)

Sample	Mean	Within-Run		Between-Run		Between-Day		Between-Site		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Panel 1	1.0313	0.0349	3.38	0.0246	2.39	0.0110	1.07	0.0407	3.95	0.0600	5.82
Panel 2	2.5296	0.0808	3.20	0.0803	3.18	0.0000	0.00	0.0486	1.92	0.1239	4.90
Panel 3	4.8604	0.0923	1.90	0.0504	1.04	0.0000	0.00	0.0888	1.83	0.1376	2.83
Panel 4	2.5654	0.0705	2.75	0.0000	0.00	0.0243	0.95	0.0572	2.23	0.0940	3.66
Panel 5	8.7739	0.0405	0.46	0.0117	0.13	0.0075	0.09	0.0389	0.44	0.0579	0.66

b. Linearity/assay reportable range:

Not applicable

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

Each assay uses its own calibrator and controls.

ARCHITECT CA 125 II Calibrator and Controls
The OC125 defined antigen is used in the ARCHITECT CA 125 II Calibrators and Controls. The concentrations are specific to each calibrator and control level. This material is obtained from Fujirebio Diagnostics, Inc. proprietary human ovarian carcinoma cell line, McDonalds. OC 125 defined antigen is produced by the McDonalds cell line. The stock solution for calibrators is prepared by adding OC 125 defined antigen to a diluent to achieve the desired concentrations. The stock solution is tested to determine its actual concentration. Each Calibrator and Control is then prepared based on the actual concentration of the stock solution.

ARCHITECT HE4 Calibrator and Controls
Ig-HE4 is a fusion protein consisting of a human Fc antibody fragment and Human Epididymis protein HE4. The Ig-HE4 antigen is used as a calibrator protein in the HE4 assay to determine HE4 concentrations in human serum samples. The protein is produced in a stably transfected Chinese Hamster Ovary (CHO) cell line. The cell line was adapted to serum free growth medium at Fujirebio Diagnostics, Inc. Recombinant antigen is used to prepare calibrators and controls for ARCHITECT HE4.

Stability

Specimen:
ARCHITECT ROMA is intended for use with serum. The specimen stability and storage claims are limited to the ARCHITECT HE4 assay. Serum can be stored at 2–8°C for 4 days before being tested. Samples can be stored at -10°C or colder for longer periods.

Calibration Curve: For ARCHITECT HE4 and ARCHITECT CA 125 II, the calibration curve is stable up to 30 days.

Reagent Closed-Vial: Users are instructed to refer to the individual stability information in the package insert of each assay. The claimed stability for ARCHITECT HE4 is up to 12 months at 2–8°C. The claimed shelf life for ARCHITECT CA 125 II is 12 months at 2–8°C.

Reagent Open-Vial: Users are instructed to refer to the stability information in the package insert for reagents used in the individual assay. The stability of the opened reagents used in ARCHITECT HE4 and ARCHITECT CA 125 II kit are listed below:

	Stability	
Component	**Opened Vial**	**Opened Vial/On-Board**
ARCHITECT CA 125 II Reagent Kit	2-8°C for 12 months	30 days at 2-8°C
ARCHITECT CA 125 II Calibrators	2-8°C for 12 months	
ARCHITECT HE4 Reagent Kit	2-8°C for 12 months	30 days at 2-8°C
ARCHITECT HE4 Calibrators	2-8°C for 12 months	

d. Detection limit:

The limits of detection and limits of quantitation reported in each assay's package insert are incorporated into the algorithm such that results outside of the measuring interval are not imported and do not yield an ARCHITECT ROMA score.

e. Analytical specificity:

Studies were performed based on guidance from CLSI Document EP7-A2. Potential interferents were evaluated to determine whether premenopausal (Pre) and postmenopausal (Post) ROMA scores were affected when using ARCHITECT ROMA. The potential interferents listed in the table below were spiked into 3 serum panels (Low, Medium, and High). The samples were assayed, and the ROMA scores of the spiked samples were compared to reference samples.

