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 16, 2016

Re: K160090
Trade/Device Name: Lumipulse® ***G*** ROMA®
Regulation Number: 21 CFR 866.6050
Regulation Name: Ovarian adnexal mass assessment score test system
Regulatory Class: II
Product Code: ONX
Dated: April 14, 2016
Received: April 15, 2016

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) 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)*
k160090

Device Name
Lumipulse® G ROMA®

Indications for Use *(Describe)*
Lumipulse® G Risk of Ovarian Malignancy Algorithm (ROMA®) is a qualitative serum and plasma (lithium heparin or dipotassium EDTA) test that combines the results of Lumipulse G HE4, Lumipulse G CA 125II and menopausal status into a numerical score.

Lumipulse G 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. Lumipulse G 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. Lumipulse G 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: Lumipulse G 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 Lumipulse G 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.

510(k) Number:

K160090

Purpose for Submission:

New device

Measurand:

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

Type of Test:

Software algorithm and 2 immunoassays

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**: May 16, 2016**

Proprietary and Established Names:

Lumipulse® *G* ROMA®

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

Intended Use:

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

   Lumipulse® ***G*** Risk of Ovarian Malignancy Algorithm (ROMA®) is a qualitative serum and plasma (lithium heparin or dipotassium EDTA) test that combines the results of Lumipulse ***G*** HE4, Lumipulse ***G*** CA125II and menopausal status into a numerical score.

   Lumipulse ***G*** 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. Lumipulse ***G*** 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. Lumipulse ***G*** 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: Lumipulse ***G*** 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 Lumipulse ***G*** 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:
   LUMIPULSE ***G***1200 system

Device Description:

Lumipulse ***G*** ROMA is a qualitative serum and plasma test that combines the results of 2 analytes, HE4 (Lumipulse ***G*** HE4) and CA125 (Lumipulse ***G*** CA 125 II) and menopausal status into a numerical score between 0.00 and 10.00. 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 Lumipulse ***G*** HE4, Lumipulse ***G*** CA 125 II, the Lumipulse ***G*** ROMA Calculator Tool and the LUMIPULSE ***G***1200 System. The LUMIPULSE ***G***1200 System is not capable of calculating the ROMA score. The immunoassays are performed according to the directions detailed in each product insert.

Both Lumipulse ***G*** HE4 and Lumipulse ***G*** CA 125 II are previously 510(k) cleared Class II devices (k151378 and k142895 respectively). The Lumipulse ***G*** HE4 assay is a chemiluminescent enzyme immunoassay (CLEIA) for the quantitative determination of HE4 antigen in human serum and plasma (lithium heparin or dipotassium EDTA) on the LUMIPULSE ***G*** System. 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. Lumipulse ***G*** CA 125 II assay is a chemiluminescent enzyme immunoassay (CLEIA) for the quantitative determination of CA125 in human serum and plasma (sodium heparin, lithium heparin, or dipotassium EDTA) on the LUMIPULSE ***G*** System. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with ovarian cancer. Serial testing for patient CA125 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

Lumipulse ***G*** ROMA scores (numerical score from 0.00 -10.00) for both premenopausal and postmenopausal women are calculated using the Lumipulse ***G*** ROMA Calculator Tool to indicate a low likelihood or high likelihood for finding malignancy on surgery using the value of the 2 immunoassays (Lumipulse ***G*** HE4 and Lumipulse ***G*** CA125II).

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		
	Lumipulse® *G* 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	Lumipulse ***G*** Risk of Ovarian Malignancy Algorithm (ROMA) is a qualitative serum and plasma (lithium heparin or dipotassium EDTA) test that combines the results of Lumipulse ***G*** HE4, Lumipulse ***G*** CA 125 II™ and menopausal status into a numerical score. Lumipulse ***G*** 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. Lumipulse ***G*** 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. Lumipulse ***G*** 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.