Potentially Interfering Substance	**Concentration**	**% Interference**					
		Low [b]		**Medium [c]**		**High [d]**	
		Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Hemoglobin [a]	2 mg/mL	12	5	1	1	6	1
	1 mg/mL	-1	-1	2	0	5	1
Bilirubin (Conjugated)	20 mg/dL	-2	0	-5	-1	-6	-2
Bilirubin (Unconjugated)	20 mg/dL	1	1	-4	-2	-2	0
Protein [a]	12 g/dL	-7	-5	-11	-7	-11	-4
	10 g/dL	-7	-3	-8	-6	-8	-3

Potentially Interfering Substance	Concentration	% Interference					
		Low [b]		Medium [c]		High [d]	
		Pre	Post	Pre	Post	Pre	Post
Triglyceride	3 g/dL	-3	-4	-3	0	0	0
Human Anti-Mouse Antibodies (HAMA)	1000 ng/mL	-2	8	-1	2	1	0
Rheumatoid Factor (RF)	500 IU/mL	-2	-2	-3	-1	0	0

[a] Samples containing hemoglobin at >1 mg/mL and protein at ≥12 g/dL demonstrated interference.
[b] approximately 15 U/mL CA 125 II and 50 pM HE4
[c] approximately 40 U/mL CA 125 II and 60 pM HE4
[d] approximately 100 U/mL CA 125 II and 100 pM HE4

f. Assay cut-off:

See Clinical Cutoff in M (4) below

2. Comparison studies:

a. Method Comparison

ARCHITECT ROMA method comparison study was performed using specimens consistent with CLSI guideline EP9-A2-IR using the Deming and Passing-Bablok regression method to compare ARCHITECT ROMA to ROMA (HE4 EIA + ARCHITECT CA 125 II). The data are summarized in the following table.

Menopausal Status	Correlation Coefficient (r)	Regression	Intercept	95% CI		Slope	95% CI	
Premenopausal	0.983	Deming	-0.097	-0.165	-0.029	0.983	0.939	1.027
		Passing-Bablok	0.005	-0.038	0.029	0.924	0.870	0.996
Postmenopausal	0.999	Deming	-0.041	-0.074	-0.007	0.997	0.988	1.006
		Passing-Bablok	-0.015	-0.044	0.005	0.997	0.987	1.004

b. *Matrix Comparison*

Serum is the only claimed matrix.

3. Clinical studies:

a. Clinical sensitivity:

See 3(c) below

b. Clinical specificity:

See 3(c) below

c. Other clinical supportive data (when a. and b. are not applicable):

Risk of Ovarian Malignancy Algorithm in Patients Presenting with an Adnexal Mass
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 459 women were evaluated in the study. For each patient, an initial cancer risk assessment was completed, providing an assessment of the patient's mass as benign or malignant. The corresponding histopathology reports were collected after surgery.

The histopathological classifications of the 459 patients (250 premenopausal and 209 postmenopausal) are summarized in the table below.

Histopathological Classification	**Total**		**Premenopausal**		**Postmenopausal**	
	N	%	N	%	N	%
Benign Pathology	374	81.5	229	91.6	145	69.4
Low Malignant Potential (LMP) /Borderline	18	3.9	7	2.8	11	5.3
Epithelial Ovarian Cancer (EOC)	48	10.5	9	3.6	39	18.7
Non-EOC	2	0.4	0	0.0	2	1.0
Other Gynecological Cancer	9	2.0	3	1.2	6	2.9
Other Cancer	7	1.5	1	0.4	6	2.9
Metastatic Cancer	1	0.2	1	0.4	0	0.0

Use of ROMA for stratification into likelihood of finding malignancy on surgery

Using a preoperatively collected serum sample, ARCHITECT ROMA was determined and the patient was stratified into a low or a high likelihood group for finding malignancy on surgery. The stratification of the 459 patients (250 premenopausal and 209 postmenopausal) presenting with an adnexal mass into high likelihood of harboring malignant disease using ARCHITECT ROMA is shown in the table below.

	Total		Premenopausal		Postmenopausal	
	N	%	N	%	N	%
All EOC [a]	45/48	93.8	9/9	100.0	36/39	92.3
EOC Stage I + II	9/12	75.0	3/3	100.0	6/9	66.7
EOC Stage III + IV	34/34	100.0	5/5	100.0	29/29	100.0
LMP Tumors	13/18	72.2	4/7	57.1	9/11	81.8
Other Cancer [b]	11/19	57.9	2/5	40.0	9/14	64.3
All Cancer and LMP Tumors	69/85	81.2	15/21	71.4	54/64	84.4

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

The stratification of 422 women, 48 with epithelial ovarian cancer and 374 with benign disease, into low likelihood and high likelihood groups for finding malignancy on surgery using ARCHITECT ROMA is shown in the table below.

	Premenopausal (N=238)		Postmenopausal (N=184)	
	% (N)	95% CI [a]	% (N)	95% CI [a]
Sensitivity	100.0 (9/9)	(70.1,99.2)	92.3 (36/39)	(79.7,97.2)
Specificity	86.5 (198/229)	(81.4,90.3)	85.5 (129/145)	(78.9,90.3)
TP - FP [b]	86.5	(81.9,91.0)	77.8	(67.5,88.2)
PPV [c]	22.5 (9/40)	(12.3,37.4)	63.2 (36/57)	(50.2,74.4)
NPV [d]	100.0 (198/198)	(98.1,99.9)	97.6 (124/127)	(93.3,99.2)
Prevalence	3.8 (9/238)		21.2 (39/184)	

[a] Confidence Interval
[b] True Positive rate - False Positive rate
[c] Positive Predictive Value
[d] Negative Predictive Value

Adjunctive use of ARCHITECT ROMA with ICRA for stratification into low likelihood and high likelihood groups for finding malignancy on surgery

The performance for the adjunctive use of ARCHITECT ROMA with ICRA (ARCHITECT ROMA and/or ICRA being positive for high likelihood of finding malignancy on surgery) was evaluated. Premenopausal and postmenopausal women combined for all cancers.

Malignancy by Pathology [a]				
		Initial Cancer Risk Assessment		
		Positive [b]	Negative [c]	Total
ARCHITECT ROMA	Positive [b]	56	12	68
	Negative [c]	6	11	17
	Total	62	23	85
No Malignancy by Pathology [a]				
		Initial Cancer Risk Assessment		
		Positive [b]	Negative [c]	Total
ARCHITECT ROMA	Positive [b]	20	32	52
	Negative [c]	39	283	322
	Total	59	315	374

[a] All malignancies found including EOC, LMP, non-epithelial ovarian cancer, other gynecologic, and non-gynecologic cancers.
[b] High likelihood of finding malignancy on surgery
[c] Low likelihood of finding malignancy on surgery

Adjunctive use ARCHITECT ROMA with ICRA produced a statistically significant improvement in the negative predictive value (NPV). The NPV for correctly classifying benign patients into the low likelihood group increased from 93.2 to 96.3%, making the adjunctive use of ARCHITECT ROMA with ICRA effective in ruling out malignancy.

	ICRA		ARCHITECT ROMA		Adjunctive	
	%	95% CI [a]	%	95% CI [a]	%	95% CI [a]
Sensitivity	72.9	62.7,81.2	80.0	70.3,87.1	87.1	78.3,92.6
Specificity	84.2	80.2,87.6	86.1	82.2,89.2	75.7	71.1,79.7
PPV [b]	51.2	42.4,60.0	56.7	47.7,65.2	44.8	37.5,52.5
NPV [c]	93.2	90.0,95.4	95.0	92.1,96.8	96.3	93.4,97.9
TP - FP [d]	57.2	46.8,67.5	66.1	56.7,75.5	62.7	54.2,71.3
PLR [e]	4.624	3.538,6.042	5.754	4.376,7.565	3.578	2.939,4.355
NLR [f]	0.321	0.226,0.457	0.232	0.152,0.356	0.171	0.098,0.298
Prevalence		18.5%				

[a] Confidence Interval
[b] Positive Predictive Value
[c] Negative Predictive Value
[d] True Positive rate - False Positive rate
[e] Positive Likelihood Ratio
[f] Negative Likelihood Ratio

4. Clinical cut-off**:**

The following cut-offs are used to interpret the result. The ARCHITECT ROMA score is between 0.0 and 10.0.