Similarities		
	Lumipulse® *G* ROMA® (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
Black box warning (PRECAUTION)	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 carries the risk of unnecessary testing, surgery, and/or delayed diagnosis	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 carries the risk of unnecessary testing, surgery, and/or delayed diagnosis
Specimen Collection Method	Routine Phlebotomy Techniques	Routine Phlebotomy Techniques
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: Lumipulse ***G*** ROMA score ≥ 1.31 = High likelihood of finding malignancy Lumipulse ***G*** ROMA score < 1.31= Low likelihood of finding malignancy Postmenopausal: Lumipulse ***G*** ROMA score ≥ 2.77 = High likelihood of finding malignancy Lumipulse ***G*** 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

Similarities		
	Lumipulse® *G* ROMA® (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
Software	Provided as separate CD-ROM for manual entry of assay values using software on a Personal Computer (PC) to produce the ROMA result	Provided as separate CD-ROM for manual entry of assay values using software on a Personal Computer (PC) to produce the ROMA result

Differences		
	Lumipulse® *G* ROMA® (Proposed Device)	**ROMA (HE4 EIA + ARCHITECT CA 125 II) (Predicate Device) K103358**
Instrument System	LUMIPULSE ***G***1200 Only	Manual ELISA for HE4 and ARCHITECT *i*2000SR for 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 Lumipulse ***G*** 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.
Type of Specimen	Human Serum and Plasma (lithium heparin or dipotassium EDTA)	Human Serum

Standard/Guidance Document Referenced (if applicable):

- CLSI EP5-A3- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
- CLSI EP7-A2 - Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition
- CLSI EP28-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)

Test Principle:

Lumipulse ***G*** HE4 is an assay system, including a set of immunoassay reagents, for the quantitative measurement of HE4 in specimens based on CLEA technology by a two-step sandwich immunoassay method on the LUMIPULSE ***G***1200 System. HE4 in specimens specifically binds to anti-HE4 monoclonal antibody (mouse) on the particles, and antigen-antibody immunocomplexes are formed. The particles are washed and rinsed to remove unbound materials. Alkaline phosphatase (ALP: calf)-labeled anti-HE4 monoclonal antibody (mouse) specifically binds to HE4 of the immunocomplexes on the particles, and additional immunocomplexes are formed. The particles are washed and rinsed to remove unbound materials. Substrate Solution is added and mixed with the particles. AMPPD contained in the Substrate Solution is dephosphorylated by the catalysis of ALP indirectly conjugated to particles. Luminescence (at a maximum wavelength of 477 nm) is generated by the cleavage reaction of dephosphorylated AMPPD. The luminescent signal reflects the amount of HE4.

Lumipulse ***G*** CA125II is an assay system, including a set of immunoassay reagents, for the quantitative measurement of CA125 in specimens based on CLEA technology by a two-step sandwich immunoassay method on the LUMIPULSE ***G*** System. CA125 in specimens specifically binds to anti-CA125 monoclonal antibody (mouse) on the particles, and antigen-antibody immunocomplexes are formed. The particles are washed and rinsed to remove unbound materials. Alkaline phosphatase (ALP: calf)-labeled anti-CA125 monoclonal antibody (mouse) specifically binds to CA125 of the immunocomplexes on the particles, and additional immunocomplexes are formed. The particles are washed and rinsed to remove unbound materials. Substrate Solution is added and mixed with the particles. AMPPD contained in the Substrate Solution is dephosphorylated by the catalysis of ALP indirectly conjugated to particles. Luminescence (at a maximum wavelength of 477 nm) is generated by the cleavage reaction of dephosphorylated AMPPD. The luminescent signal reflects the amount of CA125.

The Lumipulse ***G*** ROMA Calculator Tool will be used for calculating the ROMA score. Using and the value of the 2 analytes, Lumipulse ***G*** ROMA scores (numerical score from 0.00-10.00)

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 Lumipulse ***G*** ROMA results will be reported to the ordering physician who will decide which result to use based on patient's menopausal status.

Performance Characteristics (if/when applicable):

Both Lumipulse ***G*** HE4 and Lumipulse ***G*** CA125II are previously cleared devices. Analytical performance for Lumipulse ***G*** HE4 and Lumipulse ***G*** CA125II were validated in k151378 and k142895 respectively. There has been no modification of assay methods for Lumipulse ***G*** HE4 and Lumipulse ***G*** CA125II since the original clearance for each assay.