Premenopausal women:

ROMA score ≥1.31 High likelihood of finding malignancy
ROMA score <1.31 Low likelihood of finding malignancy

Postmenopausal women:

ROMA score ≥2.77 High likelihood of finding malignancy
ROMA score <2.77 Low likelihood of finding malignancy

5. Expected values/Reference range:

Descriptive Statistics of ARCHITECT ROMA Results for Pre- and Postmenopausal Healthy Subjects:

	Pre- and Postmenopausal Healthy Subjects Combined	Premenopausal Healthy Subjects	Postmenopausal Healthy Subjects
N	242	122	120
ARCHITECT ROMA Result			
Mean (SD)	0.83 (0.56)	0.61 (0.48)	1.05 (0.55)
Median	0.83	0.43	0.92
Range (min, max)	0.11-3.56	0.11-2.88	0.36-3.56
Reference Interval (5^{th} percentile, 95^{th} percentile)	0.24, 1.98	0.21, 1.65	0.46, 2.02
ARCHITECT ROMA Likelihood (n, %)			
High Likelihood	11 (4.5%)	9 (7.4%)	2 (1.7%)
Low Likelihood	231 (95.5%)	113 (92.6%)	118 (93.3%)

Descriptive Statistics of ARCHITECT ROMA Results for Pre- and Postmenopausal (Combined) Benign Subjects

Pre- and Postmenopausal Subjects Combined	Benign Gynecological Disease	Other Benign Disease	CHF	Hypertension	Pregnant
N	374	39	40	40	40
ARCHTECT ROMA Result					
Mean (SD)	1.13 (1.07)	2.92 (2.48)	2.47 (1.70)	2.07 (1.73)	0.58 (0.24)
Median	0.79	1.73	2.08	1.56	0.54
Range (min, max)	0.10-8.24	0.18-9.44	0.15-7.53	0.50-8.56	0.10-1.05
Reference Interval (5^{th} percentile, 95^{th} percentile)	0.26, 3.01	0.36, 7.94	0.60, 5.09	0.72, 4.75	0.29, 1.01
ARCHITECT ROMA Likelihood (n, %)					
High Likelihood	52 (13.9%)	17 (43.6%)	14 (35.0%)	10 (25.0%)	0 (0.0%)
Low Likelihood	322 (86.1%)	22 (56.4%)	26 (65.0%)	30 (75.0%)	40 (100.0%)

Descriptive Statistics of ARCHITECT ROMA Results for Pre- and Postmenopausal (Combined) Cancer Subjects

Pre- and Postmenopausal Subjects Combined	**Bladder Cancer**	**Breast Cancer**	**Endometrial Cancer**	**GI Cancer**	**Lung Cancer**
N	40	40	40	40	40
ARCHITECT ROMA Result					
Mean (SD)	3.43 (2.48)	2.52 (2.20)	4.19 (3.38)	2.67 (2.00)	3.18 (1.85)
Median	2.67	1.58	2.69	2.05	3.13
Range (min, max)	0.49-9.93	0.25-9.79	0.30-9.95	0.64-9.08	0.51-7.82
Reference Interval (5^{th} percentile, 95^{th} percentile)	0.83, 9.16	0.56, 6.86	0.39, 9.58	0.69, 7.26	0.62, 5.93
ARCHITECT ROMA Likelihood (n, %)					
High Likelihood	19 (47.5%)	16 (40.0%)	21 (52.5%)	15 (37.5%)	22 (55.0%)
Low Likelihood	21 (52.5%)	24 (60.0%)	19 (47.5%)	25 (62.5%)	18 (45.0%)

It is recommended that each laboratory establish its own reference value for the population of interest.

N. Proposed Labeling:

The labeling satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The results of these analytical (nonclinical) and clinical studies demonstrate that ARCHITECT ROMA is substantially equivalent to the performance of ROMA (HE4 EIA + ARCHITECT CA 125 II).