Data were generated using the LUMIPULSE ***G***1200 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-A3. A panel of five serum samples was tested and evaluated using both premenopausal and postmenopausal forms of the ROMA equation, using three lots of Lumipulse ***G*** HE4 Reagent Kits and three lots of Lumipulse ***G*** CA 125 II Reagent Kits, 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 Premenopausal ROMA Score (N=120 for each panel)

		Between Lots		Between Days Within Lots		Between-Runs Within Days Within Lot		Within Runs		Total	
Sample	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Panel 1	1.02	0.031	3.0	0.022	2.2	0.018	1.7	0.021	2.1	0.047	4.6
Panel 2	1.87	0.054	2.9	0.033	1.8	0.041	2.2	0.036	2.0	0.084	4.5
Panel 4	4.04	0.091	2.3	0.049	1.2	0.041	1.0	0.070	1.7	0.131	3.3
Panel 5	8.75	0.059	0.7	0.013	0.2	0.037	0.4	0.034	0.4	0.078	0.9
Panel 6	9.94	0.001	0.0	0.000	0.0	0.002	0.0	0.003	0.0	0.003	0.0

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

		Between Lots		Between Days Within Lots		Between-Runs Within Days Within Lot		Within Runs		Total	
Sample	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Panel 1	1.55	0.006	0.4	0.026	1.7	0.014	0.9	0.021	1.4	0.038	2.4
Panel 2	3.16	0.017	0.5	0.037	1.2	0.032	1.0	0.036	1.1	0.063	1.7
Panel 4	5.71	0.028	0.5	0.033	0.6	0.038	0.7	0.039	0.7	0.070	1.2
Panel 5	8.81	0.018	0.2	0.012	0.1	0.021	0.2	0.016	0.2	0.034	0.4
Panel 6	9.80	0.004	0.0	0.002	0.0	0.003	0.0	0.004	0.0	0.007	0.1

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 one lot of Lumipulse ***G*** HE4 Reagent Kits and one lot of Lumipulse ***G*** 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 Premenopausal ROMA Score (N=120 for each panel)

		Between Sites		Between Days Within Sites		Between-Runs Within Days Within Lot		Within Runs		Total	
Sample	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Panel 1	1.01	0.067	6.7	0.024	2.4	0.030	3.0	0.026	2.6	0.081	8.1
Panel 2	1.86	0.109	5.8	0.042	2.3	0.062	3.4	0.033	1.8	0.136	7.3
Panel 4	4.01	0.176	4.4	0.100	2.5	0.119	3.0	0.075	1.9	0.246	6.1
Panel 5	8.75	0.094	1.1	0.022	0.3	0.086	1.0	0.026	0.3	0.132	1.5
Panel 6	9.94	0.007	0.1	0.003	0.0	0.004	0.0	0.003	0.0	0.009	0.1

Summary for the Site-to-Site Variability for Postmenopausal ROMA Score (N=40 for each panel)

		Between Sites		Between Days Within Sites		Between-Runs Within Days Within Lot		Within Runs		Total	
Sample	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Panel 1	1.51	0.063	4.2	0.029	1.9	0.023	1.6	0.026	1.8	0.078	5.2
Panel 2	3.11	0.109	3.5	0.052	1.7	0.052	1.7	0.033	1.1	0.136	4.4
Panel 4	5.63	0.118	2.1	0.067	1.2	0.082	1.5	0.043	0.8	0.164	2.9
Panel 5	8.77	0.059	0.7	0.021	0.2	0.056	0.6	0.015	0.2	0.085	1.0
Panel 6	9.79	0.014	0.1	0.006	0.1	0.010	0.1	0.004	0.0	0.019	0.2

b. Linearity/assay reportable range:

Not applicable

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

Each assay uses its own calibrators.

Lumipulse *G* CA125II Calibrators
The Lumipulse ***G*** CA125II Calibrators are for the use in the calibration of the LUMIPULSE ***G*** System for the quantitative measurement of CA125 in serum or plasma (sodium heparin, lithium heparin, and dipotassium EDTA).

The OC125 defined antigen is used in the LUMIPULSE ***G*** CA125II Calibrators. This material is obtained from Fujirebio Diagnostics, Inc. proprietary human ovarian carcinoma cell line.

Lumipulse *G* HE4 Calibrators
The Lumipulse ***G*** HE4 Calibrators are for the use in the calibration of the LUMIPULSE ***G*** System for the quantitative measurement of HE4 in serum or plasma (lithium heparin and dipotassium EDTA).

The HE4 antigen is used in the Lumipulse ***G*** HE4 Calibrators. This material is provided by Fujirebio Diagnostics, AB. The Lumipulse ***G*** HE4 assay is standardized against the Fujirebio Diagnostics HE4 EIA.

Stability

Specimen:
Lumipulse ***G*** ROMA is intended for use with serum and plasma (lithium heparin and dipotassium EDTA). The specimen stability and storage claims are limited to the Lumipulse ***G*** HE4 assay. Samples can be stored at 2–8°C for 3 days or at -10°C or colder for up to 1 month before being tested.

Calibration Curve: For Lumipulse ***G*** HE4 and Lumipulse ***G*** CA125II, the calibration curve is stable up to 30 days.

Users are instructed to refer to the individual stability information in the package insert of each assay.

Lumipulse ***G*** HE4 when stored at 2-10^{o}C is stable until the expiration date stated on the label outside of the kit box. The current shelf life of Lumipulse ***G*** HE4 is 8 months.

Lumipulse ***G*** CA125II when stored at 2-10^{o}C is stable until the expiration date stated on the label outside of the kit box. The current shelf life of Lumipulse ***G*** CA125II is 10 months.

Kit	Stability
Lumipulse ***G*** CA125II Immunoreaction Cartridge	2-10^{o}C for 10 months
Lumipulse ***G*** CA125II Calibrators	2-10^{o}C for 10 months
Lumipulse ***G*** HE4 Immunoreaction Cartridge	2-10^{o}C for 8 months
Lumipulse ***G*** HE4 Calibrators	2-10^{o}C for 8 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 a Lumipulse ***G*** 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 Lumipulse ***G*** ROMA. The potential interferents listed in the table below were spiked into 4 serum panels. The samples were assayed, and the ROMA scores of the spiked samples were compared to reference samples.

Mean (%) percent differences of Pre and Post-Menopausal Lumipulse *G* ROMA Scores for endogenous interferents.

Interferent	Test Concentration	Mean Percent (%) Difference Pre-Menopausal ROMA	Mean Percent (%) Difference Post-Menopausal ROMA
Free Bilirubin (Unconjugated)	60.0 mg/dL	0%	0%
Bilirubin (Conjugated)	60.0 mg/dL	1%	0%
Triglycerides (Intralipid 20% Emulsion)	3,000 mg/dL	1%	-1%
Hemoglobin	500 mg/dL	0%	0%
Total Protein (Human Serum Albumin)	12 g/dL	-1%	-1%
Immunoglobulin G (IgG)	5 g/dL	-2%	-1%
Biotin	19.8 mg/dL	0%	0%
Human Anti-Mouse Antibodies (HAMA)	1000 ng/mL	-1%	0%
Rheumatoid Factor (RF)	1000 IU/mL	1%	0%

f. Assay cut-off:

See Clinical Cutoff in M (4) below

2. Comparison studies:

a. Method Comparison

Lumipulse ***G*** ROMA method comparison study was performed on the LUMIPULSE ***G***1200 System using specimens consistent with CLSI guideline EP9-A3. The weighted Deming regression method was used to compare Lumipulse ***G*** ROMA to ROMA (HE4 EIA + ARCHITECT CA 125 II). The data are summarized in the following table.

Lumipulse *G* ROMA vs. ROMA (HE4 EIA + ARCHITECT CA 125 II)
Premenopausal Women

Lumipulse *G* ROMA Score	n	Correlation Coefficient (r)	Intercept (95% CI*)	Slope (95% CI*)
0.32 - 9.99	53	0.9977	-0.004 (-0.085, 0.078)	1.005 (0.994, 1.016)

*CI = Confidence Interval

Lumipulse *G* ROMA vs. ROMA (HE4 EIA + ARCHITECT CA 125 II)
Postmenopausal Women

Lumipulse *G* ROMA Score	n	Correlation Coefficient (r)	Intercept (95% CI*)	Slope (95% CI*)
0.57 - 10.00	115	0.9953	-0.103 (-0.254, 0.047)	0.999 (0.931, 1.016)

*CI = Confidence Interval

b. *Matrix Comparison*

Lumipulse ***G*** ROMA on the LUMIPULSE ***G***1200 System was evaluated for matrix differences by performing a study using eighty six (86) matched sets of serum and K_2 EDTA plasma samples. The results demonstrated equivalency between the matrices and are presented as a regression equation in the following table:

Matrix Comparison	n	ROMA Equation	ROMA Range	Regression Equation and Correlation Coefficient
Serum vs K_2 EDTA Plasma	86	Premenopausal	0.33 – 9.93	y= 1.001(x) – 0.072; r=0.9983
Serum vs K_2 EDTA Plasma	86	Postmenopausal	0.38 – 9.78	y= 1.004(x) - 0.058; r=0.9988

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 (ROMA) in Patients Presenting with an Adnexal Mass

Lumipulse ***G*** ROMA takes into account the results of Lumipulse ***G*** HE4 and the results of Lumipulse ***G*** CA125II as well as the menopausal status of the woman. The Lumipulse ***G*** 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 Lumipulse ***G*** 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 450 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, Lumipulse ***G*** 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 450 evaluable patients are summarized in the following table:

Histopathological Classification	Total n = 450		Premenopausal n = 244		Postmenopausal n = 206	
	N	%	N	%	N	%
Benign Pathology	366	81.3	223	91.4	143	69.4
Low Malignant Potential (LMP) Borderline	18	4.0	7	2.9	11	5.3
Epithelial Ovarian Cancer	47	10.4	9	3.7	38	18.4
Non-Epithelial Ovarian Cancer	2	0.4	0	0.0	2	1.0
Other Gynecologic Cancer	9	2.0	3	1.2	6	2.9
Other Cancer	7	1.6	1	0.4	6	2.9
Metastatic Cancer	1	0.2	1	0.4	0	0.0

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

The following cut-points are used:

Premenopausal women

Lumipulse ***G*** ROMA score ≥ 1.31 = High likelihood of finding malignancy

Lumipulse ***G*** ROMA score < 1.31 = Low likelihood of finding malignancy

Postmenopausal women

Lumipulse ***G*** ROMA score ≥ 2.77= High likelihood of finding malignancy

Lumipulse ***G*** ROMA score < 2.77 = Low likelihood of finding malignancy

The reported result should include both the premenopausal and postmenopausal likelihood result and associated Lumipulse ***G*** ROMA score on a scale of 0.00-10.00.

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 Lumipulse ***G*** 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 = 244	Postmenopausal n = 206	Total n = 450
All EOC[1]	100.0% (9/9)	92.1% (35/38)	93.6% (44/47)
EOC Stage I + II	100.0% (3/3)	66.7% (6/9)	75.0% (9/12)
EOC Stage III + IV	100.0% (5/5)	100.0% (28/28)	100.0% (33/33)
LMP Tumors	57.1% (4/7)	81.8% (9/11)	72.2% (13/18)
Other Cancer[2]	40.0% (2/5)	71.4% (10/14)	63.2% (12/19)
All Cancer and LMP Tumors	71.4% (15/21)	85.7% (54/63)	82.1% (69/84)

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

The performance of Lumipulse ***G*** 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 = 232		Postmenopausal n = 181	
	Estimate	**95% CI[1]**	**Estimate**	**95% CI[1]**
Sensitivity	100.0% (9/9)	70.1%, 99.2%	92.1% (35/38)	79.2%, 97.2%
Specificity	74.9% (167/223)	68.8%, 80.1%	77.6% (111/143)	70.1%, 83.7%
TP-FP[2]	74.9%	69.1%, 80.7%	69.7%	58.5%, 80.9%
PPV[3]	13.8% (9/65)	7.5%, 24.2%	52.2% (35/67)	40.5%, 63.7%
NPV[4]	100.0% (167/167)	97.8%, 99.9%	97.4% (111/114)	92.5%, 99.1%
Prevalence	3.9% (9/232)		21.0% (38/181)	

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

Adjunctive use of Lumipulse *G* 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 Lumipulse ***G*** ROMA with ICRA (Lumipulse ***G*** 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 Lumipulse ***G*** 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 93.1% to 96.1%, making the adjunctive use of Lumipulse ***G*** ROMA with ICRA effective in ruling out malignancy.

Total counts for premenopausal and postmenopausal women combined:

Malignancy by Pathology					No Malignancy by Pathology				
		ICRA					ICRA		
		Positive (High Likelihood)	Negative (Low Likelihood)	Total			Positive (High Likelihood)	Negative (Low Likelihood)	Total
ROMA	**Positive** (High Likelihood)	56	13	69	ROMA	**Positive** (High Likelihood)	27	61	88
	Negative (Low Likelihood)	5	10	15		**Negative** (Low Likelihood)	31	247	278
	Total	61	23	84		**Total**	58	308	366

[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		Lumipulse *G* ROMA		Adjunctive	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Sensitivity	72.6% (61/84)	62.3%, 81.0%	82.1% (69/84)	72.6%, 88.8%	88.1% (74/84)	79.5%, 93.4%
Specificity	84.2% (308/366)	80.1%, 87.5%	76.0% (278/366)	71.3%, 80.0%	67.5% (247/366)	62.5%, 72.1%
TP-FP[1]	56.8%	46.3%, 67.2%	58.1%	48.6%, 67.6%	55.6%	47.0%, 64.2%
PPV[2]	51.3% (61/119)	42.4%, 60.0%	43.9% (69/157)	36.4%, 51.8%	38.3% (74/193)	31.8%, 45.4%
NPV[3]	93.1% (308/331)	89.8%, 95.3%	94.9% (278/293)	91.7%, 96.9%	96.1% (247/257)	93.0%, 97.9%
Prevalence	18.7% (84/450)					

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

4. Clinical cut-off**:**

The following cut-offs are used to interpret the result. The Lumipulse ***G*** ROMA score is between 0.00 and 10.00.

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

Expected values/Reference range**:**

The distribution of Lumipulse ***G*** ROMA determined in 120 healthy premenopausal women and 118 healthy postmenopausal women is shown in the table below:

	All Healthy Subjects	**Premenopausal Healthy Subjects**	**Postmenopausal Healthy Subjects**
N	238	120	118
Lumipulse *G* ROMA Result			
Mean	0.97	0.85	1.10
(SD)	(0.79)	(1.00)	(0.49)
Median	0.83	0.65	0.99
Range (min - max)	0.23-9.92	0.23-9.92	0.38-2.94
Reference Interval (5^{th} - 95^{th} percentile)	0.33-1.98	0.29-1.73	0.52-2.03
Lumipulse *G* ROMA Likelihood (n, %)			
High Likelihood	17 (7.1%)	15 (12.5%)	2 (1.7%)
Low Likelihood	221 (92.9%)	105 (87.5%)	116 (98.3%)

In this study, 95% of the premenopausal healthy female subjects had Lumipulse ***G*** ROMA results equal to or below 1.73 and 95% of the postmenopausal healthy female subjects had Lumipulse ***G*** ROMA results equal to or below 2.03.

The distribution of Lumipulse ***G*** ROMA in premenopausal and postmenopausal women with non-ovarian malignancy conditions is shown in the table below:

	Epithelial Ovarian Cancer	Endo-metrial Cancer	Breast Cancer	GI Cancer	Lung Cancer	Bladder Cancer
N	154	40	40	40	40	40
Lumipulse *G* ROMA Result						
Mean	7.63	3.19	2.90	2.60	3.89	3.23
(SD)	(2.83)	(2.26)	(2.47)	(1.75)	(2.42)	(2.24)
Median	9.19	2.14	1.76	1.91	3.88	2.46
Range (min - max)	0.16-10.0	1.11-9.54	0.48-9.81	0.6-8.04	0.51-9.8	0.64-9.96
Reference Interval (5^{th} - 95^{th} percentile)	1.90-9.98	1.20-7.53	0.53-8.65	0.70-5.97	0.58-8.40	0.93-7.04
Lumipulse *G* ROMA Likelihood (n, %)						
High Likelihood	143 (92.9%)	18 (45.0%)	16 (40.0%)	16 (40.0%)	27 (67.5%)	17 (42.5%)
Low Likelihood	11 (7.1%)	22 (55.0%)	24 (60.0%)	24 (60.0%)	13 (32.5%)	23 (57.5%)

The distribution of Lumipulse ***G*** ROMA in premenopausal and postmenopausal women with benign conditions is shown in the table below:

	Benign Gynecologic	Benign Non-Gynecologic	Pregnant	Congestive Heart Failure	Hypertension
N	366	40	40	40	40
Lumipulse *G* ROMA Result					
Mean	1.49	2.22	0.64	3.72	3.52
(SD)	(1.20)	(2.10)	(0.26)	(2.06)	(3.06)
Median	1.09	1.57	0.58	3.71	1.99
Range (min - max)	0.17-8.47	0.58-9.99	0.28-1.57	0.22-7.78	0.43-10
Reference Interval (5^{th} - 95^{th} percentile)	0.41-3.82	0.67-4.84	0.31-1.02	0.71-7.18	0.57-9.56
Lumipulse *G* ROMA Likelihood (n, %)					
High Likelihood	89 (24.3%)	9 (22.5%)	1 (2.5%)	24 (60.0%)	20 (50.0%)
Low Likelihood	277 (75.7%)	31 (77.5%)	39 (97.5%)	16 (40.0%)	20 (50.0%)

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

Proposed Labeling:

The labeling satisfies the requirements of 21 CFR Part 809.10.

Conclusion:

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